Author's response to reviews

Title: Improving the Use of Research Evidence in Guideline Development: 13. Adaptation, applicability and transferability

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Author's response to reviews: see over
Dear Editor,

Please find the detailed point-by-point reply to the above cited manuscript on the following pages. Our responses are labeled as “response”.

We appreciate everyone’s time and effort.

With kind regards,

Holger Schünemann, MD, PhD
Reviewer: Dr. Lavis

General observations
The paper addresses an important issue and is both well reasoned and relatively well balanced. The authors do not address the particular challenges related to assessing the transferability and local applicability of policy guidance but instead treat all types of guidance in the same way. The paper is reasonably well written.

RESPONSE: Thank you for the assessment.

Major compulsory revisions
None

Minor essential revisions
1. The authors should ensure they consider whether their observations apply to all types of guidance, including policy guidance, or whether there are particular challenges associated with assessing the transferability and local applicability of policy guidance. The authors do not cite the paper by Gruen et al. in the Bulletin of the World Health Organization that provides criteria for assessing the transferability of systematic reviews or the paper by myself and colleagues in The Lancet that provides criteria for assessing the local applicability of systematic reviews. While the authors are focused on guidelines rather than systematic reviews, the papers by Gruen et al. and by us highlight some criteria that may also be germane to policy guidance.

RESPONSE: We have included reference to the papers cited above and clarified that our article applies to all types of guidance that are covered by the definition for “guidelines” we used for this series of articles. The term “guidelines” in this document should be seen in the broad sense referring to any guideline or recommendation related to healthcare that is relevant to the mission of the WHO, including public health and health policy recommendations (as described in the article 1 of this series). The revised text reads: WHO could adapt, commission or prepare systematic reviews that are required for guideline development in collaboration with organizations such as these that conduct systematic reviews and follow suggestions to make these reviews more useful for policymakers [32]. Lavis et al. demanded that donors and international agencies can encourage more informed public policymaking by supporting national and regional efforts to undertake systematic reviews and assess their local applicability, and by supporting regional or worldwide efforts to coordinate review and assessment processes [33].

2. The authors use the phrase "adaptation, applicability and transferability" in their title yet the authors touch only briefly on transferability (in the context of discussing whether WHO should identify and endorse high-quality guidelines that are widely transferable) and instead focus on how local efforts are needed to assess the local applicability of global recommendations and (if warranted) to adapt them locally (ideally with some support by WHO). The authors should consider changing the title to something like "assessing the local applicability of and adapting guidelines" and making clear that they are otherwise discussing transferability in only two ways: first, as a source of criteria for assessing local applicability, and second, in the context of the particular situation where WHO wishes to identify and endorse high-quality guidelines.

RESPONSE: We have searched the literature on other aspects related to transferability. These reviews were conducted to answer the key questions for the WHO. We believe we covered the whole range of transferability for the WHO based on its needs for this series of articles (in regards to guidelines) and what is known about it. We are not certain we understand what in particular we would have missed.

Discretionary revisions
3. The authors should address a number of minor wording and formatting issues:
RESPONSE: We have considered these points carefully. The whole article has been reformatted based on considerations for the other articles in this series.
a. The authors use the adjectives "international" and "global" a great deal (sometimes as synonyms and other times in ways that suggest they may interpret the words differently) and sometimes in ways that are difficult to understand (e.g., is an "international scientist" someone who works for an international organization or participates in international meetings? Are "international users" a group outside the jurisdiction where the guideline was developed?). The authors may want to use the adjective "global" when referring to recommendations and avoid many if not all uses of the adjective "international."

RESPONSE: Thank you for this comment. We have now inserted a definition for the word international and used it consistently. International has been defined as “coming from, concerning or belonging to at least two or all nations”.

b. The authors use the words "transferability" and "applicability" interchangeably. For example, in the abstract the authors say that "factors that influence the applicability of recommendations across different settings" whereas given their other use of words they more likely mean "transferability" here. And on page 4 the authors say that "guidelines are locally applicable or adaptable across settings" whereas given their other use of words they more likely mean "transferable across settings or adaptable." Also, the authors sometimes use the word "generalizability" (e.g., on page 8) and don't make clear whether they use the word as a synonym for "transferability."

