Improving the use of research evidence in guideline development: 9. Grading evidence and recommendations

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Abstract

Background: The World Health Organization (WHO), like many other organisations around the world, has recognised the need to use more rigorous processes to ensure that health care recommendations are informed by the best available research evidence. This is the ninth of a series of 16 reviews that have been prepared as background for advice from the WHO Advisory Committee on Health Research to WHO on how to achieve this.

Objectives: We reviewed the literature on grading evidence and recommendations in guidelines.

Methods: We searched PubMed and three databases of methodological studies for existing systematic reviews and relevant methodological research. We did not conduct a full systematic review ourselves. Our conclusions are based on the available evidence, consideration of what WHO and other organisations are doing and logical arguments.

Key questions and answers: Should WHO grade the quality of evidence and the strength of recommendations?

- Users of recommendations need to know how much confidence they can place in the underlying evidence and the recommendations. The degree of confidence depends on a number of factors and requires complex judgments. These judgments should be made explicitly in WHO recommendations. A systematic and explicit approach to making judgments about the quality of evidence and the strength of recommendations can help to prevent errors, facilitate critical appraisal of these judgments, and can help to improve communication of this information.

What criteria should be used to grade evidence and recommendations?

- Both the quality of evidence and the strength of recommendations should be graded. The criteria used to grade the strength of recommendations should include the quality of the underlying evidence, but should not be limited to that.

- The approach to grading should be one that has wide international support and is suitable for a wide range of different types of recommendations. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which is currently suggested in the Guidelines for WHO Guidelines, is being used by an increasing number of other organizations internationally. It should be used more consistently by WHO. Further developments of this approach should ensure its wide applicability.

Should WHO use the same grading system for all of its recommendations?

- Although there are arguments for and against using the same grading system across a wide range of different types of recommendations, WHO should use a uniform grading system to prevent confusion for developers and users of recommendations.
Background
The World Health Organization (WHO), like many other organisations around the world, has recognised the need to use more rigorous processes to ensure that health care recommendations are informed by the best available research evidence. This is the ninth of a series of 16 reviews that have been prepared as background for advice from the WHO Advisory Committee on Health Research to WHO on how to achieve this.

For over 25 years a growing number of organisations have employed various systems to grade the quality of evidence (sometimes called levels of evidence) and the strength of recommendations [1]. Unfortunately, different organisations use various grading systems, which may lead to confusion among consumers.

Groups making recommendations always make judgements about the quality of evidence and the balance of benefits and downsides (harms, burden and costs). Frequently these judgements are made implicitly rather than explicitly and judgements about the quality of evidence are confused with judgements about the balance of benefits and downsides. Many systems that are used to grade the quality of evidence and the strength of recommendations also confuse these judgements by equating the strength of recommendation with the quality of evidence, for example by grading recommendations for which there is high quality evidence as strong, without explicitly considering the balance of benefits and downsides.

Knowing the quality of evidence is essential, but not sufficient for making judgements about the strength of a recommendation. For instance, high quality evidence from well executed randomized controlled trials showed that oral anticoagulation administered for more than one year reduces the risk for recurrent thromboembolic events in patients after a first episode of spontaneous deep venous thrombosis. However, because oral anticoagulation is associated with harms (bleeding risk), burden (taking medication and monitoring anticoagulation levels) and cost (anticoagulation clinics or monitoring devices) the recommendation to anticoagulate all patients is weak because the benefits and downsides are finely balanced and individual patients will make different choices [2]. Both judgements about the quality of evidence and about the strength of a recommendation are complex and require consideration of a number of factors.

In this paper we addressed the following questions:

- What criteria should be used to grade evidence and recommendations?
- Should WHO use the same grading system for all of its recommendations?
- Should WHO grade the quality of evidence and the strength of recommendations?
- What other organisations are doing

Most, but not all organizations that develop guidelines use a grading system to express the strength of a recommendation or the quality of evidence. For example, the US Preventive Services Task Force (USPSTF) uses a grading system that assigns one of three grades of evidence: good, fair, or poor [15]. The USPSTF uses its assessment of the evidence and magnitude of net benefit to make a recommendation, coded as a letter: from A (strongly recommended) to D (recommend against). The UK National Institute for Health and Clinical Excellence (NICE) has not yet made a decision as to which grading system to use [16]. The Scottish Intercollegiate Guideline Network (SIGN) has developed its own grading system for application to SIGN guidelines [17]. The Australian Medical Research Council is currently developing a grading system that will probably include grading recommendations according to strength of recommendations and quality of evidence [18]. The US Task Force on Community Preventive Services uses a system in which the quality of the evidence of effectiveness links directly the strength of the recommendation [19,20]. Professional organizations use a variety of systems, many of them, however, based on two prominent grading approaches: the system derived from the Canadian Task Force on the Periodic Health Examination [1,21] and a successor of that system, the Oxford Centre for Evidence Based Medicine approach [22].

