

## GUIDELINE FOR GUIDELINES

### Guideline Development and Approval Process:

1. **New Guideline Request:** A clinician or other group may request the development of a new Department of Veterans Affairs (VA)/Department of Defense (DoD) clinical practice guideline (CPG) utilizing the following application process:

- 1.1. Applicant completes Guideline Project Submission Form (**Appendix A**) and submits to VA/DoD Evidence Based Practice Work Group (EBPWG) through the Veterans Affairs Offices of Quality, Safety and Value (QSV) (<https://www.healthquality.va.gov>) or through the U.S Army Medical Department (AMEDD) Quality and Safety Center (<https://www.qmo.amedd.army.mil>).

At a minimum, the applicant will describe the proposed guideline, including identification of end-users, perceived gaps in care that the guideline will address, and anticipated changes in performance to be driven by the guideline, all with substantiating data as available.

- 1.2. The applicant will also submit a brief structured review of the relevant literature.

- 1.3. The VA/DoD Evidence-Based Practice Work Group may also suggest topics/areas for guideline development, particularly as they relate to the frequency of occurrence and uniqueness of our military and veteran population or as mandated by Congress or public law (e.g., Suicide, Opiate CPGs).

2. **Application review and approval:** The EBPWG will review each complete application, vote to approve or disapprove the development of a new CPG, and prioritize the timeline it for development if it is approved.

- 2.1. The respective VA or DoD Evidence Based Program office will acknowledge receipt of an application within 7 days.

- 2.2. When establishing priorities for the selection of clinical practice guidelines to be developed, the EBPWG will consider the following issues:

- High incidence or prevalence of the disease or condition to be addressed by the guideline
- Risk and cost of the disease or condition in the general veteran/military population or sub-populations targeted by Special Emphasis Programs,
- The potential for reduction of significant variations in clinical practices.
- Diagnosis, treatment, and/or clinical management of a disease or condition

- 2.3. After discussion with and decision by a quorum of EBPWG voting members, the EBPWG Co-Chairs will notify the applicant of the outcome of the review.

3. **Identification of Clinical Champions:** When a topic has been approved for guideline development, designees of the Army Medical Department (AMEDD) Quality and Safety Center and the VA Offices of Quality, Safety & Value (QSV) will identify Clinical Champions, and/or CPG Work Group Representatives. Specifically, the AMEDD and VA QSV representatives will:

- 3.1. Identify clinical leaders (without conflict of interest) who will participate in a CPG workgroup to champion the guideline development.
- 3.2. Assure there is representation from primary care and, as needed, specialty services.

- 3.3. On an ad hoc basis, consider inviting members of related VA ORD. to participate, if appropriate and available.
- 3.4. The VA and DoD program offices will convene a group of not more than 20 work group members (ideally, 10 from the VA and 10 from the DoD) to evaluate the evidence and develop the guideline. At a minimum, each CPG work group will include representatives from primary care, nursing, pharmacy, social services.
- 3.5. The VA/DoD program offices, along with a physician facilitator (contracted by the VA program office), will serve as objective evidence “chaperones” to maintain the integrity of the process. Third party subject matter experts will be utilized if needed.
- 3.6. Assign representatives from the VA & DoD Evidence Based Program offices to monitor the development process.

#### 4. Key Question Development

- 4.1. VA and DOD Champions and work group members meet in-person and/or via teleconference as needed with the contracted physician facilitator to consider the clinical practice guideline being developed and identify key questions formulated in the PICO(TS) framework:

**Population** – Characteristics of the target patient population

**Intervention** – Exposure, diagnosis, or prognosis

**Comparison** – Intervention, exposure, or control used for comparison

**Outcome** – Outcomes of interest to be answered by the evidence

**Time** (if applicable)- Describes the duration of time that is of interest

**Setting** (if applicable) – Describes the setting or context of interest

- 4.2. This is an iterative process and may require face to face and/or conference call discussions to complete the task.
- 4.3. Veteran/Patient Focus Groups. The Veteran/Patient Focus Group will be a convenience sample of not more than nine participants in accordance with General Accounting Office (GAO) guidance for interpreting Public Law 96-511 The Paperwork Reduction Act of 1980. The purpose of the focus group is to inform Key Question development.
- 4.4. Initial boundaries for admissible evidence will also be set, recognizing that no two CPGs will be the same and that additional data requirements may be discovered through the iterative process of CPG development. For example, questions of the efficacy of interventions usually means that randomized controlled trial data will be sought. In other instances, observational data, case reports or research letters may contain applicable data.

5. **Potential Conflicts of Interest:** The VA and DoD have adopted a policy of transparency with respect to disclosing potential conflicts and competing interests of all individuals who participate in the development, revision, and review of the VA/DoD clinical practice guidelines. (Details regarding conflicts of interest are available in VHA Handbook 1004.07).

- 5.1. Champion(s) and other key clinical leaders/CPG workgroup members involved with this effort will be asked to submit disclosure statements to reveal any areas of potential conflict of interest (See Appendix B) for the preceding 24 months. Conflict of Interest statements will be sent to VA Evidence Based Program office.
- 5.2. Verbal disclosures of conflict of interest: verbal attestations are conducted at each meeting, and a signed disclosure statement is required annually.
  - 5.2.1. Members may be subject to random web-based surveillance (i.e. CMMS open payments or Pro Publica) for evidence of conflict of interest.
  - 5.2.2. If there is a positive (yes) conflict of interest response (actual or potential) for any member of the EBPWG or of a CPG workgroup, then to mitigate conflict of

interest, a determination of status is made by the co-chairs of the individual CPG workgroup in conjunction with the evidence based practice program office based on level and extent of involvement in activity or relationship that represents conflict. Determination may range from restricting an individual's participation and/or voting on section(s) of a guideline related to the conflict of interest, up to removal of the individual from the work group. Recusals are determined by the individual, co-chairs and/or evidence based practice program office.

- 5.2.3 Co-chairs/champions and the evidence based practice program offices of the VA and DoD are responsible for monitoring conflict of interest compliance.

## **6. Systematic Review of the Literature Based on the Questions Identified in Step Four is Conducted & Tables of Evidence are Produced:**

- 6.1. When the initial Key Questions have been developed, the group will convene to:  
Review the Key Questions to assure that they are on track and address the Key Questions that will lead to a comprehensive, systematic review of the literature pertaining to the topic.
- 6.2. A systematic review of the literature, by a disinterested party, will be performed to minimize bias, collect all appropriate evidence available and assess its potential applicability to the clinical question under consideration.
  - 6.2.1. The first step in gathering the evidence is to determine if a suitable, recent systematic review has already been published. If a current systematic review is not available, an original systematic review will be done using an established protocol, such as those of the Cochrane Collaboration, VA Evidence Synthesis Program, or the US Preventive Services Task Force (USPSTF). At a minimum, systematic reviews will use explicit, reproducible methods to: Identify relevant, eligible studies; assess the quality of each study and the body of evidence; critically appraise key studies; synthesize results.
  - 6.2.2. To rate the quality of individual studies, the reviewers will apply the USPSTF criteria for quality (Harris, Helfand, & Woolf, 2001), adapting those to specific clinical areas. This rating is routinely completed by the group conducting the evidence review.
  - 6.2.3. The Work Group will work with staff from the VACO Office of Evidence Based Practice to ensure conformity to prevailing standards for conducting high-quality systematic literature reviews.
- 6.3. Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) will be used to assess overall strength of evidence and clinical recommendations. (Guyatt, et.al., 2008)
- 6.4. Prior to posting the reviews, the facilitator, Champion(s), (and an Evidence Chaperone as needed), will convene to ensure the adequacy of the evidence reviews.