RESPONSE: Thank you again. We made clear that we use the terminology more consistently. However, when we cited specific texts (e.g. page 8 citation of SIGN) we referred to the original wording "generalizability".

c. in the abstract the authors provide a list of other types of information needed to make recommendations and it would help the reader if they always maintain the same ordering as in other papers -- "factors that may modify effectiveness in specific settings, need (prevalence and baseline risk or status), availability of resources, costs, and values" -- and as elsewhere in the text;

RESPONSE: We modified this as suggested by the reviewer.

d. in the abstract the authors refer to WHO's role in providing local support for implementing recommendations but they never return to this issue which, while critically important, seems beyond the scope of this paper (and hopefully the focus for another paper in the series);

RESPONSE: We now return to this issue more clearly and describe that this is part of another paper in this series.

The revised text reads: Detailed guidance on appropriate methods for adapting guidelines would help WHO guideline groups to adapt existing guidelines, when this is appropriate. Implementation is topic of another paper in this series [36].

e. on page 6 the one-sentence paragraph on HIV guidelines seems awkwardly placed;

RESPONSE: Thank you. We moved this section to the appropriate section.

f. on page 10 the authors refer to analyzing existing guidelines for guidelines yet the background section reads as if it includes the results of this undertaking (instead of being included in the Findings section);

RESPONSE: We made clearer what the objectives were and how the background section was developed.
The revised text in the introduction reads:
In this paper we addressed the following questions:
• Should WHO develop international recommendations?
• What should be done centrally and locally?
• How should recommendations be adapted?

And in the methods it reads: For this review we analyzed existing guidelines for guidelines of national or international organizations to identify processes that these organizations use to adapt guidelines locally beyond what was known for existing organizations as described in the background section.

g. on page 12 the authors introduce the acronym LMIC without having introduced it before;

RESPONSE: The term had been defined on page 8.

h. on page 13 the authors provide a list of examples of ways that WHO could develop capacity but the list is ordered differently from the one provided in the abstract;

RESPONSE: We believe the order is congruent – exact overlap is not possible because the findings section is somewhat more detailed.

i. on page 13 the word guidelines appears to be missing after the phrase "Who global HIV/AIDS;"

RESPONSE: We fixed this mistake.

j. on page 14 the authors may want to drop the unnecessary phrase "help to ensure that this was done well, and help to address considerations or adaptation in new guidelines;"

RESPONSE: We agree.

k. on page 14 the authors introduce two approaches for identifying candidate guidelines for local adaptation but they separate the brief mention of each approach with a paragraph that doesn’t clearly pertain to either approach;

RESPONSE: The paragraph Dr. Lavis refers to described the first approach and we made this clearer.

l. on page 14 the authors introduce figure 2 but I couldn't find where they had introduced figure 1;

RESPONSE: It had been introduced on page 9.

m. on page 14 the authors mention involving consumers but not the policymakers and other stakeholders who may have much to say about policy guidance.

RESPONSE: We fixed this mistake and included the suggested groups.
Reviewer: Ian Graham

General
The paper addresses a topic that is increasingly being recognized as important if improvements in the uptake of guidelines are to occur.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. It may be helpful for readers less familiar with the topic to be explicit that some models of adaptation have been developed by/for guideline developers (eg SIGN, the NZ and ADAPTE approaches) and other have been developed for use more by the local implementers or end user (the guidelines evaluation and adaptation cycle). While both approaches have similar goals the focus is different.

RESPONSE: We included this suggestion.

The revised text reads:

The other as of yet unpublished approach (ADAPTE) by GIN is similar to the PGEAC approach [16, 17]. This approach is still under development and undergoing pilot testing. Whichever adaptation process is chosen the process should be made explicit, undergo review by peers, and involve consumers, policymakers and other stakeholders who may provide input about policy guidance. These models of adaptation have been developed for use more by the local implementers or end user (e.g. PGEAC) and for guideline developers (e.g. ADAPTE approaches). While both approaches have similar goals the focus is different.