More recently, medical societies have begun to form collaborations within specialties to develop grading systems...
on their own. For example a group of specialty societies in rehabilitation sciences formed a panel to develop an approach to grading the quality of evidence and strength of recommendations [23]. This panel developed a set of criteria for grading the strength of both the evidence and the recommendation. Similarly, the world leading urology associations have come together to adopt a uniform grading system and approach that would be useful for urologists around the world rather than each association using a different grading system [24]. This latter collaboration named, Evidence Based Urology, is exploring using the GRADE approach. The GRADE approach is being used increasingly by organisations around the world [25-28], although in some cases with slight modifications [29]. It has been used for public health questions such as the pharmacological management of human influenza A(H5N1) infection (avian flu) [30], although it more commonly has been used for clinical questions up to now. A group of family practice and primary care journals has also developed a system to grade the strength of a recommendation [31].

**Methods**

The methods used to prepare this review are described in the introduction to this series [32]. Briefly, the key questions addressed in this paper were vetted amongst the authors and the ACHR Subcommittee on the Use of Research Evidence (SURE). We did not conduct a full systematic review. We reviewed existing guidelines for guidelines to identify grading system currently in use. We also searched PubMed using (grading system) and (methods) (MESH headings/keywords) for systematic reviews and studies of methods for grading the quality of evidence. In addition, we searched databases maintained by the Agency for Healthcare Research and Quality (AHRQ, [33]) and the Guidelines International Network (GIN, [34]). These searches were supplemented with information obtained directly from guideline development organizations and our own files. Because of our involvement with organizations that produce guidelines and prior work with grading systems, in particular the GRADE system, we had in depth knowledge about several systems [25,28,29,35,36].

**Findings**

We identified one systematic review dealing with the evaluation of grading systems. In 2002, the US Agency for Healthcare Research and Quality (AHRQ) published a systematic review of existing systems to grade the quality of evidence and strength of recommendations [37]. The AHRQ review considered 40 systems until the year 2000 that addressed grading the strength of a body of evidence. The important domains and elements for the systems to grade the strength of evidence that the authors agreed on were quality (the aggregate of quality ratings for individual studies, predicated on the extent to which bias was minimized), quantity (magnitude of effect, numbers of studies, and sample size or power) and consistency (for any given topic, the extent to which similar findings are reported using similar and different study designs).

More recently, independent work by the Canadian Optimal Medication Prescribing and Utilization Service (COMPUS) used a detailed process to evaluate and select an evidence grading system and expanded the work by AHRQ (while accepting it) until the year 2005 [38]. COMPUS, which identifies, evaluates, promotes and facilitates best practices in drug prescribing and use among health care providers and consumers in Canada [39], is a nationally coordinated program, funded by Health Canada and delivered by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA, [39]). They assembled a working group of internal researchers, information specialists, methodology experts, and external researchers to update the work of AHRQ. COMPUS searched for and selected review articles for the period 2000 to 2005. This resulted in more than 3,000 citations for selection. Eleven review articles were selected for further analysis based on a priori selection criteria specified by the working group. Nearly 50 evidence grading systems were identified from the 11 review articles. Canadian and international experts in evidence evaluation methodology helped identify an additional 10 instruments or systems not included in the list of identified grading systems. The identified instruments and systems were evaluated using the AHRQ evaluation grids. The highest scoring instruments were the GRADE and the SIGN approach [38]. A second round of expert consultation and stakeholder input from all interested parties confirmed the selection of these instruments.

The GRADE system was developed through an intensive international collaboration of methodologists, guideline developers and clinicians and incorporates the factors identified in the AHRQ review and described above [35,36].

