

Guidelines 2.0: Do No Net Harm—The Future of Practice Guideline Development in Asthma and Other Diseases

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Abstract Decisions are like double-edged swords: they always come with benefits and downsides. That is, any decision in life bears desirable and undesirable consequences, even if the latter only involves the time it takes to make or think about the decision, which can be considered the harm of decision making. Therefore, it is impossible to adhere to the Hippocratic Oath's concept of "*primum non nocere*," which is frequently interpreted as "never do harm." The guiding principle for health care decision making should be to ensure that there is, in summary, more benefit than harm—in other words, "to do no net harm" ("*primum non net nocere*"). Practice guidelines support decision making and, as a consequence, would require the explicit consideration of both desirable and undesirable consequences, and assigning due considerations depending on the magnitude and importance of the consequences. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (<http://www.gradeworkinggroup.org>) has made these considerations more explicit when developing health care recommendations. This article briefly summarizes the work of the GRADE working group based on examples of its application in the field of allergy and asthma, and provides an outlook for advances in the field of guideline development. These developments focus on funding of guidelines and handling conflict of interest, working with observational and diagnostic test accuracy studies, developing appropriate group processes, and the integration of values and preferences in the formulation of recommendations.

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Introduction

Decisions are like double-edged swords: they always come with benefits and downsides. That is, an decision in life bears desirable and undesirable consequences, even if the latter only involves the time it takes to make or think about the decision. Thus, the key to decision making on any level, however simple, is that decisions should achieve more benefit than harm. These considerations apply to decisions in health care on a population level and an individual level. Sometimes the harms (in the broader sense of undesirable consequences) are minimal and should require little further consideration, such as taking a history in sick patients, stopping bleeding, or using a car's seat belt. However, the field of medical decision analysis teaches us that potentially undesirable consequences or downsides require, at a minimum, consideration in decision making, particularly if these downsides occur frequently (eg, headache, mild allergic reactions to medication, or bleeding) or if they are important (eg, severe allergic reactions to medication). Therefore, the Hippocratic Oath's "*primum non nocere*," frequently interpreted as "never do harm," is impossible to adhere to for a physician or any other clinician. As medical schools have moved away from asking their graduates to swear the original Hippocratic Oath, it probably has been realized that one of the main reasons is that it is impossible to inflict no downsides at all during medical decision making (ie, treatment and diagnosis). Therefore, the guiding principle for health care decision making is to ensure that there is, in summary, more benefit than harm (in situations in which harm includes burden of

disease). In other words, decision making, and health care decision making in particular, requires in-depth consideration of doing no *net* harm, or “*primum non net nocere*.”

If they are based on the best available evidence and developed according to best methods, recommendations in practice guidelines are the ideal way to provide advice to practitioners in clinical and public health practice and the population targeted in the guidelines. Practice guidelines support decision making and therefore would require a consideration of benefits and harms during development and implementation to ensure that net harm can be avoided. In guideline development, the explicit consideration of both desirable and undesirable consequences—and assigning due considerations depending on the magnitude and importance of the consequences—however, is a more recent conceptual phenomenon. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (<http://www.gradeworkinggroup.org>), a multidisciplinary group including more than 250 guideline developers, epidemiologists, clinicians, public health officers, health policy makers, and others, has made these considerations more explicit when developing health care recommendations since it began its work in 2000 [1, 2, 3, 4]. The GRADE approach to developing recommendations asks for the following: 1) transparent description of benefits and downsides, 2) integration of the importance of the benefits and downsides by decision makers through consideration of values and preferences, 3) the required resources, and 4) the confidence that decision makers can balance all these factors via a thorough assessment of the quality of the evidence related to these factors. Previously, these domains were frequently ignored in summarizing evidence and health care recommendation development. Perhaps as a result of recognizing the limitations of prior approaches, more than 50 major organizations, including the World Health Organization (WHO), the Cochrane Collaboration, the National Institutes for Health and Clinical Excellence in the United Kingdom (NICE), and professional organizations such as the American College of Physicians, use the GRADE approach [5].

In this article, supported by some key references, I briefly and narratively review and describe developments in the field of guideline development, focusing on the GRADE approach and the work of the working group, and provide an outlook to the future of guideline development using some examples from the field of asthma and allergy.

