Developing clinical practice guidelines for epilepsy: A report from the ILAE Epilepsy Guidelines Working Group

*†Khara M. Sauro, *†Samuel Wiebe, ‡Emilio Perucca, §Jacqueline French, ¶Colin Dunkley, #Alejandro de Marinis, **Martin Kirkpatrick, and *†Nathalie Jetté

Khara Sauro is a doctoral candidate at the University of Calgary.

SUMMARY

Clinical practice guidelines (CPGs) contain evidence-based recommendations to guide clinical care, policy development, and quality of care improvement. A recent systematic review of epilepsy guidelines identified considerable variability in the quality of available guidelines. Although excellent frameworks for CPG development exist, processes are not followed uniformly internationally, and resources to develop CPGs may be limited in certain settings. An International League Against Epilepsy (ILAE) working group was charged with proposing methodology to guide the development of future epilepsy-specific CPGs. A comprehensive literature search (1985–2014) identified articles related to CPG development and handbooks. Guideline handbooks were included if they were publicly available, and if their methodology had been used to develop CPGs. The working group's expertise also informed the creation of methodologies and processes to develop future CPGs for the ILAE. Five handbooks from North America (American Academy of Neurology), Europe (Scottish Intercollegiate Guidelines Network & National Institute for Health and Care Excellence), Australia (National Health and Medical Research Council), World Health Organization (WHO), and additional references were identified to produce evidence-based, consensus-driven methodology for development of epilepsy-specific CPGs. Key components of CPG development include the following: identifying the topic and defining the scope; establishing a working group; identifying and evaluating the evidence; formulating recommendations and determining strength of recommendations; obtaining peer reviews; dissemination, implementation, and auditing; and updating and retiring the CPG. A practical handbook and toolkit was developed. The resulting CPG development toolkit should facilitate the development of high-quality ILAE CPGs to improve the care of persons with epilepsy.
KEY WORDS: Evidence-based medicine, Guideline development, Knowledge translation, Knowledge to action, Practice parameters.

Clinical practice guidelines (CPGs) are documents that include recommendations intended to optimize patient care using a synthesis of the best available evidence.[1] Guidelines are systematically developed and can assist practitioners and patients in choosing appropriate health care for specific clinical circumstances.[2] Evidence-based recommendations

---

KEY POINTS

- When implemented, clinical guidelines can facilitate clinical care and improve the quality of care of persons with epilepsy
- High-quality guidelines are needed in many areas of epilepsy to bridge gaps
- Barriers to implementing clinical guidelines can be mitigated by improved guideline-development processes
- Minimum standards for guideline-development processes are outlined and associated tools are provided
- This toolkit should promote development of high-quality guidelines to fill knowledge gaps and optimize the care of persons with epilepsy

---

are the cornerstone of CPGs and take into consideration the risks and benefits of each intervention while incorporating the clinical judgment of an expert panel.[1–8] In addition to clinical practice recommendations, CPGs should include a detailed description of the development process and methods, the literature search results and evidence appraisal, and suggestions for implementing the recommendations.

CPGs can improve quality of care.[9–11] A systematic review of the influence of CPGs on the process and outcome of care found that most studies reported improvements after the introduction of guidelines.[9] This finding was echoed in a more recent systematic review, despite considerable heterogeneity between included studies.[11]

Two of the main limitations of CPGs are their heterogeneity and insufficient integration into clinical practice. Heterogeneity likely results from the lack of widely accepted standards for developing and reporting CPGs,[3–8,12–14] in turn contributing to the variability in CPG quality. In the absence of reporting standards for CPGs, the Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool was developed to evaluate the quality of CPGs.[15]

CPGs can only improve care if they are adopted and change clinical practice, which may explain why improvement in quality of care from CPGs has not always been the experience in epilepsy.[16,17] A randomized controlled trial of guideline implementation in Scotland found that, despite a multipronged implementation strategy, these guidelines did not result in significant improvements in process of care or patients' quality of life.[17] This study highlights an important issue: evidence-based practice using CPGs is poorly done even when resources for their implementation are available. A study conducted in the United States examined changes in surgical referral patterns following the publication of CPGs that recommend that people with drug-resistant "complex partial seizures" be referred for surgical evaluation.[18,19] The authors found that there was little change in

the length of time from diagnosis to referral in people who were appropriate for a surgical referral as outlined in the CPG.[18] An accompanying editorial highlights the need for appropriate implementation strategies that are not "one size fits all."[16] To avoid this limitation of CPGs, the development process should consider and define the target users of the CPG and how the CPG should be implemented in clinical practice.

The goals and mission of the International League Against Epilepsy (ILAE) include the dissemination of knowledge to improve services and care for people with epilepsy, and to promote education and training about epilepsy. The development and dissemination of CPGs can assist in accomplishing these goals. To ensure that the ILAE endorses recommendations of the highest quality, it is of great importance that systematic processes for CPG development are followed. The remainder of this document outlines the methods and processes recommended by the ILAE for CPG development that are produced by groups seeking endorsement of their epilepsy-related CPG from the ILAE.