**Should WHO grade the quality of evidence and the strength of recommendations?**

We did not identify published studies that compared graded with non-graded recommendations. The only evidence we are aware of are three unpublished studies. The first was conducted by UpToDate®, an electronic textbook, that asked a small group of users to compare graded with non-graded recommendations and explore – in a focus group setting – reasons for their answers (UpToDate®, personal communication). The second is our own study asking a small group of the general public interested in health care issues (Akl E, et al, manuscript in preparation). The third is a study by researchers in Norway who provided patients with back problems with graded evidence of the
effects of alternative interventions graded with the GRADE approach. Users of the website intuitively understood the meaning of the quality grades for each outcome (Claire Glenton, personal communication). The findings of these evaluations suggested that users preferred graded over non-graded recommendations.

Despite the lack of stronger direct evidence, there is agreement among most guideline developers that grading the quality of evidence has advantages, because health care decisions involve a trade-off between likely benefits on the one hand, and downsides (harms, burden and costs) on the other hand [40]. To integrate these recommendations with their own judgment, guideline users need to understand the basis for the recommendations that guidelines offer them. A systematic approach to grading the strength of recommendations should minimize bias and aid interpretation about benefits and downsides. In addition, a systematic and explicit approach to making judgments about the quality of evidence and the strength of recommendations is likely to help prevent errors, facilitate critical appraisal of these judgements, and can help improve communication of this information [36].

What criteria should be used to grade evidence and recommendations?

In a series of 16 international meetings and correspondence over five years the GRADE Working Group has derived a set of criteria to assess the quality of evidence (Table 1) and the strength of recommendations (Table 2) [25,29,35,36,41,42]. The GRADE system has several advantages over other systems including explicit definitions and sequential judgments during the grading process; a detailed description of the criteria for the quality of evidence for single outcomes and for the overall quality of the evidence; weighing the relative importance of outcomes; consideration of the balance between health benefits versus harms, burdens and cost; and the development of evidence profiles and summaries of findings. In addition the GRADE group is supported by an international collaboration [36]. The main limitation and criticism of the GRADE system is its complexity. Work in progress is addressing this limitation including the development of user friendly software to develop evidence profiles (G. Vist, personal communication and [26,29]).

Should WHO use the same grading system for all of its recommendations?

We did not identify evidence for or against using a single grading system for all types of recommendations, including clinical, public health and health policy recommendations. The arguments for and against using a single grading system are summarised in Table 3. The most important reasons for using a consistent system are a) minimising confusion amongst users of WHO recommendations; b) the risk of bias if groups can select a system that makes the quality of evidence and the strength of recommendations look better for their preferred interventions; and c) being intellectually honest about recognising the limits of the evidence rather than having a double standard. If an approach can be identified that is suitable across a wide range of interventions and contexts both methodologically and politically, the advantages outweigh the disadvantages.

Some developers and users of GRADE believe that GRADE can be consistently and usefully applied across clinical and non-clinical interventions, based on conceptual arguments and experience up to now applying this approach to a wide range of interventions, including public health and health system interventions. Others disagree because they believe it is unlikely to be an appropriate approach for some areas for the reasons summarised in table 3. There is not yet an empirical evidence base with which to mediate this disagreement for GRADE or any other grading system. Up to now GRADE has been used mostly for clinical interventions and few examples of its use with public health questions have been published. There is an

Table 1: GRADE quality assessment criteria

| Quality of evidence | Study design | Lower if* | Higher if* |
|---------------------|-------------|-----------|------------|
| High                | Randomised trial | Study quality:  |
|                     |             | - Serious limitations  |
|                     |             | - Very serious limitations  |
|                     |             | - Important inconsistency  |
|                     |             | Directness:  |
|                     |             | - Some uncertainty  |
|                     |             | - Major uncertainty  |
|                     |             | - Sparse data  |
|                     |             | - High probability of Reporting bias  |
| Moderate            | Observational study | Strong association:  |
| Low                 |             | +1 Strong, no plausible confounders, consistent and direct evidence**  |
| Very low            |             | +2 Very strong, no major threats to validity and direct evidence**  |
|                     |             | +1 Evidence of a Dose response gradient  |
|                     |             | +1 All plausible confounders would have reduced the effect  |

* 1 = move up or down one grade (for example from high to intermediate) 2 = move up or down two grades (for example from high to low)