## **7. Evidence Review Face to Face Meeting:** Convened once the evidence tables have been completed.

- 7.1. The CPG Work Group will meet face to face to review the evidence, and begin development of clinical recommendations.
- 7.2. Prior to the face to face meeting, CPG work group members will be asked to re-submit another disclosure statement regarding any potential conflicts of interest. These statements will be reviewed in advance of meeting to assure the integrity of the group that is forming.
- 7.3. Each meeting will begin with a brief session that will permit full disclosure to the group of any conflicts related to the guideline.
- 7.4. Key points of the guideline will be identified.
- 7.5. A contracted physician facilitator will ensure that the meeting stays focused and that the evidence remains the driving force behind the guidelines.
- 7.6. Each guideline will include a clinical algorithm outlining step-by-step decision points in the disease management process.
- 7.7. The quality of evidence and strength of recommendation are provided at the end of the discussion section for each Recommendation in the guideline per the USPSTF quality of

evidence rating scheme and the GRADE criteria for determining the strength or recommendations (Appendix D).

- 7.8. The review of the evidence will summarize the quality and consistency of the evidence and the magnitude of benefits and harms.
- 7.9. The VA and DoD Champions will lead discussions to develop Recommendations with the clinical experts. The discussion will include interpretation of the evidence, assessment of its ability to be applied in the clinical setting, its applicability to the population of interest, and an assessment of the overall strength of the evidence for the Recommendation.
- 7.10. Recommendations based solely on clinical judgment and experience will be thoroughly scrutinized to eliminate bias and self-interest.

#### **8. Carrying recommendations forward to the new Guideline from prior VA/DoD Guidelines**

- 8.1. The CPG Work Group will refer to the available evidence as summarized in the body of the previous guideline.
- 8.2. The group will consider the previous recommendations, the strength of evidence supporting those recommendations, and the availability of new evidence. The group will then decide which recommendations will be brought forward to the new guideline.
- 8.3. The group will consider each intervention's harms and benefits, values and preferences, and other implications where possible.

**Work group members will evaluate the quality of evidence using the rating system established by the USPSTF and grade the recommendations in the guideline using the GRADE format.**

#### **9. The USPSTF system is described in USPSTF Methods and Process, August 2012. See Appendix D**

- 9.1. When making recommendations, the CPG Work group members will consider the level of supporting evidence using the definitions shown in Appendix D, Table 1 and the Overall Quality of evidence using the definitions in appendix D, Table 2.
- 9.2. Based on the level and quality of evidence and the magnitude of net harms versus benefit, the clinical experts will assign a strength to each recommendation using the GRADE definitions in Appendix D.

#### **10. Strength and Direction of Recommendations will be assigned using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system established by the World Health Organization**

- 10.1. GRADE offers two categories of recommendations: "for" or "against". Within each of those categories the Recommendation can be graded as "strong" or "weak" based on the strength of the evidence, balance of benefits and harm, and provider/patient preference. The recommendation and narrative should reflect the quality of the supporting evidence. The contracted facilitator will ensure that the recommendation and the narrative are consistent.
- 10.2. GRADE is described in the series of tables in Appendix D and a reference in Appendix F.

#### **11. Developing the first and second drafts of the guideline**

- 11.1. Follow Up conference calls of the CPG work group will be conducted to discuss unresolved issues and compile the annotations of the guideline.
- 11.2. The first draft of the guideline will be distributed to members of the work group.
- 11.3. The Champions and the Facilitator confirm the timeline for completion of the guideline and assure that the recommendations are consistent with the evidence.
- 11.4. The second draft of the guideline will be provided to the EBPWG members via the website link and/or CPG draft copy for optional content feedback to the CPG work group.

#### **12. The Third Draft of the guideline will be posted on a development website for field review and public comment. Veteran/patient focus group participants will also be**

invited to comment.

13. **The Third Draft of the guideline is also sent to outside national experts who have agreed to perform an independent external peer review via the identified website for each guideline.**
  - 13.1. This independent review is directed towards an evaluation of the content of the guideline, as well as the format and usability of the guideline (See appendix C for format).
  - 13.2. The reviewer's comments and recommendations regarding the content of the guideline will be provided to the champions / the executive panel of the working group.
  - 13.3. All reviewers will be asked to identify any Conflicts of Interest prior to performing review.
14. DoD Evidence-based Practice Division, Patient Care Services and the VA Network Clinical Managers will solicit feedback regarding a draft guideline from a broader group of end users, to include patients.
15. VA Network designated staff and DoD end users will be asked to review the guideline and provide feedback to the guideline contractor and/or directly to the VA and DoD program offices via the wiki web page that is available for online comment. This portion of the field test is more specifically directed towards an evaluation of the content and the logic and flow of the guideline.
  - 15.1. Comments and recommendations regarding proposed changes to the content of the guideline must be supported by evidence.
  - 15.2. The VA/DoD Guideline Champions will integrate comments and suggestions into the guideline as appropriate. The guidelines contractor will provide the EBPWG a copy of the document with comments and how they were addressed.

**16. Presentation of Guideline to full VA/DoD EBPWG for Approval:**

- 16.1. An electronic copy of the guideline along with a summary of the comments from the reviewers will be provided to the entire VA/DoD EBPWG at least two weeks in advance of the meeting
- 16.2. The VA and DoD program offices review comments from independent reviewers and verifies that all appropriate suggestions have been incorporated into the final document.
- 16.3. When the EBPWG is convened, the Champion(s) and representatives of the guidelines contractor will present the guideline to the EBPWG.
- 16.4. Following the presentation, EBPWG members will have the opportunity to ask questions of the Champion(s) and provide feedback that will be entered into the meeting minutes.
- 16.5. The Guideline will then be either approved or recommendations will be made for further modifications to the guideline.
- 16.6. Once approved, the contractor/vendor will put the CPG and associated documents, [tools aren't even developed at this point, delete] into final format.

**17. The Guideline and Other Related Documents are Posted on the Office of Quality and Performance internet and intranet and the DoD internet sites**

DoD Internet: <https://www.qmo.amedd.army.mil/pguide.htm>

VA Internet: <http://www.healthquality.va.gov/>

VA Intranet: <http://vaww.oqsv.med.va.gov/functions/mindfulness/cp/clinicalPractic.aspx>

All guidelines placed on the Web will conform to the requirements described in Section 508 of the Rehabilitation Act of 1973, as amended. 29 U.S.C. §798 (see <http://www.access-board.gov/sec508/guide/act.htm>)

**18. Guideline Adaptation:** The overall objective of adaptation is to take advantage of existing guidelines to enhance the efficient production and use of high quality adapted guidelines. Cultural and organizational differences can lead to legitimate variations in recommendations, even when the evidence base is the same. However, with a systematic approach to guideline modification, adaptations can be used as an alternative to *de novo* guideline development. Deleted sentence didn't make sense.

18.1. The adaptation process is based on the following core principles:

- 1.18.1. Respect for the evidence based principles of guideline development
- 1.18.2. Reliable and consistent methods to ensure quality of the adapted guideline
- 1.18.3. Participative approach involving key stakeholders, to foster acceptance and ownership of the adapted guideline
- 1.18.4. Explicit consideration of context during adaptation to ensure organizational relevance for practice
- 1.18.5. Transparent reporting to promote confidence in the recommendations of the adapted guideline
- 1.18.6. Format consistent with VA/DoD guideline development
- 1.18.7. Accountability to the primary guideline sources

18.2. A panel of at least four members including the VA/DoD CPG Work Group Champions, will utilize the AGREE II Instrument ([www.agreetrust.org](http://www.agreetrust.org)) to assess the quality of the proposed CPG and adaptability for VA/DoD specific population use.

18.3. Following the consensus process the panel, along with a facilitator, may decide the following:

- 3.18.1. Reject the whole guideline: After reviewing all the assessments, the panel decides to reject the complete guideline. The decision will reflect how the panel weighs the assessment (e.g. poor AGREE scores, guideline is out of date, or the recommendations do not apply).
- 3.18.2. Accept a whole guideline and all its recommendations: After reviewing all the assessments, the panel accepts the guideline as is.
- 3.18.3. Accept specific recommendations: After reviewing the recommendations from the guideline the panel decides which recommendations to accept and which to reject (e.g. those recommendations needing major modification would be rejected).
- 3.18.4. Modify specific recommendations: After reviewing the recommendations from the guideline, the panel decides which are acceptable but need to be modified (e.g. new data may be added to the original recommendation or the wording might be changed to better reflect the panel's context). (ADAPTE Collaboration, 2009). Care must always be taken when modifying existing guidelines and/or recommendations not to change the recommendations to such an extent that they are no longer in keeping with the evidence upon which they will be based.