The GRADE Approach

The GRADE approach to developing health care recommendations asks for a stepwise approach in the assessment

of the quality of evidence of the factors that influence decision makers' confidence that adherence to a recommendation leads to more desirable than undesirable consequences. This is done prior to developing recommendations based on their strength. In the GRADE approach, the assessment of the quality of evidence reflects the extent to which a guideline panel's confidence in an estimate of the effect was adequate to support a particular recommendation. The quality of a body of the best evidence is assessed, beginning with an evaluation of the underlying study design (randomized trials vs observational studies). This is followed by a detailed assessment of limitations in the design and execution of the studies (risk of bias), imprecision, inconsistency, indirectness, publication bias, magnitude of effect, dose–effect relations, and an assessment of the effect of plausible residual confounding and bias. Quality is categorized on four levels, ranging from ⊕⊕⊕⊕ as the lowest quality to ⊕⊕⊕⊕, the highest quality based on these assessments (Table 1).

For each recommendation, a panel should explicitly consider and agree upon the quality of the evidence, the balance of benefits and downsides, the assumptions about values and preferences associated with the decision, and resource use. Ideally, the assessment of the evidence is completed independently by a multidisciplinary team led by those experienced in research methodology and informed by clinicians who are well-informed. Finally, for each recommendation, the panel should then provide its strength and the quality of the best supporting evidence. As described above, for strong recommendations, a panel may use the terminology *we recommend*, and for weak (also known as conditional) recommendations, *we suggest*. Table 2 provides interpretation aids for strong and weak/conditional recommendations and for the quality of evidence.

In the most recent Allergic Rhinitis in Asthma (ARIA) guideline update, an independent team of methodologists with experience in respiratory and allergic disease completed the evidence review and assessment of the quality of the evidence. The guideline panel, made up largely of international clinical experts in addition to two lead methodologists, formulated recommendations. Only 12 of the approximately 70 graded individual recommendations are strong recommendations (ie, <20%) [6•]. This is a result of several factors: 1) the often lower-quality evidence for all patient important outcomes that are critical to decision making, and the resulting lowered confidence that the benefits clearly outweigh the downsides; 2) the influence (ie, uncertainty or variability) of values and preferences that decision makers would assign to the important patient outcomes; and 3) the possible uncertainty that the benefits and the required resources for an

Table 1 Criteria for assessing the quality of a body of evidence using the GRADE approach

Study design	Initial quality of a body of evidence	Lower if	Higher if	Quality of a body of evidence
Randomised trials	High	Risk of Bias Inconsistency	Large effect Dose response	A/High (four plus: ⊕⊕⊕⊕)
		Indirectness	All plausible residual confounding & bias:	B/Moderate (three plus: ⊕⊕⊕○)
Observational studies	Low	Imprecision Publication bias	-Would reduce a demonstrated effect -Would suggest a spurious effect if no effect was observed	C/Low (two plus: ⊕⊕○○) D/Very low (one plus: ⊕○○○)

intervention may not outweigh less resource-intensive alternative actions. Laying out the reasons for moving from a strong to a weaker or conditional recommendation is most informative for those using the recommendations. The following shows an example of a conditional recommen-

dation in the ARIA guidelines and the transparent description of the underlying reason [6••].

Example Should sublingual allergen-specific immunotherapy be used in patients with allergic rhinitis (AR) and asthma?

Table 2 Interpretation aids for strong and weak/conditional recommendations and for the quality of evidence

Interpretation of strong and conditional (weak) recommendations		
	Strong recommendation	Conditional (weak) recommendation
For patients	Most individuals in this situation would want the recommended course of action; only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that clinicians must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals make decisions consistent with their values and preferences.
For policy makers and developers of quality measure	The recommendation can be adapted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policy making will require substantial debate and involvement of various stakeholders. An appropriately documented decision-making process could be used as quality indicator.
Interpretation of the categories of the quality of evidence		
High: ⊕⊕⊕⊕	There is high confidence that the true effect lies close to that of the estimate of the effect.	
Moderate: ⊕⊕⊕○	There is moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	
Low: ⊕⊕○○	The panel's confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.	
Very low: ⊕○○○	There is little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.	

Recommendation In patients with AR and asthma, we suggest sublingual specific immunotherapy for treatment of asthma (conditional recommendation/low-quality evidence).

Underlying values and preferences This recommendation places a relatively high value on possible reduction of asthma symptoms, and a relatively low value on avoiding adverse effects and limiting the cost of sublingual specific immunotherapy.