** A statistically significant relative risk of >2 (< 0.5), based on consistent evidence from two or more observational studies, with no plausible confounders

** A statistically significant relative risk of > 5 (< 0.2) based on direct evidence with no major threats to validity

http://www.health-policy-systems.com/content/4/1/21
Table 3: Pros and cons of using the same system for grading evidence and formulating recommendations for a wide range of health care interventions, including clinical and non-clinical interventions

| Arguments for having a common approach                                                                 | Arguments against having a common approach                                                                 |
|--------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| • Having less demanding systems for some kinds of questions might result in false positive conclusions. | • Having an infeasible system for some kinds of questions might result in false negative conclusions.       |
| • People with vested interests in particular interventions could choose the system that makes their intervention look best. | • False negative conclusions due to inappropriate evaluation requirements may have negative political and health consequences; for example, effective programs that cannot be studied with randomised trials might experience funding cuts. |
| • People with vested interests in particular evaluation approaches could choose the system that makes their preferred evaluation approach look best. | • Interventions that cannot be studied with randomised trials might not be evaluated.                      |
| • Having different systems for different types of interventions might be confusing.                      | • A single system may not discriminate adequately within the range of evidence that is appropriate to consider for clinical and non-clinical interventions. |
| • It is intellectually honest to recognise the limits of evidence where this is appropriate.            | • A system that can adequately address evidence across a wide range of interventions and contexts may be overly complex. |
| • Admitting the limitations of evidence, if this is appropriate, might promote more and better research. |                                                                                                           |

ongoing international collaborative effort to apply the GRADE approach to public health and health systems interventions, and it is possible that modifications may be needed to ensure its usefulness for non-clinical interventions. For example, in one recent review of drug policies the authors felt that it was important to distinguish between different types of observational studies (interrupted time-series analyses and controlled before-after studies) when making judgements about the quality of evidence for important outcomes [43].

Discussion

WHO has made a decision to use a grading system to grade the quality of evidence and strength of recommendations that is sensible and is being used widely, the GRADE system [36]. WHO has been involved in the development of this system from the beginning, and consideration has been given to the potential for application of the system to WHO guidelines in developing the GRADE approach. This might have been expected to facilitate the dissemination and adoption of this approach by WHO guideline developers. However, interest in GRADE workshops at WHO has been limited, there is not a tradition of grading the quality of evidence or strength of recommendations at WHO, and few resources have been invested in supporting the use of GRADE specifically, or in supporting more rigorous guidelines development methods generally.

More recently, however, the WHO rapid advice guideline panel for the pharmacological management of human infection with avian influenza A (H5N1) virus applied GRADE successfully [30] and several WHO guidelines are under development using GRADE (Sue Hill, personal communication). In general, the evidence that graded recommendations have advantages over non-graded recommendations is limited, but there are strong arguments, including the clear and transparent communication of how much confidence users can place in recommendations and the evidence underlying them. Another limitation is that both the quality of evidence and the strength of recommendations exist on a continuum. Categorization of quality into four categories and recommendations for or against treatments into two grades, strong and weak, may oversimplify complex health care recommendations, but guidelines consumers are generally likely to benefit from this simplification as they are most interested in which recommendations to follow.

Further work

We have found a large body of work on the development and evaluation of various grading systems. Problems have arisen because many different grading systems exist. Future efforts should focus on forging a consensus on using a sensible and uniform approach to grade the quality of evidence and strength of recommendations, building on the work of the GRADE working group. Use of the
GRADE system by WHO, as is currently recommended by the Guidelines for WHO Guidelines, could help by obtaining more experience, particularly with non-clinical interventions, contribute to improvements in the existing system, contribute to agreeing on a common international approach to grading of recommendations and help to ensure the quality and transparency of the judgements that are made across various groups that make recommendations on behalf of WHO. Development of software and a detailed manual to simplify the use of the GRADE system is underway and should facilitate the use of this system and its further development.

Competing interests
ADO and AF work for the Norwegian Knowledge Centre for the Health Services, an agency funded by the Norwegian government that produces systematic reviews and health technology assessments. All three authors are contributors to the Cochrane Collaboration. ADO and HJS are members of the GRADE Working Group. HJS is documents editor and chair of the documents development and implementation committee for the American Thoracic Society and senior editor of the American College of Chest Physicians’ Antithrombotic and Thrombolytic Therapy Guidelines.