Although this document is not an ILAE policy, it has been approved by the ILAE.

METHODS

The objective of the working group was to develop, in the absence of widely accepted standards, a framework for CPG development in epilepsy that will yield high quality guidelines. A literature search for available CPG development frameworks was conducted to guide the creation of the ILAE's recommended CPG development framework. In keeping with the ILAE's international constituency, a global perspective was taken when reviewing CPG development frameworks to account for regional differences in resources and practices.

Literature review

The literature search to identify CPG development frameworks included gray literature and hand searching of CPGs included in a previously conducted systematic review of current epilepsy CPGs published between 1985 and 2014 in any language.[20] CPGs identified were in English, French, Spanish, and Italian in the aforementioned systematic review, and all were included and reviewed for CPG development methodology. International epilepsy experts (including English, French, Spanish, Portuguese, German, and Italian speakers) and others familiar with CPG development were consulted to ensure that other relevant development frameworks were not omitted.

Inclusion criteria for CPG frameworks

Guideline development frameworks were included if the CPG development handbook was published or publicly available, the organization was relevant to epilepsy, and the organization produced good quality guidelines using the

processes outlined in their handbook. Using these eligibility criteria, the handbooks of five organizations were identified: the World Health Organization, American Academy of Neurology, National Institute of Care Excellence (United Kingdom), Scottish Intercollegiate Guideline Network, and National Health and Medical Research Council (Australia).[5,8,12,13,21] The Institute of Medicine's documents on CPGs and other pertinent publications were also used to supplement the information provided by the organizations listed.[1–4,7]

Developing a framework to create ILAE-approved epilepsy CPG

Given the complexity of developing epilepsy CPGs for the ILAE's diverse constituency, a single existing CPG development framework was not chosen. Rather, a detailed comparison of the methods used by each of the identified CPG framework for each CPG component was completed. Through consensus among the ILAE guidelines' working group members, components of the identified CPG development frameworks and pertinent literature were considered to develop the CPG development framework presented here.

RECOMMENDATIONS FOR CLINICAL PRACTICE GUIDELINE DEVELOPMENT

Based on the results of our literature review and working group consensus, recommendations on the suggested

methodology are presented below for the key components of CPG development (also summarized in Appendix S1). Each section outlines the minimum requirements (bolded) for developing CPGs according to the ILAE, and provides suggestions for improving the quality of CPGs where more resources are available. A checklist is also provided to ensure that the recommendations are followed throughout the CPG development process (Appendix S2).

The key components to develop CPGs include identifying the topic and clarifying the clinical question, establishing a working group, identifying and reviewing the evidence, formulating the recommendations, obtaining peer reviews, dissemination and implementation, and updating (Fig. 1).

Identifying the Topic and Developing the Clinical Question

Why is this guideline needed?

The development of CPGs can be complex and resource intensive. It has been suggested that the cost of developing a single CPG can range from $5,000 to $1 million dollars depending on methods used.[3] Therefore, choosing a clinical topic for the CPG requires careful consideration and prioritization. The first consideration should be the novelty of the proposed CPG: does a CPG already exist for the clinical topic of interest? If a CPG already exists but is outdated, then updating the CPG is less resource intensive and should be undertaken. If a CPG already exists for a similar
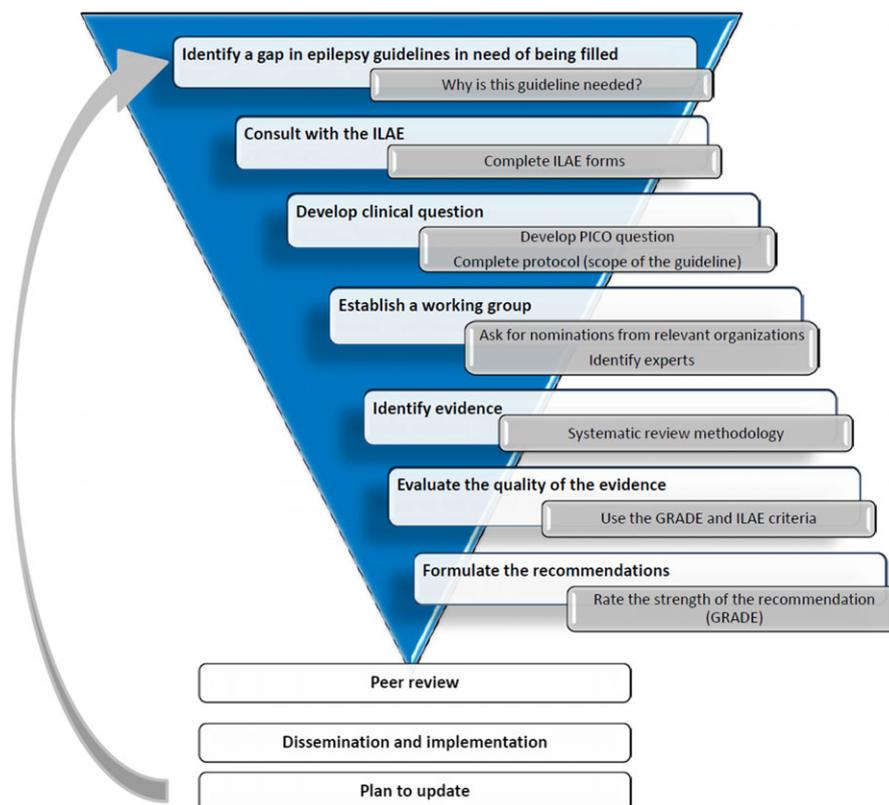
Figure 1.
Key components to the guideline development process.
Epilepsia © ILAE