Remarks Sublingual specific immunotherapy may also be used in patients with asthma and concomitant AR for treatment of rhinitis. Resource limitations will have stronger implications for the implementation of this recommendation.

In addition to providing the rationale for the recommendations, evidence profiles—that is, systematic tabular summaries of the evidence underlying each recommendation—accompany each recommendation (see online appendix to [6••]). The recommendation provides the necessary transparency so that users of the guideline can understand the rationale and, if appropriate, deviate with their patients from the recommended course of action.

While government-sponsored guidelines and organizations such as the WHO are increasingly responding to the demands and challenges for transparency and explicitness [7, 8], these characteristics are also becoming an expected standard for guidelines that are developed by professional societies and similar efforts. The recent World Allergy Organization Guidelines on Cow's Milk Allergy Management serve as another example of guidelines in allergic disease that achieve a high degree of transparency [9, 10].

Funding of Guidelines

Guideline development itself is resource intensive. However, a systematic summary of the best available evidence, ideally in the form of a recommendation based on a systematic review, is a *sine non qua* for evidence-based practice. We recently suggested examining new models for funding of guideline development and implementation that combine resources from funding organizations, professional societies, governmental agencies, and patient interest groups and manage revenues [11]. We emphasized that “funding organizations supporting the fight against allergic diseases around the world must recognize that generating knowledge, for example through clinical trial research, by itself is insufficient for improvement of patient care if it is not followed by appropriate systematic evidence summaries of all research and appropriate guidance development” [11].

We also recommended that a large proportion of the required resources could be generated by avoiding overlap of current expenditures. Professional societies produce a large proportion of clinical practice guidelines through various funding models. An international collaboration of organizations relevant to allergic disease, such as ARIA or the Global Initiative for Asthma (GINA), will require new models for funding for best guidance development and even broader collaboration with other guideline developers. These models should include multiple stakeholders and their contributions to developing, updating, and implementing clinical practice guidelines and be free from unmanaged conflict of interest (COI).

Many professional societies and other groups developing guidelines rely on commercial sponsors to cover some or all of these costs. The perception that for-profit commercial entities, especially pharmaceutical and medical device companies, could have influenced the conclusions and recommendations of a clinical practice guideline committee could in turn undermine the credibility of the guidelines and the group that produced them [12, 13]. A study of the US Food and Drug Administration advisory committees reported that committee members regularly disclose financial interests of considerable monetary value but might not be recused from the committees. The authors discovered a weak relationship between conflicts with competing companies and voting behavior overall [14].

Some authors have requested that professional medical organizations reject all industry funding for practice guidelines [13] and that guidelines group members be held to the most stringent COI standards [15]. An Institute of Medicine report suggests that adequate firewalls between funders and those developing guidelines must exist [16], but there was no consensus regarding whether all sources of funding should be disclosed by guideline developers (eg, from journal advertisement). However, there was consensus that there should be no direct industry funding of clinical practice guidelines and that there should be increased public funding of systematic reviews and clinical practice guidelines [16].

Explicit Consideration of Conflicts

Financial, intellectual, and other investment increases the risk of biased judgement about a topic of interest, a concept generally termed *conflict of interest*. Several organizations have defined COI. The Institute of Medicine's definition is broad: “A conflict of interest is a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest” [17]. A recent comprehensive review of COI policies of organizations developing guidelines

yielded the following definition: “a divergence between an individual’s private interests and his or her professional obligations such that an independent observer might reasonably question whether the individual’s professional actions or decisions are motivated by personal gain, such as financial, academic advancement, clinical revenue streams or community standing,” or “a financial or intellectual relationship that may impact an individual’s ability to approach a scientific question with an open mind” [18]. The latter definition makes the inclusion of potential intellectual conflicts more transparent.

That COI can misinform health care decision makers is widely recognized [19, 20]. Omission of consideration for COI can damage an organization’s reputation or require time-consuming processes of dealing with perceived influence of COI [12, 21–28]. Declaration and management of COI is therefore of increasing importance for medical professional societies and other organizations developing practice guidelines [29–32].

Financial COI is the best known type of COI and typically is a result of direct financial benefit related to topics discussed or products recommended in guidelines. However, indirect financial interests are a reality, as academic advancement can be related to topics discussed in guidelines and that may be related to intellectual conflicts of interest.