18.4. Based on the above decisions, the panel can create an adapted guideline acceptable for VA/DoD specific clinical practice guidelines. Note: All adapted guidelines shall conform to the VA/DoD CPG standard to include algorithmic format. Adapted guidelines follow the same VA/DoD CPG process as identified from step 10 forward.

### **Guideline Update and Approval Process:**

**19. Evidence Based Practice Work Group Approves Schedule for Update of Clinical Practice Guidelines:** The immediate update of guidelines will be triggered if any recommendation contained in a guideline is identified as harmful to patients (i.e., pharmaceutical or device recall, etc.) Routine guideline updates will ideally occur every three

to five years. The process that will be followed mirrors that of guideline development. It is recognized that there may be areas of significant evidence advancement in between update periods. Guideline champions may bring focused update requests forward to the EBPWG at any time for consideration.

19.1. EBPWG considers request for focused update.

19.2. If approved, then convene a small work group consisting of the champions and 1-2 subject matter experts.

19.3. Focused evidence review (typically limited to Medline, Cochrane library).

19.4. Results and recommendations from the focused review will be presented to the EBPWG for approval.

19.5. Once approved by EBPWG, results will be posted to the electronic version of the CPG as an addendum.

19.6. CPG focused update will be posted to the ECRI Guidelines Trust website.

<https://guidelines.ecri.org/>

**Appendix A**

**VA/DoD Evidence-Based Clinical Practice Guidelines  
Guideline Project Submission Form**

<b>Project Name</b>			
<b>Project Description</b>			
<b>Project Champion</b>			
<b>Last Name</b>		<b>First Name</b>	<b>Title</b>
<b>Service/Organization/Command</b>			
<b>Address</b>			
<b>City</b>		<b>State</b>	<b>Zip Code</b>
<b>Phone</b>		<b>Fax</b>	<b>E-mail</b>

**MAKING A CASE FOR CHANGE** – Provide narrative to support guideline development.

***Perceived gap in health status:***

[Is there new information from the medical literature? What about current outcomes (e.g., prevalent conditions, diagnosis)? Are there clinical areas for improvement suggested by clinicians? Are there benchmarks available that suggest a need to change practice? Are there existing evidence-based guidelines on this subject? What is the impact of this guideline on patient outcomes?]

***Perceived gap in patient satisfaction:***

[Is there survey information available addressing patient satisfaction that indicates an opportunity for improvement? Are there benchmarks available that suggest a need to change practice?]

***Perceived gap in provider satisfaction:***

[Are there surveys or suggestions addressing provider satisfaction that indicate an opportunity for improvement? Are there benchmarks available that suggest a need to change practice?]

***Perceived gap in cost/utilization:***

[Are there areas of care with high utilization? Is there significant variation or an opportunity for improvement in utilization patterns (e.g. drug utilization, lab utilization, referral rates, or local variation)? Are there benchmarks available that suggest a need to change practice? Rational and supporting evidence of relevance/importance of topic to the VA and/or DoD population?]

***Perceived organizational issues:***

[Are there political or organizational reasons why a change in practice might be warranted? Are there benchmarks available that suggest a need to change practice? Is the implementation of this project feasible? Is there evidence available to support evidence-based guideline development?]

**Appendix B**

# Disclosure Form (Guideline Co-Chair – Working Group Member- Evidence Synthesis Team- Contractor)

<b>Title of Program:</b>		<b>Program Date(s):</b>	
<b>Contact Person:</b>		<b>Evidence Based Practice Program</b>	
<b>Contact Person Email:</b>		<b>810 Vermont Ave, NW (10E2B)</b>	
<b>Phone:</b>		<b>Washington, DC 20002</b>	
<b>Fax:</b>		<b>DUE DATE:</b>	

<b>Your Name:</b>					
<b>Your Role:</b>	<i>(Check all that apply)</i>	<input type="checkbox"/> Co Chair	<input type="checkbox"/> Workgroup member	<input type="checkbox"/> Evidence Synthesis team	<input type="checkbox"/> Contractor

The VA/DoD Evidence Based Practice Working Group (EBPWG) must insure balance, independence, objectivity, and scientific rigor in all VA/DoD EBPWG sponsored development activities. VA/DoD EBPWG is concerned about maintaining transparency in their guideline development process and is concerned about situations where an individual might have incentives to use VA/DoD Clinical Practice Guidelines (CPGs) to market or promote commercial products or where they otherwise receive or stand to receive financial gain from a commercial source as a result of the content of the CPG. All persons involved in the planning, and the workgroup participating in a VA/DoD-sponsored activity, are expected to disclose to VA/DoD EBPWG any \*relevant financial and intellectual interests or other relationship with: (1) the manufacturer(s) of any commercial product(s) and/or (2) the provider(s) of commercial services discussed in this CPG activity as well as any commercial supporters of the activity. **Financial interest (Commercial or non-commercial) or other relationship may include such things as grants or research support, employee, consultant, major stock holder, member of speakers' bureau, etc. within the past 24 months, for yourself or a close family member.** The information will be reviewed by VA/DoD EBPWG. In most cases, such relationships will simply be reported to the audience. There are some relationships that might be judged a conflict. In such cases, VA/DoD EBPWG must work with you to resolve the conflict prior to your participation in the CPG development.

\*The ACCME defines "relevant financial relationships" as financial relationships in any amount that creates a conflict of interest.

<b>PLEASE COMPLETE:</b>		<i>If more space is needed to fully respond to questions, please attach a separate sheet.</i>									
<b>1a</b>	<p><u>Within the last 24 months</u> have you participated in research funded by pharmaceutical or supplement companies, medical device manufacturers, or other companies that support use of these products? If YES, please list the company(ies), product(s), devices and disease state(s) and conditions potentially impacted:</p> <p><b>Check only those which apply:</b></p> <table border="1"> <tr> <td><input type="checkbox"/> Speaker's Bureau for drug/device company</td> <td><input type="checkbox"/> Speakers Bureau for communication company</td> </tr> <tr> <td><input type="checkbox"/> Research grant paid to you direct from company</td> <td><input type="checkbox"/> Research grant paid from company to employer/institution</td> </tr> <tr> <td><input type="checkbox"/> Consultant</td> <td><input type="checkbox"/> Stockholder</td> </tr> <tr> <td><input type="checkbox"/> Patent Owner</td> <td><input type="checkbox"/> Other - Please describe:</td> </tr> </table>	<input type="checkbox"/> Speaker's Bureau for drug/device company	<input type="checkbox"/> Speakers Bureau for communication company	<input type="checkbox"/> Research grant paid to you direct from company	<input type="checkbox"/> Research grant paid from company to employer/institution	<input type="checkbox"/> Consultant	<input type="checkbox"/> Stockholder	<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Other - Please describe:		
<input type="checkbox"/> Speaker's Bureau for drug/device company	<input type="checkbox"/> Speakers Bureau for communication company										
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<input type="checkbox"/> Consultant	<input type="checkbox"/> Stockholder										
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Other - Please describe:										
<b>1b</b>	If you checked any in 1a above, please list the manufacturer(s) or product(s), device(s), or disease state(s) and condition(s) potentially impacted.										
<b>2a</b>	Have you received (from any source) training, scripts, slides, or other resources that will be used in this activity?	<b>YES</b>	<b>NO</b>								
<b>2b</b>	If YES to 2a, please describe:										
<b>3a</b>	<u>Within the last 24 months</u> have you had relationship(s) with the commercial supporter(s) of this activity? (If applicable)	<b>YES</b>	<b>NO</b>								
<b>3b</b>	If YES to 3a, please list the commercial supporter(s) and describe the nature of the relationship(s).										
<b>4</b>	Do you receive remuneration for activities (such as board member or member of an advisory council) for any organization or company that has, or may have in the foreseeable future, a financial stake in a device, assessment, product or intervention that is coming to market? If YES, please list the organization(s), company(ies), product(s), device(s), intervention(s), and the disease state(s)/conditions potentially impacted.	<b>YES</b>	<b>NO</b>								
<b>5</b>	Do you have any financial holdings (to include, but not limited to, company stock, bonds, or other shares, etc.) of said organizations, companies and or products?	<b>YES</b>	<b>NO</b>								
<b>6</b>	Are there other relationships or activities that could be perceived to have influenced, or that give the appearance of potentially influencing, what you wrote in your contributions to the guideline?	<b>YES</b>	<b>NO</b>								

**Workgroup Member:**

Signature: \_\_\_\_\_ *I will update this form if my disclosure status changes.* Date: \_\_\_\_\_

*Appendix C-External Reviewer Form*

**VA/DoD CLINICAL PRACTICE GUIDELINES**

**(Guideline Rating Tool 4-1-2010)**

\*\*\*\*\*

Reviewer \_\_\_\_\_ Date \_\_\_\_\_

Title of the  
Guideline \_\_\_\_\_

Do you have any conflict of interest or potential conflict of interest in reviewing this guideline?