population or setting, the possibility of adapting the CPG for the new population or setting of interest should be explored. Among several tools that are available to assist with the process of adapting CPGs, the ADAPTE process[22] provides a systematic and feasible approach to modifying and adapting already existing CPGs for use in different settings.[22]

Some questions that should be asked when deciding to undertake the development of a CPG include[1,23]:

1 Has a need for a CPG in this area been voiced by relevant stakeholders?
2 Will a large number of individuals benefit from the development of this CPG?
3 Is there considerable variation in clinical care that could be reduced by a CPG?
4 Will the care of this population (clinical outcomes, prevention, or process of care) be improved through the development of a CPG?
5 Will the development of this CPG improve the costs associated with the care of this population (including the costs to the patient)?

If the answer to the majority of these questions is yes then there is likely a need for a CPG for the clinical topic.

Developing an answerable clinical question (PICO approach)

Once a clear need for a CPG has been established, the first step is to develop an answerable clinical question. The PICO approach (Population, Intervention, Comparator, and Outcome) is most commonly used for this. Each of the four PICO components should be explicitly indicated and clearly defined in the clinical question(s) for the CPG (Table 1), while taking into consideration the type of PICO question being asked (therapy, diagnosis, prognosis, other).

Table 1. Key elements for designing the PICO question[5,8]	
Population	Who is the patient population of the recommendations?
	What are the relevant demographic factors (e.g., age, sex, and ethnicity)?
	What is the setting?
	Are there any excluded populations or settings?
Intervention	What is the intervention of interest?
	Is the intervention a treatment, diagnostic tool, or prognostic tool?
	Are there any variations in the intervention (e.g., dose/titration)?
Comparator	What are the alternatives to the intervention?
	Is the comparator no treatment, a placebo, or an alternative intervention?
Outcome	What are the outcomes of interest?
	Are the outcomes positive and/or negative?
	Are these outcomes of clinical relevance and importance?
	How are these outcomes measured (e.g., seizure reduction by 50% or greater vs. seizure freedom)?
	What is the duration of the outcome?

Box 1

1 **Answerable clinical questions must be clearly stated and be developed using the PICO format. The type of question (therapy, diagnosis, prognosis, etc.) should be identified at the outset.**
2 **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.**
3 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 Appendix S3.

Preparing a protocol

The protocol will help define the purpose and scope of the CPG and guide the CPG development process. The CPG scope should not be so narrow that it applies only to a small proportion of people with epilepsy, but also not so broad that the task becomes overwhelming. The scope of the guideline should be dictated by the specific health care gap and needs to be addressed, while considering available resources. The suggested number of clinical PICO questions addressed in the CPG ranges between 2 and 10 (Box 1).

Establishing the CPG Working Group

A working group must be established to develop the CPG and assist in the formulation of the clinical practice recommendations. Important aspects of the working group include the composition of the group, the method of inviting members to participate, and the identification and reporting of conflicts of interest.

Group composition

The working group will influence the clinical practice recommendations. Research examining group dynamics suggests that individuals and their biases may have an influence on the group as a whole. For instance, the opinion of a respected expert is likely to carry greater weight than that of more junior group member, potentially resulting in biased recommendations.[8,12,24,25] Therefore, the CPG working group should be composed of members representing various relevant disciplines (including the CPG end users) and demographics (i.e., gender, geography). There is evidence that multidisciplinary groups have less extreme responses, suggesting that biases are minimized compared to a group consisting of only one specialty.[25] Physicians are also more likely to implement CPGs into their clinical practice if they are included in their development, even if only to review the drafts.[26] To this end, the target audience needs to be determined prior

---

Box 2

1 **The target audience that will be implementing the CPG should be determined and explicitly stated, and should be represented in the CPG working group.**
2 **The CPG working group should include around 10 members, and at a minimum should be composed of:**
   a **A member assigned by the ILAE executive to represent the ILAE as a stakeholder**
   b **Experts in the clinical area of the guideline**
   c **A member with expertise in CPG development methodologies (if none of the other members has such experience)**
   d **A representative from the target audience (i.e., general practitioners)**
   e **Representatives of other relevant professional group(s)**
3 **Although 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.**

Box 3

1 **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.**
2 **Each member of the CPG working group must complete an ILAE declaration of interests form (Appendix S4) prior to beginning work on that guideline.**
3 **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.**
4 **All declarations of interest should be published with the guideline.**

---

to establishing a CPG working group to ensure they are represented on the CPG working group.