2. Page 12 - 1st para - define what is meant by modifying factors (including system/organizational factors).

Similarly in Table 1 Q4, maybe useful to include an example of a system/organizational factor that could be affecting applicability. Differences in health systems is an important factor affecting the need to adapt some recommendations. The example of available human resources might be another example.

RESPONSE: We included an example.

The revised text reads: ....modifying factors (factors that modify translation of recommendation into practice such as microbiological resistance patterns) can be key components that influence the strength of a recommendation and should be specified in recommendations formulated by the WHO [29].

An illustration of the need for adaptation is provided by Rhinehart and colleagues who attempted to implement a nosocomial infection control program based on the US Centers for Disease Control (CDC) guidelines in an urban Indonesian public hospital. Adoption of unmodified CDC guidelines was impeded by modifying factors such as conditions of the physical plant, absence of an infection control infrastructure, limited sterilization capabilities, lack of clinical microbiologic laboratory support, and the expense of single use medical devices. After on-site evaluations, CDC guidelines were extensively modified so that they were appropriate for local conditions and culture [30]. After implementation, many physical changes had been accomplished, and handling of reusable and disposable medical devises had improved considerably although adoption of clinical practice policies was incomplete.

3. Figure 2 - please use the figure from the Graham et al 2005 paper as this is the latest version of the PGEAC and includes under the adaptation step- assessing guideline quality, currency and content.

RESPONSE: We used this figure.
Discretionary Revisions (which the author can choose to ignore)

1 P12-13- what should be done centrally and locally? a discussion of the role of GIN might be warranted as much of the motivation for developing this group was to reduce duplication in guideline development by finding ways to share reviews and data tables etc.

RESPONSE: We have mentioned GIN as being one of the potential key resources for WHO.

2 P13- 1st para- could perhaps also make explicit that while the review of the evidence and interpretation of the evidence should probably be similar regardless of the group doing/using the review (further justification for centralizing this), the recommendations based on the evidence/review may well be quite different depending on the circumstances and local factors of the group- and hence the need to expect local adaptation

RESPONSE: Thank you. A good suggestion to clarify this.

We added: Adaptation of recommendations is required because several judgments influence recommendations. Therefore, recommendations dealing with identical questions may differ between developers despite reliance on the same evidence. Implementation that would follow the process of adaptation is topic of another review in this series [36].


RESPONSE: We cited the book chapter.

4 P14- re discussion of ADAPTE- I believe that the ADAPTE group is actually independent of GIN although supported by GIN.

RESPONSE: We made this change.

5 Here is a reference to the ADAPTE process
http://meeting.jco.org/cgi/content/abstract/23/16_supp/6094
and I am also under the impression that Beatrice Fervers et al have a publication is press describing their adaptation process. It may also be of interest that Graham et al of the CPEAC and Fervers et al of the ADAPTE group have merged and retained the name ADAPTE. This group is finalizing a draft manual that will describe how to adapt guidelines and will be pilot testing the manual and the process shortly.


6 P15, 4th line- might be useful to also say why involvement of consumers is desirable (eg their values are important)

RESPONSE: We included this.
7 P15 - further work, some thoughts on how GIN might be engaged in the process might be helpful

RESPONSE: We have shied away from making specific reference to GIN here, but are emphasizing that collaborations in general should be sought.

8 The official web address for the AGREE instrument should be provided- www.agreetrust.org

RESPONSE: Done.

Reviewer: Metin Gulmezoglu

General
General comment: I think the paper makes good suggestions about how the adaptation process can be conducted in a more explicit and transparent way. I am not sure about the relevance of question 1 because that is within the WHO mandate and there are probably reasons for it that are still valid. A more appropriate question would be how can WHO do a better job at this and attain the current best standards. It should also be acknowledged that the adaptation issues are much more complex for WHO than for Scottish or New Zealand guidelines.

RESPONSE: Thank you for the encouragement. We have emphasized in the revised version that the reasons for international recommendations – as the reviewer indicates – are still valid. The question whether WHO should develop recommendations for all countries is valid but there was a need to examine this question given the many judgments that are involved in making international recommendations. We did include how WHO can make the process better. We also included the following the background section:

In this background section we provide selected examples of organizations that have specifically provided information relevant to the key questions we posed although the WHO is unique in that its mandate includes the more complex task of providing international guidance.