No  Yes  (Specify if yes.)

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

<b>SCOPE AND PURPOSE</b>	Strongly Agree	Agree	Disagree	Strongly Disagree
1. Targeted patient population is specified.				
2. Intended users of guideline are specified.				
3. Guideline addresses a documented gap in performance, safety, or quality.				
<b>B. COMMENTS</b>				
<b>PRESENTATION</b>	Strongly Agree	Agree	Disagree	Strongly Disagree
4. The guideline is clearly written.				
5. Guideline defines unfamiliar terms and those that are critical to applying the recommendations.				
6. The recommendations are specific and unambiguous.				

<b>PRESENTATION</b>	Strongly Agree	Agree	Disagree	Strongly Disagree
7. The algorithm is logically complete and internally consistent.				
<b>C. COMMENTS</b>				

<b>SYSTEMATIC REVIEW METHODS</b>	Strongly Agree	Agree	Disagree	Strongly Disagree
8. Systematic methods were used to search for evidence.				
<i>The criteria for selecting the evidence are clearly described.</i>				
10. <i>The quality of the studies was explicitly assessed.</i>				
<b>SYSTEMATIC REVIEW METHODS</b>	YES	NO	NOT SURE	
11. Eligible studies were summarized in evidence tables.				
<b>COMMENTS</b>				
<b>INTERGRATING EVIDENCE INTO RECOMMENDATIONS</b>	Strongly Agree	Agree	Disagree	Strongly Disagree
12. The methods used to formulate the recommendations are clearly described?				
13. There is an explicit link between the recommendations and the supporting evidence.				
14. Was sufficient information provided to understand the rationale behind key or controversial recommendations?				
<b>COMMENTS (on D. Integrating the Evidence)</b>				
<b>BENEFITS, HARMS AND OUTCOMES</b>	Strongly Agree	Agree	Disagree	Strongly Disagree
15. All important benefits and harms of recommended treatments or procedures are specified.				
16. Benefits and harms of recommended treatments and procedures are quantified.				

17. The effect of the recommended interventions on health care costs is quantified.				
<b>COMMENTS</b>				

<b>AUTHORSHIP</b>	Strongly Agree	Agree	Disagree	Strongly Disagree
18. The guideline clearly notes author(s).				
19. The guideline clearly notes the authors' conflicts of interest.				
20. All relevant disciplines are represented including primary care?				

<b>COMMENTS</b>				

<b>G. TESTING AND REVIEW</b>	Strongly Agree	Agree	Disagree	Strongly Disagree
21. The guideline has been evaluated by field testing.				
22. An expiration date or procedure for updating the guideline is specified.				

<b>COMMENTS</b>				

<b>FLEXIBILITY</b>	Strongly Agree	Agree	Disagree	Strongly Disagree
23. The guideline clearly indicates the intended flexibility of the recommendation(s).				
24. The role of patient preferences is discussed.				
25. The guideline addresses special patient populations when appropriate.				

<b>COMMENTS</b>				


FEASIBILITY OF IMPLEMENTING THE GUIDELINE	Strongly Agree	Agree	Disagree	Strongly Disagree
26. The guideline recommendations are feasible to implement in all intended care settings (consider organizational characteristics, implementation costs, opportunity costs.)				
<b>COMMENTS</b>				

**OVERALL ASSESSMENT**

**27. Describe the predominant method(s) used to develop this guideline:**

- Evidence-based (key recommendations are supported by fair or good evidence with explicit estimation of benefits and harms)
  - Evidence-based (all recommendations are supported by fair or good evidence)
  - Structured consensus with systematic literature reviews
  - Global subjective judgment or consensus panel
  - Other (describe)
- 

**28. Would you recommend these guidelines for use in practice?**

- STRONGLY RECOMMEND**
- RECOMMEND**
- WOULD NOT RECOMMEND**
- UNSURE**

**COMMENT: (What is this guideline’s specific strengths? What is this guideline’s specific weaknesses? Use additional space as necessary.)**

**Additional Review Comments: How can/might this guideline be improved?**

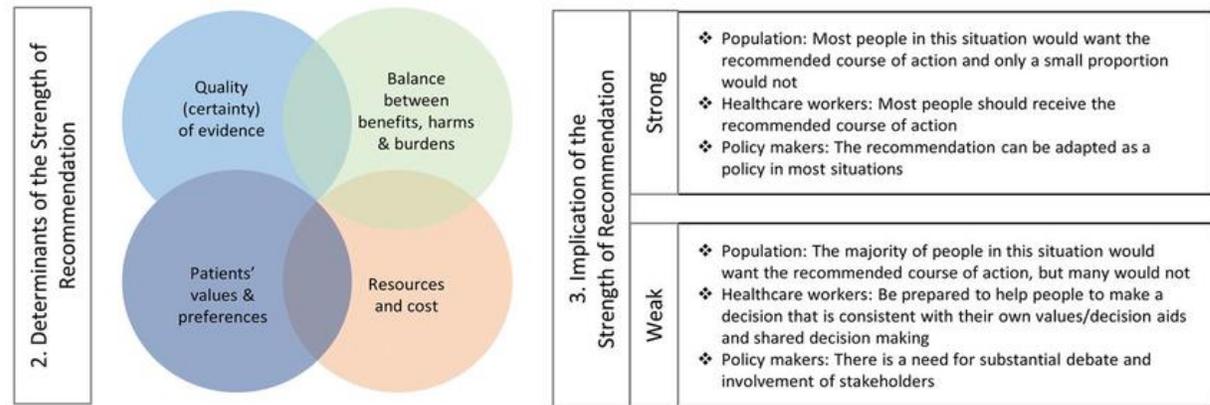
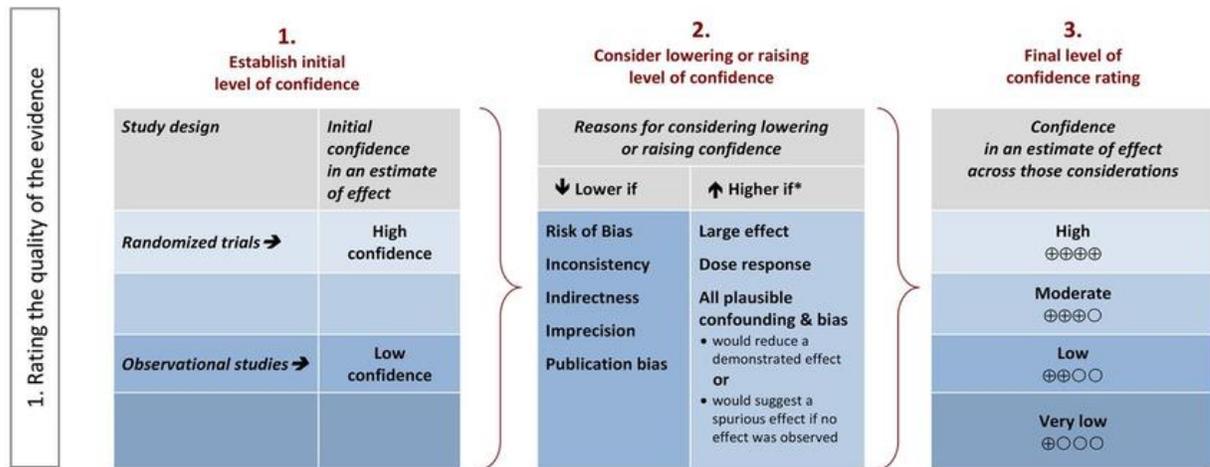

**Name of Reviewer** \_\_\_\_\_

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**E-Mail** \_\_\_\_\_

**Appendix D: Quality of the Evidence (USPSTF) and Developing Recommendations (GRADE)**



Approach and implications to rating the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (unrestricted use of the figure granted by the US GRADE Network).