The size of the working group must be carefully considered. The CPG development handbooks suggest that a group ranging from 5 to 25 members is large enough to include representation, but small enough to be effective; however, studies of consensus methodology suggest that 5–10 members is generally better for reaching consensus (Box 2).[5,6,8,12,24,25,27]

How to identify and handle conflict of interest?

Financial conflicts of interest can be influential in formulating recommendations.[5] A group with real, potential, or perceived conflicts of interest can impact the CPGs and compromise its credibility. However, it is rarely feasible to have an appropriately representative working group that is void of conflicts of interest. Transparency of conflicts of interest (financial or otherwise) to mitigate potential bias can be accomplished by requiring all group members to declare their conflict(s) of interest (Box 3).

Reviewing the Evidence

By definition, CPG recommendations are evidence-based statements that require identifying, reviewing, and synthesizing of the evidence to inform the recommendations. It is widely agreed that systematic review methodology be used

to achieve this objective[3–8,12,13] to ensure a rigorous synthesis of the evidence.

The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement (www.prisma-statement.org) should be consulted when conducting a systematic review. It provides a checklist to ensure all required steps of the systematic review are followed (Appendix S5).[28] The Cochrane handbook on systematic reviews is also a useful reference for answering methodologic questions regarding systematic reviews and meta-analyses (handbook.cochrane.org) (Box 4).

Evaluating and Managing Limitations of the Evidence

Once the evidence has been identified and synthesized, the quality of the evidence must be evaluated, and CPG recommendations should be given a strength rating that is related to the strength of the evidence.[29] This helps convey to the guideline users how confident they can be that the CPG recommendations will produce the desired outcome. It is of the utmost importance to rate the strength or quality of the evidence identified in the systematic review. Depending on the research question at hand and availability of high quality evidence, low quality evidence may need to be included. Regardless of the level of evidence available, transparency of the quality of the evidence is essential.

There are several methods to evaluate the strength of the evidence and of the recommendations (i.e., GRADE, SORT, SIGN, etc.).[12,30,31] The GRADE system is a well-known, user-friendly grading system that facilitates the interpretation of the evidence and of the resulting recommendations. The GRADE has been adopted by >60 guideline developers internationally, including the WHO (www.gradeworkinggroup.org). One of the greatest merits of GRADE is that it requires explicit and transparent judgments. This in turn can impact the implementation of the CPG, as is reflected in a

---

Box 4

1 **Systematic review methodology, as per the PRISMA checklist (Appendix S5) should be used to synthesize the evidence.**

2 **The search strategy should be done, at minimum, using Medline or PubMed and EMBASE (Appendix S6).**

3 If resources permit, a librarian with expertise in health research should assist with developing the search strategy. In addition, the search strategy should be run in other relevant databases, especially Cochrane Central and Cochrane Database of Systematic Reviews, and gray literature sources.

4 **A flow diagram of study selection (PRISMA flow diagram, Appendix S7) should be generated. The criteria for inclusion and exclusion of studies should be clearly stated.**

5 **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.**

6 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.

7 **The strengths and limitations of the current evidence should be discussed.**

---

study where physicians were more likely to implement CPG recommendations in their clinical practice when the GRADE system was used, compared to other grading systems.[32]

Because the GRADE is highly regarded and relatively easy to use, the ILAE has adopted the GRADE approach to evaluate the strength of the evidence and the resulting recommendations for future ILAE-endorsed guidelines. The GRADE working group's software can assist in evaluating the evidence and formulating clinical practice recommendations, and can be downloaded for free from the GRADE working group's website (http://www.gradeworking-group.org/). Alternatively, an online platform can be accessed at: www.guidelinedevelopment.org. Additional GRADE-related resources are included in this document (see Appendices S8–S11).

Evaluating the evidence

There are four possible evidence levels using the GRADE: high, moderate, low, and very low (Table 2), each

---

Table 2. Definition of quality of evidence according to the GRADE

GRADE	Definition
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

GRADE, The Grading of Recommendations Assessment, Development and Evaluation.

---

representing varying degrees of confidence in the estimates of effect.

The quality of the evidence can be downgraded or upgraded, based on specific factors and should be done in the context of all of the elements that influence such quality (i.e., downgrading one quality criterion may or may not influence how the next quality criterion is dealt with). The initial rating is based on study design. For example, for questions related to therapy, randomized-controlled trials are given a high initial rating, and observational studies are given a low initial rating. Once the initial rating is determined, it can be downgraded or upgraded based on risk of bias, inconsistency, directness, imprecision, and publication bias (Table 3).