Therefore, intellectual COI is another type of more recently recognized conflict that results from a guideline group member being invested in his or her intellectual work [18]. Examples include authorship of original studies and peer-reviewed grant funding directly related to the recommendations under consideration [18]. Additional types of COI include academic conflicts (eg, competition for funding) and conflicts related to clinical revenue streams (eg, from performing an advanced diagnostic procedure, such as nitric oxide testing in asthma when it is considered for making a recommendation).

The question arises as to why conflicted individuals are not categorically excluded from guideline development. There are several possible reasons. The most knowledgeable individuals are frequently conflicted because of their expertise in the area of interest. These “experts” often possess unique insight into appropriate health care questions to be asked in guidelines. Furthermore, through involvement in research, they may possess unique insight into aspects of the existing evidence, such as study design and decisions made during conduct of studies. Although GRADE does not recognize expert opinion as a form of evidence (but rather as an interpretation of evidence), the unsystematic observations of experts, however, in particular for rare conditions, could provide the best, albeit very low-quality evidence available on a topic. Interest in the subject matter can lead to both COI and the willingness to provide service to guideline developers, such as professional

societies. Such individuals may be instrumental to good guideline development because of the unique insights they provide. Conflicted experts frequently can offer their services (ie, evidence synthesis and work on guidelines) without direct compensation because they have secure academic positions and because of their interest in the field (which does not mean that no funding is required, as academic institutions provide the indirect funding under those circumstances!).

The key is to manage the potential COI appropriately, which can range from informal consultation and exclusion from a group to participation without influencing recommendations. Approaches to doing this were described in a policy of the American Thoracic Society that was established following a review of the COI policies of various organizations [18]. An operationalization of this approach was achieved in a WHO guideline on avian influenza (and subsequently has been applied by many WHO guideline panels), in which nonconflicted methodologists prepared evidence summaries and wrote the first draft of the guideline [7, 33]. A further implementation including a clearer separation of nonconflicted methodologists from the influence of potentially conflicted experts is currently undertaken by the executive committee of the American College of Chest Physicians Antithrombotic Guideline [34]. In this latter approach, nonconflicted methodologists also led the formulation of recommendations in collaboration with experts who may have been conflicted to a degree that would not preclude them from participating but may have precluded them from actually formulating the recommendations. Because conflicts are sometimes unavoidable, to deal with COI, participants in guideline development should submit written disclosures of all potential interests that may cause a COI before becoming involved.

Disclosure should be made through a standard form, ideally through a uniform online process that could span across organizations and must go beyond the declaration used by the International Collaboration of Medical Journal Editors.

However, what should the disclosure statement include? An example of the content follows: disclosure of any direct financial benefit derived from work performed for for-profit companies (per company), or any direct financial interest or investment in industry (per company) over a time period that precedes the participation and generation of any future income. The type of received benefit (see American Thoracic Society policy above) to report includes the following:

- Employment by a commercial entity
- Consultancies
- Board or advisory board participation
- Lecture fees (honoraria)

- Expert witness fees
- Industry-sponsored grants, including contracted research
- Patents received or pending
- Royalties
- Stock ownership or options, including sector mutual funds with areas of concentration in an industry or industries relevant to the activity
- Other personal financial interests.

There is agreement by many guideline developers that financial relationships should be disclosed as detailed amounts. Publication of dollar amounts will enhance transparency. Disclosures and conflicts should be reviewed by those managing COIs in an ongoing manner. All participants (committee/group members and/or presenters) should be asked and reminded to consider their own conflicts and conflicts of others during discussions and decision making. Participants should abstain from discussion and voting if they or a sizable proportion of the other participants identify a COI. The chair of the group should be free of relevant COI.

Challenges: Observational Studies, Diagnostic Test Accuracy Studies, Decision Modeling, Values and Preference Integration, and Finding Consensus

One of the evolving challenges in guideline development is the appropriate consideration of the mix of randomized controlled trial evidence and observational studies. Although the general framework for the assessment of the quality of evidence is well-described by the GRADE approach and does not differ for these different study designs, there is a requirement for further work that provides guidance for the assessment of observational studies with regard to the limitations of design and execution, also known as *risk of (internal) bias domain*. These efforts are ongoing, but agreement on approaches will help guideline developers. Efforts in this respect are currently made by the Cochrane Collaboration, the Campbell Collaboration, and the Agency for Health Care Research and Quality.