### Quality of evidence and definitions

<b>High quality</b> — Further research is very unlikely to change our confidence in the estimate of effect
<b>Moderate quality</b> — Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
<b>Low quality</b> — 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
<b>Very low quality</b> — Any estimate of effect is very uncertain”

From: Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., Schünemann, H. J. & the GRADE Working Group. (2008). GRADE; An emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*, 336, 924-926.

## Appendix E: Evidence Evaluations

<b>Table 1: Level of Evidence (LE)</b>	
<b>I</b>	At least one properly done RCT
<b>II-1</b>	Well-designed controlled trial without randomization
<b>II-2</b>	Well-designed cohort or case-control analytic study, preferably from more than one source
<b>II-3</b>	Multiple time series evidence with/without intervention, dramatic results of uncontrolled experiment
<b>III</b>	Opinion of respected authorities, descriptive studies, case reports, and expert committees

<b>Table 2: Overall Quality [QE]</b>	
<b>Good</b>	High grade evidence (I or II-1) directly linked to health outcome
<b>Fair</b>	High grade evidence (I or II-1) linked to intermediate outcome; <i>or</i> Moderate grade evidence (II-2 or II-3) directly linked to health outcome
<b>Poor</b>	Level III evidence or no linkage of evidence to health outcome

USPSTF Methods and Process.  
<http://www.uspreventiveservicestaskforce.org/methods.htm>, August 2012.



## GRADE guidelines: 15. Going from evidence to recommendation – determinants of a recommendation's direction and strength

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### Abstract

In the GRADE approach, the strength of a recommendation reflects the extent to which we can be confident that the composite desirable effects of a management strategy outweigh the composite undesirable effects.

This article addresses GRADE's approach to determining the direction and strength of a recommendation. The GRADE describes the balance of desirable and undesirable outcomes of interest among alternative management strategies depending on four domains, namely estimates of effect for desirable and undesirable outcomes of interest, confidence in the estimates of effect, estimates of values and preferences, and resource use. Ultimately, guideline panels must use judgment in integrating these factors to make a strong or weak recommendation for or against an intervention. © 2013 Elsevier Inc. All rights reserved.

**Keywords:** GRADE; Quality of evidence; Strength of evidence; Guideline development; Recommendation; Evidence

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### 1. Introduction

In prior articles in this series devoted to the GRADE approach to systematic reviews and practice guidelines, we have dealt with the process before developing recommendations, namely framing the question and choosing critical and important outcomes [1], rating the

confidence in effect estimates for each outcome [2e8],  
dealing with resource

use [9], rating the confidence in effect estimates across outcomes [10], and creating an evidence profile and a Summary of Findings table [11-13]. The immediately previous article described GRADE's approach to classifying the strength and direction of recommendations and discussed the implications of strong and weak recommendations, and the options for presentation and wording [14]. The present article presents GRADE's approach to moving from evidence to recommendations. As we did in the previous article, we will refer to guideline developers as 'the panel.'

### 1.1. Globalizing evidence and localizing decisions

The pithy summary by Eisenberg [15] on the relationship between evidence and recommendations, 'globalize the evidence, localize the decisions,' provides fundamental guidance for those working to produce evidence-based recommendations [15]. Summaries of evidence regarding alternative management strategies from the medical literature should ideally be very similar, no matter the site of the application of the recommendation.

Rating of confidence in estimates of effect (quality of evidence) may, however, differ for a variety of reasons. First, desirable and undesirable outcomes may be valued differently, leading to different thresholds of acceptability. This could lead to different judgments regarding imprecision, as we have highlighted in the article in this series dealing with imprecision [5].

Second, differences in values and preferences could lead to differences in the overall balance of desirable and undesirable outcomes and the rating of confidence in estimates: an outcome judged as critical by one panel (and thus included in the rating of overall confidence in estimates) may be judged important but not critical by another (and thus not included in the overall rating).

Finally, ratings of confidence may also differ as a result of uncertainties in the risk profile of untreated populations (baseline risk). We may be very confident of baseline risk in one setting but not at all confident in another. This could lead to rating down confidence in estimates for indirectness. Continued rapid uptake of GRADE by organizations that produce systematic summaries of evidence will greatly facilitate the production of transparent evidence summaries. If organizations work together to produce summaries, there will be an enormous gain in efficiency [16]-even if, in the end, judgments about confidence in estimates will differ across settings, for reasons described in the preceding paragraphs. We now turn to a systematic presentation of the determinants of direction and strength of recommendations.

## 2. Determinants of direction and strength of recommendations

GRADE has identified six determinants of the direction and strength of recommendations, namely the magnitude of

estimates of effect of the interventions on important outcomes, confidence in those estimates, estimates of typical values and preferences, confidence in those estimates, variability of values and preferences, and resource use. In the presentation here, we will present these six determinants in four domains. We package magnitude of effect and typical values and preferences together with the label balance of desirable and undesirable consequences or 'trade-offs.' We also include uncertainty regarding typical values, and variability in values, in a single domain (Table 1).

Alternative groupings may work better, depending on the circumstances. We believe that the approach we present here is best for presenting the rationale for the recommendations to the guideline consumer audience. In developing recommendations, panels may want to keep all six determinants separate or group the three values and preferences determinants together.

Ultimately, guideline panels must integrate these six determinants to make a strong or weak recommendation for or against an intervention. Table 2 illustrates how the elements of the GRADE framework for moving from evidence to recommendations can be applied in making strong and weak recommendations, and Table 3 provides an example of the application in the management of chronic obstructive pulmonary disease.

### 2.1. Trade-offs between desirable and undesirable consequences of alternative management strategies

When we consider the balance between desirable and undesirable outcomes ('trade-offs'), we are considering two domains. The first is our best estimates of the magnitude of desirable effects and the undesirable effects. If a guideline panel has adhered to the GRADE process, they will find the best estimates of effect in the evidence profiles that they have prepared or accessed.

The second element that determines the balance among desirable and undesirable outcomes is the typical values that patients - or a population - apply to those outcomes. This can be otherwise conceptualized as the relative preferences for those outcomes-and thus the term we generally use, values and preferences (Box 1).

Ideally, to inform estimates of typical patient values and preferences, guideline panels will conduct or identify systematic reviews of relevant studies of patient values and preferences [18]. Given the paucity of empirical examinations of patients' values and preferences, however, well-resourced guideline panels will usually complement such studies with consultation with individual patients and patients' groups. The panel should discuss whose values these people represent, namely representative patients, a defined subset of patients, or representatives of the general population.

For example, the Canadian Collaboration for Immigrant and Refugees Health (CCIRH) guidelines sought to advance understanding of immigrant patient perspectives in

**Table 1.** Domains that contribute to the strength of a recommendation

Domains that contribute to the strength of a recommendation	Comment
Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical) (trade-offs)	The larger the differences between the desirable and undesirable consequences, the more likely a strong recommendation is warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely a weak recommendation is warranted
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes)	The higher the quality of evidence, the more likely a strong recommendation is warranted
Confidence in values and preferences and variability values and preferences, the more likely a weak recommendation is warranted	The greater the variability in values and preferences, or uncertainty in
Resource use less likely a strong recommendation is warranted	The higher the costs of an intervention (the more resources consumed), the

two ways, namely they searched and synthesized evidence for immigrant perspectives in relation to each health condition, and worked closely with a community-based organization representing 18 ethnic groups to inform perceptions of immigrant patient perspectives [19]. Less well-resourced panels, without systematic reviews of values and preferences or consultation with patients and patient groups, must rely on unsystematic reviews of the available literature and their clinical experience of interactions with patients. How well such estimates correspond to true typical values and preferences is likely, in any particular situation, to be uncertain.