The factors that influence the downgrading or upgrading of the evidence are slightly different for PICO questions

---

Table 3. Factors that reduce or increase the quality of the evidence for therapeutic studies

Factor	Impact on quality of evidence
Initial rating	
Study design	RCT = high
	Observational = low
Factors that reduce the quality of the evidence	
Limitation in study design or execution (risk of bias)	↓1 or 2 levels
Inconsistency of results (heterogeneity)	↓1 or 2 levels
Indirectness of evidence (external validity)	↓1 or 2 levels
Imprecision (random error)	↓1 or 2 levels
Publication bias (systematic reviews)	↓1 or 2 levels
Factors that increase the quality of the evidence	
Large magnitude of effect	↑1 or 2 levels
All plausible confounding would reduce or increase the demonstration of effect	↑1 level
Dose–response gradient	↑1 level

RCT, randomized controlled trial.
More information on the specific criteria for decreasing and increasing the level of the evidence for each type of study design can be found in the GRADE handbook, available in the help section of GRADEpro or at: http://www.guide-linedevelopment.org/handbook/ 30 (Appendix S8).

<div style="border:1px solid #000;padding:8px;">

Box 5

1 **The GRADE system should be used to evaluate the quality of the evidence, in conjunction with the criteria outlined in Appendix S8.**
2 **The GRADE evidence profiles should be included in the CPG as an appendix.**

</div>

addressing interventions versus PICO questions addressing diagnostic tests. Although the factors outlined in Table 4 are relevant for all types of PICO questions, determining whether to downgrade or upgrade the evidence differs depending on the type of question (Appendix S8). The GRADE handbook, section 5 on quality of the evidence should be consulted for those undertaking a review of diagnostic tests.

After grading the evidence based on the factors discussed, an Evidence Profile is produced (Appendix S9), which provides detailed information about the body of evidence, the judgments about each factor underlying the quality of the evidence, and the statistical results (i.e., odds ratio, risk ratio, and so on) for each outcome. The Evidence Profile allow the CPG working group to be transparent about their judgment of the available evidence (Box 5).

Formulating the Recommendations: From Evidence to Recommendations

The strength of the evidence is one of the largest determinants of the strength of the recommendation. Once the evidence has been synthesized and its quality assessed, guideline developers can begin to formulate the clinical practice recommendations.

The working group's confidence that the recommendation will produce the desired outcomes (i.e., decrease mortality and morbidity) should be presented for each recommendation in the form of a rating. The GRADE system uses a binary rating for the strength of the recommendation: weak or strong. A strong recommendation is one in which most of the population of interest would benefit from the recommended course of action. A weak recommendation is one in which fewer members of the population of interest would benefit from the recommended course of action. In the case of a weak recommendation, the individual's circumstances, preferences, and values play a particularly important role.

Although the evidence is the most impactful factor, only in rare instances is strong evidence available to singularly drive a clinical practice recommendation. Other factors to consider when formulating recommendations include the balance between desirable and undesirable effects, the variability in values and preferences, and the use of resources (Table 4).[29] With regard to the use of resources, consideration should be given to the considerable

Table 4. Determinants of the strength of recommendations

Factor	Considerations
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Costs and resource allocation	The higher the cost and resources consumed, the lower the likelihood that a strong recommendation is warranted

Table adapted from Guyatt et al.[29]

variation of the clinical settings in different regions of the world.

After considering the above three factors, it is possible that a recommendation based on low evidence be given a strong rating. For example, the strength of a recommendation may be upgraded from low to strong if the majority of patients in the given clinical setting would choose the recommended intervention (and few would not choose the intervention), most clinicians would be likely to use the intervention in the clinical setting, the intervention is in line with patient values and preferences, and the resource use associated with this intervention is favorable. A list of questions to be considered for each of these four domains is provided in Appendix S10. In the end, the strength of the recommendation is a judgment that must be agreed upon, through consensus, by the CPG working group.

How should the recommendation be worded?

The CPG recommendations must be clear and reflect the working group's position. Specific verbs are associated with the two grades of recommendations: weak or strong recommendations. Strong recommendations should use "we recommend. . ." or "clinicians should. . ."; and weak recommendations should use "we suggest. . ." or "clinicians might. . .".[30] (Box 6)

Peer Review

Peer review can be viewed as "quality assurance" or a way of ensuring that the CPG recommendations are valid (a measure of face validity). Peer review occurs at various stages of the CPG development process, and through a variety of reviewers.