Authors’ contributions
HJS prepared the first draft of this review. AF and ADO authors contributed to drafting and revising it. All authors read and approved the final manuscript.

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References
1. Anonymous: Canadian Task Force on the Periodic Health Examination. The periodic health examination. CMAJ 1979, 121:1193-1254.
2. Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE: Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004, 126(3 Suppl):401S-428S.
3. Oxman AD Fretheim A: Improving the Use of Research Evidence in Guideline Development: 7. Deciding what evidence to include. Health Res Policy Syst 2006.
4. Oxman AD Schünemann HJ: Improving the Use of Research Evidence in Guideline Development: A: Improving the Use of Research Evidence in Guideline Development: A: Improving the Use of Research Evidence in Guideline Development: B: Synthesis and presentation of evidence. Health Res Policy Syst 2006.
5. Oxman AD Fretheim A, Schünemann HJ: Improving the Use of Research Evidence in Guideline Development: 14. Reporting guidelines. Health Res Policy Syst 2006.
6. The Russian Federation. Making Pregnancy Safer/Promoting Effective Perinatal Care. National Orientation and Planning Meeting. Moscow, 11-14 February 2003.
7. Fourth Futures Forum of High-Level Decision-Makers Tools for decision-making in public health. Brussels, Belgium 16-17 June 2003.
8. Global Programme on Evidence for Health Policy. Guidelines for WHO Guidelines. EIP/GPE/QEC/2003.1. Geneva . World Health Organization; 2003.
9. Schünemann HJ Hill S, Kakad M, Bellamy R, Uyeki T, Hayden F, Yazdananpar Y, Beigel J, Chotpitayasunondh T, Vist G, Del Mar C, Farrar J, Fukuda K, Hien TT, Shindo N, Stockman L, Sugaya N, Tomson G, Nagdialyev A, Ozbay B, Roth C, Croisier A, Oxman AD: WHO Rapid Advice Guidelines: Perinatal Guidelines for the pharmacological management of human infection with avian influenza A (H5N1) virus. Lancet companion paper: submitted
10. Schünemann HJ Hill S, Kakad M, Vist G, Bellamy R, Stockman L,Uyeki T, Del Mar C, Shindo N, Fukuda K, Hayden F, Yazdananpar Y,Oxman, AD: WHO Rapid Advice Guidelines: Quick and Transparent. Lancet companion paper: submitted
11. World Health Organization. Prevention of Recurrent Heart Attacks and Strokes in Low and Middle Income Populations: Evidence-based Recommendations for Policy Makers and Professional Organisations. World Health Organization; 2003.
12. Guidelines for the Prevention of Malaria . Geneva . World Health Organization; 2006.
13. Oxman AD Lavis J, Fretheim A: The use of research evidence in WHO recommendations. (submitted)
14. Panisset U: A Review of H40: Recommendations published in 2005. Health Res Policy Syst 2006.
15. Harris RP, Helfand M, Lohr KN, Mulrow CD, Teutsch SM, Atkins D: Current methods of the U.S. Preventive Services Task Force: A review of the process. American Journal of Preventive Medicine 2001, 20(3, Supplement 1):21-35.
16. National Institutes for Health and Clinical Excellence [http://www.nice.org.uk/pdf/GDM_Allchapters_0305.pdf].
17. Harbour R Millier J: A new system for grading recommendations in evidence based guidelines. BMJ 2001, 323:334-336.
18. Middleton P TR Salibian D, Coleman K, Norris S, Grimmer K, Hillier S: Assessing the body of evidence and grading recommendations in evidence-based clinical practice guidelines: Melbourne, Australia. Edited by: Collaboration C.; 2003-42.
19. Briss PA, Zaza S, Pappanoion M, Fielding J, Wright-De Aguero L, Trumman BI, Hopkins DP, Mullien PD, Thompson RS, Woolf SH, Carandekulis VG, Anderson L, Himan AR, McQueen DV, Teutsch SM, Harris JR: Developing an evidence-based Guide to Community Preventive Services--methods. The Task Force on Community Preventive Services. Am J Prev Med 2000, 18(1 Suppl):35-46.
20. Truman BI, Smith-Akin CK, Himan AR, Hagie KM, Brownson R, Novick LF, Lawrence RS, Pappanoion M, Fielding J, Evans CA JR., Guerra FA, Vogel-Taylor M, Mahan CS, Fullilove M, Zaza S: Developing the Guide to Community Preventive Services--overview and rationale. The Task Force on Community Preventive Services. Am J Prev Med 2000, 18(1 Suppl):18-26.
21. Sackett DL: Rules of evidence and clinical recommendations on the use of antithrombotic agents. Archives Int Med 1986, 146:664-665.
22. Phillips B Ball C, Sackett D, Badenoch D, Straus S, Haynes B, Dawes M: Levels of Evidence and Grades of Recommendation. Centre for Evidence-Based Medicine .
23. Philadelphia Panel evidence-based clinical practice guidelines on selected rehabilitation interventions: overview and methodology. Phys Ther 2001, 81(10):1629-1640.
24. Evidence Based Urology Task Force [http://www.gradeworkinggroup.org/EBUro/intro.htm].
25. Guyatt G, Vist G, Falck-Ytter Y, Kunz R, Oxman AD: A new system for grading recommendations in evidence-based guidelines. Cochrane Database of Systematic Reviews (CD001197), Issue 1. (page number not for citation purposes)
recommendations and quality of evidence in clinical guidelines.  *Chest* 2006, 129:174-181.