Whatever the source of estimates of typical values and preferences, explicit, transparent statements of the panel's choices are imperative. For example, in their recommendation regarding unmet contraceptive needs, the CCIRH attributed more value to supporting informed choice (empowerment) and less value to concern about causing couple

and family discord [19]. Clinicians recognizing a family in which avoiding discord is paramount will therefore be aware that the recommendation is in that instance not appropriate.

Maximal explicitness requires quantification. For example, in the ninth iteration of the American College of Chest Physicians Antithrombotic Guidelines, the panel specified that they considered typical patients would value preventing one stroke equivalent to avoiding three serious gastrointestinal bleeds [18,20].

Having established their best estimates of typical values and preferences, a panel is in a position to assess the trade-off between the desirable and undesirable outcomes of an intervention vs. a comparator. The larger the gradient between the desirable and undesirable effects, the higher the likelihood that a panel will provide a strong recommendation. For example, the very large gradient between the benefits of low dose aspirin on reductions in death and

**Table 2.** Examples of strong and weak recommendation determinants

Factor	Example of strong recommendation	Example of weak recommendation
Balance between desirable and undesirable consequences of alternative management strategies. <b>The closer the balance, the less likely a strong recommendation</b>	Aspirin following myocardial infarction reduces mortality with minimal toxicity, inconvenience, and cost	Anticoagulation vs. aspirin in patients with atrial fibrillation with a CHADS <sub>2</sub> score of 1 (moderate risk of stroke); benefit in stroke reduction closely balanced with increased bleeding risk Only case series have examined the utility of pleurodesis in pneumothorax
Confidence in estimates of effect (quality of evidence). <b>The lower the confidence, the less likely a strong recommendation</b> Uncertainty or variability in values and preferences. The less the confidence in estimates of typical values and preferences, and the greater the variability, the less likely a strong recommendation	Many high quality randomized trials have shown the benefit of inhaled steroids in asthma Relative confidence: evidence from empirical studies shows that patients place a substantially higher value on avoiding a debilitating stroke than on avoiding a serious gastrointestinal bleed Little variability: young patients with lymphoma will invariably place a higher value on the life-prolonging effects of chemotherapy than on avoiding treatment toxicity The low cost of aspirin vs. no antithrombotic prophylaxis against stroke in patients with transient ischemic attacks	Uncertainty: there is no empirical evidence regarding the relative value patients place on avoiding a postoperative bleed that requires reoperation vs. a postoperative serious but nonfatal pulmonary embolus Greater variability: some older patients with lymphoma will place a higher value on the life-prolonging effects of chemotherapy than on avoiding treatment toxicity but others will not The high cost of clopidogrel and of combination dipyridamole and aspirin vs. aspirin as prophylaxis against stroke in patients with transient ischemic attacks
Resource use. The higher the resource use, the less likely a strong recommendation		

**Table 3.** Evidence to recommendation framework: enhancing transparency when moving from evidence to recommendations

Question/recommendation: Should pulmonary rehabilitation vs. usual community care be used for COPD with recent exacerbation? Population: Patients with COPD and recent exacerbation of their disease				
Intervention: Pulmonary rehabilitation vs. no rehabilitation				
Setting (if relevant): Outpatient				
Decision domain	Judgment		Reason for judgment	Subdomains influencing judgment
Balance of desirable and undesirable outcomes Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	The desirable consequences are substantial (including substantial reduction in hospitalization, small but important reduction in mortality, and improvement in quality of life that exceeds the minimal important difference) and valued highly. The undesirable consequences, inconvenience, and burden are relatively minor and associated with minimal disutility.	Baseline risk for desirable and undesirable outcomes: <ul style="list-style-type: none"> <li>• Is the baseline risk similar across subgroups?</li> <li>• Should there be separate recommendations for subgroups?</li> </ul> Relative risk for benefits and harms: <ul style="list-style-type: none"> <li>• Are the relative benefits large?</li> <li>• Are the relative harms large?</li> </ul> Requirement for modeling: <ul style="list-style-type: none"> <li>• Is there a lot of extrapolation and modeling required for these outcomes?</li> </ul> Typical values: <ul style="list-style-type: none"> <li>• What are the typical values?</li> <li>• Are there differences in the relative value of the critical outcomes?</li> </ul> Confidence in estimates of benefits and downsides, confidence in estimates of resource use. Consider all critical outcomes, including the possibility that some may not be measured. Key reasons for rating evidence down or rating up
Confidence in estimates of effect (quality of evidence) Is there high or moderate quality evidence?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	⊕⊕⊕○	There is moderate-(mortality, function, and quality-of- life outcomes)-to-high (hospitalizations) quality evidence for the desirable consequences, and quality evidence for the undesirable (burden)
Values and preferences Are you confident about the typical values and preferences and are they similar across the target population?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	We can be confident that patients place a high value on avoiding hospitalizations and mortality as well as improving quality of life and a low value on avoiding the inconvenience associated with rehabilitation. We can be confident that these values vary little among patients with chronic respiratory disease.	Source of typical values (panel or study of general population or patients) Source of estimates of variability and extent of variability Method for determining values satisfactory for this recommendation
Resource implications Are the resources worth the expected net benefit from following the recommendation?	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>	There are resources required to provide pulmonary rehabilitation but these are balanced by decreased resource needs as a result of decreased hospitalizations and net cost is well worth it given the desirable outcomes.	What are the costs per resource unit? Feasibility: <ul style="list-style-type: none"> <li>• Is this intervention generally available?</li> </ul> Opportunity cost: <ul style="list-style-type: none"> <li>• Is this intervention and its effects worth withdrawing or not allocating resources from other interventions?</li> </ul> Differences across settings: <ul style="list-style-type: none"> <li>• Is there lots of variability in resource requirements across settings?</li> </ul>
Overall strength of recommendation rehabilitation (Note: this is a hypothetical recommendation developed for this article and not intended for clinical decision making).	Strong		The guideline panel recommends that patients with recent exacerbations of their COPD undergo pulmonary rehabilitation	

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Evidence to recommendation synthesis                      The moderate-to-high confidence in the moderate-to-large magnitude of effects on highly valued outcomes, and the moderate-to-high confidence that undesirable outcomes are modest and their avoidance not highly valued suggest a strong recommendation.

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*Abbreviation:* COPD, chronic obstructive pulmonary disease.

### Box 1 Terminology for “values and preferences”

Values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life [17]. More precisely, they refer to the processes that individuals use in considering the potential benefits, harms, costs, limitations, and inconvenience of the management options in relation to one another. For some, the term "values" has the closest connotation to these processes. For others, the connotation of "preferences" best captures the notion of choice. Thus, we use both words together to convey the concept.

recurrent myocardial infarction (MI) after an MI [21] and the undesirable consequences of minimal side effects and costs make a strong recommendation very likely (Table 2).

In contrast, the narrower the magnitude of the gradient between desirable and undesirable consequences, the higher the likelihood that a guideline panel will make a weak recommendation. For instance, consider the choice of immunomodulating agents, namely cyclosporine and tacrolimus in kidney transplant recipients [22]. Tacrolimus results in better graft survival (a highly valued outcome), but at the important cost of a higher incidence of diabetes (the long-term complications of which can be devastating). Table 2 presents a second example of a close trade-off in which patients with atrial fibrillation typically are more stroke averse than bleeding averse. If, however, the risk of stroke is sufficiently low, the trade-off between stroke reduction and increase in bleeding risk with anticoagulants is closely balanced.

Without considering the associated values and preferences, assessing large vs. small magnitude of effects may be misleading. For instance, in patients with cancer, chemotherapeutic agents may have large (albeit temporary) adverse effects such as nausea, fatigue, hair loss, and paresthesias. The chemotherapy may have only a small effect on reducing mortality. Despite the discrepancy in magnitude of effect, most patients may choose chemotherapy because of the very high value they place on a small mortality reduction.

#### 2.2. Uncertainty and variability in values and preferences

We have noted that systematic study of patients' values and preferences are very limited. As a result, panels will often be uncertain about typical values and preferences. The greater is that uncertainty, the more likely they will make a weak recommendation.