Box 6

1 **The GRADE should be used to formulate CPG recommendations. Each recommendation should contain a grading of its strength (weak or strong).**
2 **The criteria for each of the four factors that influence the strength of the recommendations should be clearly stated using Appendix S10.**
3 **The recommendations should be easy to identify (i.e., through the use of larger font, bold font, or headings).**
4 **The recommendations should be clear and unambiguous, and should be formulated using the wording recommended by GRADE.**
5 **Key recommendations should be accompanied by a discussion of other management options based on the four factors that impact the strength of the recommendations.**

Box 7

1 **The CPG protocol (Appendix 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.**
2 **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.**
3 **A final draft will be submitted to *Epilepsia* for publication where it will undergo standard editorial and peer review.**

Peer review is first done through the ILAE's organizational review of the CPG protocol (Appendix S3) for groups who are seeking future endorsement of their CPG from the ILAE. It is also common for CPGs to be disseminated to members of relevant professional organizations or groups, and for public comments before a final draft is submitted for review by a journal, in this case, *Epilepsia*.[4,5,7]

Experts and stakeholders, other than the CPG working group, should review the CPG to ensure that all relevant evidence has been identified and interpreted correctly. Review by methodological experts can increase the likelihood that the proper methodologies were used (i.e., systematic review and GRADE). A sample of target users and other key stakeholders should also review the CPG to identify any issues with clarity and applicability to the group implementing the CPG recommendations in clinical practice.

At each stage of the peer review process, the comments, suggestions, and modifications in response to these reviews (when applicable and necessary) should be documented to increase transparency of the CPG development process (Box 7).

Dissemination, Implementation, Adapting, and Auditing

Dissemination and implementation

CPGs are often disseminated through peer-reviewed journals and the websites of professional organizations. However, this method of dissemination is rarely sufficient to make a substantial change to clinical practice. A systematic review of CPG implementation found that up to 94% of physicians are unaware of CPGs and up to 89% of physicians are unfamiliar with the content of CPGs.[33] This issue can be minimized by including stakeholders in the CPG working group to assist with the creation of a dissemination plan.

The implementation of CPGs and evaluation of CPGs influence continue to be challenging in the field of epilepsy.[17,34–36] CPGs can improve the quality of care when implemented into clinical practice,[11] yet epilepsy CPGs are often poorly adopted in clinical practice.[16,17,36,37] For example, a guideline for the surgical management of temporal lobe epilepsy published in 2003 using the highest class of evidence, strongly recommended that people with "medically intractable epilepsy" be referred to an epilepsy center for consideration for temporal lobe resection.[19] Despite the publication of this guideline in several high impact journals, referral patterns have not changed.[16]

To improve the integration of CPGs into clinical practice, dissemination and implementation should be considered throughout the CPG development process through an integrated knowledge translation approach. Improvements to dissemination are recommended in Box 8 (bullets 1 and 2). The inclusion of target users in the CPG working group can also facilitate the implementation of the CPG by voicing concerns regarding its applicability in the target users' clinical practice.

There are many implementation strategies available in the field of knowledge translation, including education, persuasion, incentivization, coercion, training, enablement, modeling, environmental restructuring, and restriction.[38] To obtain the best results, the implementation strategies should be tailored to the specific behavior, setting, and target users.[39 (p.150)] A multifaceted approach, including multiple strategies, is likely to improve the implementation of the knowledge.[39]

Adapting to the local context

Because of the importance of tailoring implementation strategies to the local context and setting, local organizations or chapters are best suited to develop implementation strategies that tailor the CPG to their local context. A tool

Box 8

1 **Epilepsy-related CPGs should be freely disseminated through publication in *Epilepsia*, on the ILAE website, and communication to all chapter members electronically.**

2 **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.**

3 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.

4 **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).**

5 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.

6 Although CPGs can help inform practitioners 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.

Box 9

1 **A "review by" date should be associated with the CPG and should be based on the date that the systematic review was conducted.**

2 A systematic review of the evidence (using the same search strategy used to initially develop the CPG, unless new terminology has been developed) should be conducted every 2 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 due to the lack of new evidence.

3 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.

the quality of care over time using a before-and-after or interrupted time series design.[35,42] Because quality indicators are based on CPGs, it is not onerous to propose auditing measures or quality indicators that could be assessed based on the recommendations made in the CPG.

Updating and Retiring

Given the abundance of new knowledge generated in medicine on an ongoing basis, it is important to update CPGs as new evidence arises. As such it is important to use systematic methods, such as a systematic review to identify new research that may pertain to CPGs.

There are no hard and fast rules regarding how often a CPG should be updated. It is stated by most organizations developing CPGs that updating of CPGs should occur every 2–5 years or as new evidence emerges.[3–8,12–14] A recent study examined the length of time for recommendations made in CPGs to become out of date using a survival analysis.[43] This study found that recommendations become out-of-date after 2–3 years (Box 9).[43]

Concluding Statements

High-quality CPGs can play a crucial role in guiding appropriate care for persons with epilepsy and may improve quality of care as in other clinical settings.[9] A recent systematic review of epilepsy CPGs revealed a gap in the availability of CPGs for all populations with epilepsy, and a gap in the availability of high-quality CPGs.[20]

This document outlines suggested methodology to support the development of high-quality CPGs to bridge this gap.