30. WHO Rapid Advice Guidelines on pharmacological management of humans infected with avian influenza A (H5N1) virus  [http://www.who.int/csr/disease/avian_influenza/guidelines/en/index.html]

31. Ebell MH, Siwek J, Weiss BD, Woolf SH, Susman J, Ewigman B, Bowman M: Strength of recommendation taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature.  *J Am Board Fam Pract* 2004, 17(1):59-67.

32. Oxman AD Fretheim A, Schünemann HJ: Improving the Use of Research Evidence in Guideline Development: Introduction.  Health Res Policy Syst 2006.

33. Agency for Healthcare Research and Quality  [http://www.guidelines.gov]

34. Guidelines International Network  [http://www.g-i-n.net]

35. Atkins D, Eccles M, Flottorp S, Guyatt GH, Henry D, Hill S, Liberati A, O’Connell D, Oxman AD, Phillips B, Schunemann Hj, Edejer TT, Vist GE, Williams JW Jr.: Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group.  *BMC Health Serv Res* 2004, 4(1):38.

36. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O’Connell D, Oxman AD, Phillips B, Schunemann Hj, Edejer TT, Varonen H, Vist GE, Williams JW Jr., Zaza S: Grading quality of evidence and strength of recommendations.  *Bmj* 2004, 328(7454):1490.

37. West S, King V, Carey TS, Lohr KN, McKoy N, Sutton SF, Lux L: Systems to Rate the Strength of Scientific Evidence.  In Evidence Report/Technology Assessment Volume AHRQ Publication No. 02-E016. Rockville, MD , Agency for Healthcare Research and Quality; 2002.

38. Canadian Optimal Medication Prescribing and Utilization Service  [https://www.ccohta.ca/compus/compus_pdfs/COMPUS_Evaluation_Methodology_draft_e.pdf]

39. Canadian Coordinating Office for Health Technology Assessment  [https://www.ccohta.ca/]

40. Schünemann Hj, Fretheim A, Oxman, AD: Improving the Use of Research Evidence in Guideline Development: 6. Determining which outcomes are important.  Health Res Policy Syst 2006.

41. Atkins D, Briss PA, Eccles M, Flottorp S, Guyatt GH, Harbour RT, Hill S, Jaeschke R, Liberati A, Magrini N, Mason J, O’Connell D, Oxman AD, Phillips B, Schunemann H, Edejer TT, Vist GE, Williams JW Jr.: Systems for grading the quality of evidence and the strength of recommendations II: pilot study of a new system.  *BMC Health Serv Res* 2005, 5(1):25.

42. Schünemann HJ, Best D, Vist G, Oxman AD: Letters, numbers, symbols and words: how to communicate grades of evidence and recommendations.  *Cmaj* 2003, 169(7):677-680.

43. Aaserud M Dahlgren A, Kosters JP, Oxman AD, Ramsay C, Sturm H.: Pharmaceutical policies: effects of pricing and purchasing policies on rational drug use.  In The Cochrane Library Chichester, UK : John Wiley & Sons, Ltd; 2006.