Given the sparse systematic study of patients' values and preferences, one could argue that large uncertainty always

exists about the patients' perspective. On the other hand, some systematic study of values and preferences and decision making has been completed, and clinicians' experience with patients may provide considerable additional insight.

Indeed, on occasion, panels will, on the basis of clinical experience, be confident regarding typical patients' values and preferences. Pregnant women's strong aversion to even a small risk of important fetal abnormalities may be one such situation [20].

A second concern that may make a weak recommendation more likely is large variability in values and preferences. To the extent large variability exists, it is less likely that a single recommendation would apply uniformly across all patients, and the right course of action is likely to differ between patients.

Empirical evidence may inform estimates of variability in recommendations. For instance, Devereaux et al. [23] asked patients at risk of atrial fibrillation how many serious gastrointestinal bleeds they would tolerate and still be willing to use an anticoagulant to prevent a stroke. Although most patients placed a high value on avoiding a stroke and were ready to accept a bleeding risk of 22% to reduce their chances of having a stroke by 8%, diversity in values and preferences was also apparent. A few patients were ready to accept only a small risk of bleeding to reduce their stroke risk by 8%. These data, consistent with other studies of values and preferences regarding anticoagulation in atrial fibrillation [18], suggest that only in patients at appreciable risk of stroke would a strong recommendation for warfarin be warranted.

Although systematic study will lead to the highest confidence, panelists may express confidence in their estimates of variability in values and preference on the basis of clinical experience. In the example cited earlier, clinicians may be confident not only that the typical expectant mother will have a strong aversion to even a small risk of important fetal abnormalities but also that these values and preferences are virtually uniform across the population.

On the other hand, clinical experience may leave a panel confident that values and preferences differ widely among patients. For example, clinical experience makes it clear that an expectant couple's desire to undergo a genetic test that increases the risk of spontaneous miscarriage will differ greatly depending on their willingness to act on knowledge about a fetal anomaly and their attitude toward the loss of a normal pregnancy. Situations such as these when recommendations are particularly dependent on differing values and preferences may dictate, in addition to making a weak recommendation, including descriptions of how varying values and preferences will determine the optimal decision [14].

A hopeful patient may place more emphasis on a small chance of benefit, whereas a pessimistic, risk-averse patient may place more emphasis on avoiding the risks associated with a potentially beneficial therapy. Some patients may

have a belief that even if the risk of an adverse event is low, they will be the person who will suffer such an adverse effect.

For example, in patients with idiopathic pulmonary fibrosis, evidence for the benefit of steroids warrants only low confidence, whereas we can be very confident of a wide range of adverse effects associated with steroids. The hopeful patient with pulmonary fibrosis may be enthusiastic about use of steroids, whereas the risk-averse patient is likely to decline.

### 2.3. Confidence in estimates of effect (quality of evidence)

Another determinant of the direction and strength of recommendations is our confidence in the estimates of effect.

Typically, a strong recommendation is associated with high, or at least moderate, confidence in the effect estimates for critical outcomes. If one has high confidence for some critical outcomes (typically, benefits of an intervention), but low confidence for other outcomes considered critical (often long-term harms), then a weak recommendation is likely warranted. The more closely balanced the trade-offs between desirable and undesirable outcomes, the more likely that low confidence for any critical outcome will result in a weak recommendation.

Even when an apparently large gradient exists in the balance of desirable vs. undesirable outcomes, panels will be appropriately reluctant to offer a strong recommendation if their confidence in effect estimates is low. This is in part because when confidence in the estimate of effect is lower, choice is more preference dependent.

For instance, the GRADE approach provides insight into how guideline panels should have handled the decision regarding hormone replacement therapy (HRT) in postmenopausal women in the 1990s when observational studies suggested a substantial reduction in cardiovascular risk

[24] (which randomized trials subsequently proved false [25], at least in women appreciably past the menopause), and equally low quality evidence suggested an increase in the risk of breast cancer (which proved true [26]).

Guideline panels during the 1990s made recommendations that were presented, or at least interpreted, as strong recommendations. Many primary care physicians, responding to these recommendations, enthusiastically encouraged their postmenopausal patients to use HRT. Appropriately considering the lack of confidence in estimates, women with a low level of risk aversion might indeed have been inclined to use HRT. Those with a high level of risk aversion would, however, have declined HRT. Clearly, a weak recommendation for (or perhaps even against) HRT would have been warranted.

For some questions, investigators may not have directly measured critical outcomes (in particular quality of life). In such instances, even if surrogates are available, confidence in estimates is very likely to be low.

#### 2.3.1. Low confidence in effect estimates may, rarely, be tied to strong recommendations

In general, we discourage guideline panels from making strong recommendations when their confidence in estimates of effect for critical outcomes is low or very low. We have identified five paradigmatic situations, however, in which strong recommendations may be warranted despite low or very low quality of evidence (Table 4). These situations can be conceptualized as ones in which a panel would have a low level of regret if subsequent evidence showed that their recommendation was misguided.

One paradigmatic situation occurs when panels have low confidence regarding the benefit of an intervention in a life or death situation. Consider patients suffering from life-threatening disseminated blastomycosis [27]. High quality evidence suggests that amphotericin is more toxic than itraconazole, and low quality evidence that it reduces mortality in this context. When considering the subpopulation of patients with life-threatening blastomycosis, panels may reason that all or virtually all patients would choose the more toxic therapy given the very high risk of death and the possibility that amphotericin may decrease that risk. If they did so, they would make a strong recommendation for amphotericin.

In a second paradigmatic situation, panels may make a strong recommendation against an intervention when there is uncertainty of benefits, but they are confident about adverse effects and resource use. For example, it remains very uncertain whether whole-body computed tomography scan or magnetic resonance imaging screening confers benefits in terms of reduction of cancer risk, but there is no doubt that such tests generate false positives that result in anxiety and possibly invasive tests with their own discomfort and complications [28]. Such tests also consume scarce resources. Despite the low confidence with regard to benefits, guideline panels might legitimately make strong recommendations against screening imaging.

A third situation occurs when we have low quality evidence regarding relative benefit, but high quality evidence of lower harm for one of the competing alternatives. For instance, in patients who have early-stage, low-grade, *Helicobacter pylori*-positive gastric mucosa-associated lymphoid tissue lymphoma, low quality evidence suggests that initial

*H. pylori* eradication therapy results in similar rates of complete response (50-80%) in comparison with the alternatives of radiation therapy or gastrectomy [29]. The evidence warrants high confidence in the increased morbidity associated with either radiation or gastrectomy vs. pharmacologic therapy. Furthermore, in patients without complete response, there is the option of later use of the higher risk alternatives. Thus, despite low confidence in estimates of effects, a strong recommendation for *H. pylori* eradication therapy appears appropriate.

In a fourth situation, panels may make strong recommendations for one of the two competing alternatives if they are confident of similarity of benefits, but have only

Table 4. Paradigmatic situations in which a strong recommendation may be warranted despite low or very low confidence in effect estimates

Situation	Condition	Example
1	When low quality evidence suggests benefit in a life-threatening situation (evidence regarding harms can be low or high)	Fresh frozen plasma or vitamin K in a patient receiving warfarin with elevated INR and an intracranial bleed. Only low quality evidence supports the benefits of limiting the extent of the bleeding
2	When low quality evidence suggests benefit and high quality evidence suggests harm or a very high cost	Head-to-toe CT/MRI screening for cancer. Low quality evidence of benefit of early detection but high quality evidence of possible harm and/or high cost (strong recommendation against this strategy)
3	When low quality evidence suggests equivalence of two alternatives, but high quality evidence of less harm for one of the competing alternatives	<i>Helicobacter pylori</i> eradication in patients with early stage gastric MALT lymphoma with <i>H. pylori</i> positive. Low quality evidence suggests that initial <i>H. pylori</i> eradication results in similar rates of complete response in comparison with the alternatives of radiation therapy or gastrectomy; high quality evidence suggests less harm/morbidity
4	When high quality evidence suggests equivalence of two alternatives and low quality evidence suggests harm in one alternative	Hypertension in women planning conception and in pregnancy. Strong recommendations for labetalol and nifedipine and strong recommendations against angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARB) all agents have high quality evidence of equivalent beneficial outcomes, with low quality evidence for greater adverse effects with ACE inhibitors and ARBs
5	When high quality evidence suggests modest benefits and low/ very low quality evidence suggests possibility of catastrophic harm	Testosterone in males with or at risk of prostate cancer. High quality evidence for moderate benefits of testosterone treatment in men with symptomatic androgen deficiency to improve bone mineral density and muscle strength. Low quality evidence for harm in patients with or at risk of prostate cancer

Abbreviations: INR, international normalized ratio; CT, computed tomography; MRI, magnetic resonance imaging; MALT, mucosa-associated lymphoid tissue.

low or very low confidence regarding increased harm for one alternative. Reasoning that there is nothing to lose, and possibly a lot to gain in terms of a lower incidence of adverse effects, guideline panels may reasonably make a strong recommendation for the agent apparently free from serious toxicity. For instance, consider the management of hypertension in women who are planning conception and who are pregnant. There is high quality evidence of equivalent effectiveness for labetalol, nifedipine, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs). There is low quality evidence of harms for ACE inhibitors and ARBs. Panels have appropriately made strong recommendations for labetalol and nifedipine and strong recommendations against ACE inhibitors and ARBs [30].