With regard to the recognition that observational studies can provide high-quality evidence, GRADE has made the considerations leading to greater confidence in results from observational studies explicit [35]. A frequently used example, published in a *BMJ* Christmas edition in 2003 as a humorous contribution to evidence-based medicine on the use of parachutes to prevent death from gravitational challenges, provides a good illustration [36]. No randomized trials were found in the search for studies leading to the conclusion that a decision to use parachutes would not be evidence based. It would be absurd to require random-

ized trials. However, it deals with a common misunderstanding that only research from randomized trials fulfills the requirements to act based on evidence. The paradigm of evidence-based medicine, recognized and implemented by the GRADE approach to assess the quality of a body of evidence, suggests a different approach. That is, when such confidence in effects of interventions exists, there usually is an evidentiary basis that suggests this high confidence. In the case of parachutes, this evidence does exist. It is not the laws of physics (many early models and trials of parachutes based on such considerations failed miserably) that generate this confidence, but rather observations in the world (that is, evidence). In the case of parachute use, the observations that parachutes work in the overwhelming number of users suggest a large effect, indeed a very large effect. Although one could blindly rely on the interpretation and judgment of experts about these observations, it is not challenging to support the statement with more systematically collected evidence. In fact, a simple search of the data of the US Parachute Association, which routinely registers use of parachutes (and is possibly doing a more thorough job than we find in many medical areas), reveals that in 2007, of 2.2 million attempts, there were only 18 deaths (and 821 injuries), yielding a relative risk reduction of greater than 99.9% (<http://www.uspa.org>). Such an effect would raise the quality in the GRADE approach to high quality, indicating that there is no need for randomized trials to further increase our confidence. Thus, it is not the belief in the laws of physics alone but observations that raise an observer's confidence. However, such large effects are rare for medical interventions, and examples are far and few between. Oral contraception for the prevention of pregnancy is one of the rare examples. Examples in single patients based on before-and-after assessment have been provided by Glasziou and colleagues [37]. Allergen avoidance in the face of demonstrated severe allergic reactions, such as to peanuts or cow's milk, provides an example in the field of allergy. However, the interventions to achieve allergen avoidance would need to be evaluated to determine whether they achieve this degree of risk reduction. The example of large effects demonstrates that observational study designs can provide high-quality evidence, but an assessment of the quality of evidence is required.

Using observational studies to develop appropriate baseline risk estimates, a requirement for developing recommendations, is another field of study that will influence how guidelines will be developed. Furthermore, users of guidelines are to expect progress in the development of guidelines based on diagnostic test accuracy [38].

The formulation of recommendations requires the integration of values and preferences, as described in the example above [39, 40]. Unfortunately, studies that systematically evaluate underlying values and preferences are

rare. The use of evidence and transparent description of evidence does not eliminate the requirement for consensus methods during the formulation of recommendations. The best ways of moving from evidence to recommendations need further refinement of consensus methods.

Impact Evaluation

Oxman and colleagues [41] have requested that health policy decisions be followed by mandatory impact decisions. Decisions about health care recommendations are frequently influenced or a direct result of or contributor to policy decisions, and it can be argued that impact evaluation related to policies resulting from guidelines should become a priority. Guidelines produced by organizations such as the WHO may fall into this area. It is obvious, however, that when guidelines are used for policy making, this should be preceded by an assessment of the quality of clinical practice guidelines. The AGREE (Appraisal of Guidelines Research and Evaluation) instrument that focuses on the assessment of the quality or validity of a guideline serves this purpose and is now in its second iteration [42].

Conclusions

In summary, guideline development is a multidisciplinary science requiring contributions and input from many stakeholders, including clinicians, methodologists, policy makers, patients, and many other groups, and better international collaboration. The methods for assessing the evidence and developing recommendations should provide transparency and explicitness, such as the one suggested by the GRADE Working Group. New models require, in addition to other efforts, careful development of funding structures, appropriate management of COI, and implementation, including frameworks for impact evaluation, as recently suggested by Oxman and colleagues [41] for health policy decisions. Finally, I refer readers with an interest in guideline development to two series of articles. First, a 15-part series to be published in the *Proceedings of the American Thoracic Society* focuses on methods for the development of clinical practice guidelines. Second, a 20-part series of articles in the *Journal of Clinical Epidemiology* describes the GRADE approach and its application, including the development of recommendations in detail, for guideline developers [43].

Disclosure Dr. Schünemann is a member of the GRADE Working Group (currently co-chair) that developed the GRADE approach.

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