This guideline development toolkit was created using the available evidence on CPG development processes and the input of international epilepsy experts with experience in CPG development. It is acknowledged that additional CPG

designed to assist in tailoring CPGs to the local context while maintaining the integrity of the CPG, the ADAPTE process,[40] should be consulted.

Auditing

Auditing refers to the evaluation of the impact of the CPG on clinical practice including, but not limited to, changes in clinical processes of care and clinical outcomes.

The effectiveness of CPGs and the associated implementation strategies are only as strong as the degree of knowledge used. Therefore, before evaluating the outcome of a CPG, the degree of knowledge as a result of implementation must first be measured.[41,42] Many of the principles used to evaluate any other intervention (i.e., temporal lobe resection in people with epilepsy) apply to evaluating the implementation of CPGs. The accepted gold standard for evaluating an intervention is a randomized control trial (RCT); however, conducting an RCT to evaluate the impact of every CPG on clinical practice is not always feasible. Therefore, quality indicators or metrics are often developed to measure

development handbooks may exist. However, CPGs identified through a previously conducted systematic review of clinical guidelines published in any language and input from the international ILAE Guidelines Task Force (n = 13 members) and Working Group members (n = 8 members), reveal that the most commonly used international CPG development handbooks were identified.

The present document highlights and presents tools to assist with the development of CPGs that meet the ILAE's high standards for quality and rigor, while taking into consideration settings where resources may be more limited.

DISCLOSURE OF CONFLICT OF INTEREST

Dr. Emilio Perucca has received support from, and/or has served as a paid consultant from Eisai, GlaxoSmithKline, GW Pharma, Supernus, UCB Pharma, Upsher-Smith, Viropharma, and Vertex. Dr. Jacqueline French is President of the Epilepsy Study Consortium. All consulting is done on behalf of the consortium, and fees are paid to the consortium. The NYU Comprehensive Epilepsy Center receives salary support from the consortium; JF has acted as a consultant for Acorda, Anavex, Biotie, Brabant Pharma, Bio-Pharm Solutions, Eisai Medical Research, Glaxo Smith-Kline, GW Pharma, Impax, Johnson and Johnson, Marathon Pharmaceuticals, Marinus, Neusentis, Novartis, Pfizer, Sage, Sunovion, SK life sciences, Supernus Pharmaceuticals, Takeda, UCB, Upsher-Smith, Ultragenyx, Vertex, Zogenix, Zynerba, Scientific Advisory Board for Anavex, UCB, grants and research from Acorda, Alexza, LCGH, Eisai Medical Research, Lundbeck, Pfizer, SK life sciences, UCB, Upsher-Smith, and Vertex, grants from National Institute of Neurological Disorders and Stroke (NINDS), Epilepsy Therapy Project, Epilepsy Research Foundation, and the Epilepsy Study Consortium. She is on the editorial board of *Lancet Neurology*, *Neurology Today*, and *Epileptic Disorders*, and is an Associate Editor of *Epilepsia*, for which she receives compensation. Dr. Jetté is an Associate Editor of *Epilepsia*, for which she receives a fee. The remaining authors have no potential conflicts of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