A fifth paradigmatic situation occurs when we have moderate-to-high confidence about an intervention's modest benefits, but remain uncertain about its likelihood of causing catastrophic harm. For example, high quality evidence supports the inference that testosterone is beneficial for men with symptomatic androgen deficiency, improving their quality of life and markers of bone and muscle strength. However, low quality evidence links testosterone use to an increased risk of prostate cancer. As a result, a panel of endocrinologists formulated a strong recommendation against testosterone use in men with prostate cancer and in men pending evaluation of palpable prostate nodule or induration or prostate-specific antigen (PSA) level of

4 ng/mL or PSA level of 3 ng/mL in men at high risk of prostate cancer [31].

#### 2.4. Resource use

Panels may or may not consider resource use in their judgments about the direction and strength of recommendations. Reasons for not considering resource use include a lack of reliable data, the intervention is not useful and the effort of calculating resource use can be spared, the desirable effects so greatly outweigh any undesirable effects that resource considerations would not alter the final judgment, or they have elected (or been instructed) to leave resource considerations up to other decision makers.

Once again, panels should be explicit about the decision they made not to consider resource utilization and the reason for their decision. If they elect to include resource utilization when making a recommendation, but have not included resource use as a consequence when preparing an evidence profile, they should be explicit about what types of resource use they considered when making the recommendation and whatever logic or evidence was used in their judgments.

For example, a panel making a recommendation about oseltamivir for treatment of patients hospitalized with avian influenza (H5N1) in nonpandemic situations considered the cost of oseltamivir, but did not explicitly consider the quality of the evidence for resource use. Overall, the quality of

the underlying evidence for all recommendations was rated as very low because it was based on small case series of H5N1 patients, on extrapolation from preclinical studies, and high quality studies of seasonal influenza. A strong recommendation to treat H5N1 patients with oseltamivir was made in part because of the severity of the disease. With only very low quality evidence of the beneficial and adverse effects of oseltamivir for avian influenza, the panel decided not to consider quality of evidence for resource use. The panel summarized their thinking regarding resource use as a factor in making their recommendation by stating: The cost is not high for treatment of sporadic cases [32]. We discuss special challenges related to rating the confidence in estimates for resource use in another article in this series [9].

### 3. Special considerations of the determinants of direction and strength of recommendations

#### 3.1. Baseline risk (control event rate) can influence the balance

Table 3 presents an example of how guideline panels can move from evidence to recommendations in an explicit and transparent way. The final column in Table 3 presents the issues (if one calls the four determinants domains, then one might call these issues subdomains) that guideline panels should consider under each domain. One of these subdomains, which may be critical in the decision, is baseline risk.

Because, we usually determine absolute risk differences through applying the relative risk reduction to a baseline risk [11], large baseline risk differences will result in large absolute risk differences. For example, recommendations for duration of anticoagulation in patients with deep venous thrombosis will differ depending on the likelihood of recurrent thrombosis. The likelihood of recurrent thrombosis differs in those with and without clear precipitating factors for the original thrombotic event-in particular, patients whose deep venous thrombosis is precipitated by a surgical procedure have a low risk of recurrence. Anticoagulation is associated with inconvenience and a risk of serious bleeding. Therefore, indefinite anticoagulation will seldom be appropriate in those at low risk of recurrence whose absolute benefit with anticoagulation is small, but may well be mandated in patients at much higher risk. Thus, the strength of recommendations and likely the direction-will differ in high- and low-risk groups [33].

#### 3.2. Recommendations may differ by setting and perspective

In our introductory discussion of globalizing evidence, localizing recommendations, we noted that we do not expect uniformity of recommendations across settings. Here, we expand the reasons for the anticipated diversity, and how differences in perspective can contribute. The impact of an intervention may differ across geographic settings depending on the risk of adverse events

in untreated population (e.g., risk of coronary events is much lower in low income countries), or the capacity to deliver the intervention (e.g., monitoring of anticoagulant therapy).

Values and preferences may differ among cultures, even if those cultures appear very similar. For example, after viewing the same evidence, American and New Zealand guideline developers came to different conclusions about the trade-offs associated with colon cancer screening [34-36].

Values may also differ in subcultures vs. mainstream culture within a population. For example, in formulating the CCIRH guidelines, the panel's awareness of immigrant populations' vulnerability to family disruption and possible deportation supported the recommendation against routine screening for intimate partner violence [37].

Finally, resource implications and opportunity cost may differ. For instance, a year's supply of an expensive drug may cost the equivalent of a single nurse's salary in the United States, 4 nurses' salaries in Poland, and 20 nurses' salaries in China.

In the face of the same evidence, recommendations may also differ according to perspective. Our discussion in this article has addressed, almost exclusively, guideline panels making recommendations from the perspective of patients and the health care providers looking after those patients. Sometimes, however, a panel may make recommendations from a public health or societal perspective.

For example, panels making recommendations about H1N1, avian, or seasonal influenza may place a large value on outcomes that may not be directly critical or important to individual patients, such as reducing the spread of disease [32,38]. Other times, a panel may make recommendations from the perspective of the government or a private insurance company, placing a large value on costs (or alternative uses of resources) within a fixed budget. Equity, feasibility, and burden of illness may be other considerations important to public policy decision making, but of much less relevance to individual decision making. Panels should explicitly state the perspective they are taking, particularly when they are not taking a patient-centered perspective.

#### 3.3. Evidence to recommendations synthesis

As in Table 3, GRADE suggests that guideline panels present a synthesis of their judgments about the domains determining direction and strength of recommendations, and how this synthesis informs the recommendation. Disagreement between panels is common [39 - 41], and disagreement may be a result of variability in judgments about the domains or of how panels synthesize those judgments. Presentation and publication of frameworks

summarizing the rationale for recommendations can support transparency in the decision process and be used for stakeholder engagement (Table 3).

Consider, for example, views expressed in the literature concerning the merits of perioperative use of beta-blockers in patients undergoing noncardiac surgery. Some assert that lower doses of beta-blockers administered well before surgery could prevent the documented increase in stroke risk with beta-blockers [42,43]. Others do not agree [44]. An evidence to action synthesis from the former group would emphasize the heterogeneity of results from trials that used different doses and different periods of administration of beta-blockers before surgery, and the latter would not.

Alternatively, disagreement in recommendations might be because they have different views of the relative value of reducing the risk of MI with beta-blocker use (approximately 1.5% in those at 5% baseline risk) vs. the increase in stroke risk (approximately 0.5% in those at 0.5% baseline risk of stroke). Both may agree that patients value preventing stroke more than preventing MI, but the synthesis from a panel recommending against beta-blockers would emphasize that the patients generally place very high value in avoiding disabling stroke and the asymptomatic nature of many perioperative MIs.

#### 4. Conclusion

Patients, clinicians, and policy makers will all be better served by a more systematic and transparent system for judging the direction and strength of recommendations. Explicit presentation of how panels view the four domains to consider in the direction and strength of recommendations could play an important role in improving the transparency of panel decisions (Table 3).

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