REFERENCES

1. Graham R, Mancher M, Wolman DM, et al. , Eds. *Clinical practice guidelines we can trust*. Washington, DC: The National Academies Press; 2011.
2. Field MJ, Lohr KN, Eds. *Clinical practice guidelines: directions for a new program*. Washington, DC: The National Academies Press; 1990.
3. Field MJ, Lohr KN, Eds. *Guidelines for clinical practice: from development to use*. Washington, DC: The National Academies Press; 1992.
4. Turner T, Misso M, Harris C, et al. Development of evidence-based clinical practice guidelines (CPGs): comparing approaches. *Implement Sci* 2008;3:45.
5. World Health Organization, Ed. *WHO handbook for guideline development*. Geneva, Switzerland: World Health Organization; 2012.
6. Davis D, Goldman J, Palda VA. *Handbook on clinical practice guidelines*. Toronto, ON: The Canadian Medical Association; 2007.
7. Shekelle PG, Woolf SH, Eccles M, et al. Developing clinical guidelines. *West J Med* 1999;170:348–351.
8. Gronseth GS, Woodroffe LM, Getchius TSD. *Clinical practice guideline process manual*. St. Paul, MN: The American Academy of Neurology; 2011.
9. Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. *Lancet* 1993;342:1317–1322.
10. Feder G, Griffiths C, Highton C, et al. Do clinical guidelines introduced with practice based education improve care of asthmatic and diabetic patients? A randomised controlled trial in general practices in east London. *BMJ* 1995;311:1473–1478.
11. Lugtenberg M, Burgers JS, Westert GP. Effects of evidence-based clinical practice guidelines on quality of care: a systematic review. *Qual Saf Health Care* 2009;18:385–392.
12. SIGN. *SIGN 50: a guideline developer's handbook*. Edinburgh, UK: SIGN; 2011.
13. NICE. *The guidelines manual*. London, UK: NICE; 2012.
14. Browman GP, Levine MN, Mohide EA, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13:502–512.
15. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010;182:E839–E842.
16. Wiebe S. Still and elusive target. Guiding practice for epilepsy surgery. *Neurology* 2010;75:678–679.
17. Davis J, Roberts R, Davidson D, et al. Implementation strategies for a Scottish natioal epilepsy guideline in primary care: results of the Tayside Implementation of Guidelines in Epilepsy Randomized (TIGER) trial. *Epilepsia* 2004;45:28–34.
18. Haneef Z, Stern J, Dewar S, et al. Referral pattern for epilepsy surgery after evidence-based recommendations: a retrospective study. *Neurology* 2010;75:699–704.
19. Engel J Jr, Wiebe S, French J, et al. Practice parameter: temporal lobe and localized neocortical resections for epilepsy. *Epilepsia* 2003;44:741–751.
20. Sauro K, Wiebe S, Perucca E, et al. (eds.) *Current state of epilepsy guidelines*. Istanbul, Turkey: International Epilespy Congress; 2015.
21. *Cochrane handbook for systematic reviews of interventions version 5.1.0*, 2011. Accessed March, 2011.
22. Fervers B, Burgers JS, Voellinger R, et al. Guideline adaptation: an approach to enhance efficiency in guideline development and improve utilisation. *BMJ Qual Saf* 2011;20:228–236.
23. Oxman AD, Schunemann HJ, Fretheim A. Improving the use of research evidence in guideline development: 2. Priority setting. *Health Res Policy Syst* 2006;4:14.
24. Jones J, Hunter D. Consensus methods for medical and health services research. *BMJ* 1995;311:376–380.
25. Hutchings A, Raine R. A systematic review of factors affecting the judgments produced by formal consensus development methods in health care. *J Health Serv Res Policy* 2006;11:172–179.
26. Browman GP, Newman TE, Mohide EA, et al. Progress of clinical oncology guidelines development using the Practice Guidelines Development Cycle: the role of practitioner feedback. *J Clin Oncol* 1998;16:1226–1231.
27. Murphy MK, Black NA, Lamping DL, et al. Consensus development methods, and their use in clinical guideline development. *Health Technol Assess* 1998;2:i–iv, 1–88.
28. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010;8:336–341.
29. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–926.
30. *Handbook for grading the quality of evidence and the strength of the recommendations using the GRADE approach*. http://www.guidelinedevelopment.org/handbook/2013. Accessed November 12, 2014.

31. Ebell MH, Siwek J, Weiss BD, et al. Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician* 2004;69:548–556.

32. Cuello Garcia CA, Pacheco Alvarado KP, Perez Gaxiola G. Grading recommendations in clinical practice guidelines: randomised experimental evaluation of four different systems. *Arch Dis Child* 2011;96:723–728.

33. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. *JAMA* 1999;282:1458–1465.

34. Ishii LE. Closing the clinical gap: translating best practice knowledge to performance with guidelines implementation. *Otolaryngol Head Neck Surg* 2013;148:898–901.

35. Grimshaw JM, Thomas RE, MacLennan G, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. *Health Technol Assess* 2004;8:iii–iv, 1–72.

36. Dunkley C, Cross JH. NICE guidelines and the epilepsies: how should practice change? *Arch Dis Child* 2006;91:525–528.

37. Fitzsimons M, Normand C, Varley J, et al. Evidence-based models of care for people with epilepsy. *Epilepsy Behav* 2012;23:1–6.

38. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. *Implement Sci* 2011;6:42.

39. Oxman AD, Thomson MA, Davis DA, et al. No magic bullets: a systematic review of 102 trials of interventions to improve professional practice. *CMAJ* 1995;153:1423–1431.

40. Harrison MB, Legare F, Graham ID, et al. Adapting clinical practice guidelines to local context and assessing barriers to their use. *CMAJ* 2010;182:E78–E84.

41. Graham ID, Logan J, Harrison MB, et al. Lost in knowledge translation: time for a map? *J Contin Educ Health Prof* 2006;26:13–24.

42. *Knowledge translation in health care: moving from evidence to practice*. 2nd Ed: Oxford, UK: Wiley; 2013.

43. Martinez Garcia L, Sanabria AJ, Garcia Alvarez E, et al. The validity of recommendations from clinical guidelines: a survival analysis. *CMAJ* 2014;186:1211–1219.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Summary of recommendations for developing Clinical Practice Guidelines.

Appendix S2. Clinical Practice Guideline development processes checklist.

Appendix S3. Clinical Practice Guideline protocol.

Appendix S4. Conflict of interest form.

Appendix S5. PRISMA 2009 checklist.

Appendix S6. An example of a search terms related to the PICO for drug-resistant epilepsy and search strategy

Appendix S7. PRISMA 2009 flow diagram.

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

Appendix S9. Example of a GRADE evidence profile generated using GRADE Pro.

Appendix S10. Example of an evidence to recommendation profile.

Appendix S11. Useful links and resources.