The paper quotes the GWG of WHO but does not refer to the fact that these guidelines have not been operationalised (or implemented) since they were announced several years ago (it is mentioned in other papers but not on this one)

RESPONSE: We have included this limitation.

The inserted text reads: However, one of the limitations of the GWG is that they have not been operationalized or implemented consistently. Only few WHO guideline processes have followed the GWG [7].

The search strategy outlined is unlikely to capture the literature related to the question: Should WHO develop international recommendations? Further, this is probably not the right question. The WHO mandate is to develop international guidelines in fulfilling its role as a standard setting organization and the question is whether the WHO is doing a good job at it? My response would be that WHO is probably doing some good and some not so good. The problem is that there is currently no system or structure to do this or even to monitor and evaluate how good this is being done. These issues are slightly different to the local adaptation issue though. Nobody in WHO would argue with the importance of adaptation to local needs and most WHO guidelines would probably include some plans for adaptation. The paper makes some important recommendations on how that task can be done better.

RESPONSE: The question we focused on was whether WHO should develop international recommendations. Despite this being one of the WHO’s mandates, the mandate can be questioned and this is what we did. We identified methodological literature and examples through our search that dealt with this question. Again, the question whether WHO is doing a good job was not the focus of our project (while suggestions how it can be done were).
Naturally, when there are likely to be differences in local circumstances the generalizability (or applicability) of an international guideline is going to be more limited. However, that does not necessarily mean that international guidelines should not be issued.

RESPONSE: We agree, but we searched for evidence whether this can be done and whether there are strong reasons against it. We did not find strong evidence against international recommendations but developed strategies based on the findings how this can be done better.

The major problem is how to issue evidence-based guidance when there is a culture of expert-opinion based decision-making and that is more affordable? The solution, in my opinion, is to create an organization-wide initiative to improve the standards.

RESPONSE: We agree. This is part of another article in this series.

The other problem related to adaptation is often WHO technical departments publish authoritative guidance documents aimed at peripheral levels of care. These guidelines often make assumptions about what is available, what is doable and the local adaptation processes (without necessarily involving all major stakeholders). These guidelines are also (sometimes necessarily so) fairly basic and have the problem of having the (standard) bar too low to make sure that the guidance is applicable to poorest settings. Often, these guidelines lack a description of the evidence-base and explicit descriptions of the judgements utilized.

RESPONSE: We also agree on this point. We have noted that there should be better cross-referencing to the other reviews in this series that deal with this issue. We have done this now.

Minor points:
--Redundancy: I was not sure of the meaning where it's used. It may be better to use duplication?

RESPONSE: We changed this to “duplication”

Reviewer: Jako Burgers

General
This is a well-written paper discussing the opportunities and barriers of guideline adaptation in the WHO context. Last years, the development of clinical practice guidelines on the international level has not been encouraged because of local factors influencing healthcare decisions. (Eisenberg JM. Globalize the evidence, localize the decision: evidence-based medicine and international diversity. Health Aff (Millwood) 2002;21:166-8. De Maeseneer J, Derese A. European general practice guidelines:a step to far? Europ J Gen Pract 1999;5:86-104). Therefore, adaptation of guidelines is an interesting approach to transfer global evidence in recommendations for the own context. However, the WHO is an international organisation that is active in international guideline development. The authors could be more specific in which cases this is still a good option, for instance by providing a table with topics for international guidelines (e.g. prevention and management of infectious diseases, prevention of cardiovascular disease, etc.).

On page 14, the authors describe two approaches to guideline adaptation (Graham et al. and ADAPTE). However, these two groups have merged since January 2006. They are preparing a manual for guideline adaptation integrating both approaches (draft available for comment in summer 2006). The results of the preparatory literature review, similar to this paper, will be published in the International Journal for Quality in Health Care this year.

RESPONSE: Thank you for this comment, suggestion and up to date information. We have references the paper by Fervers. One of the other reviewers, the author of PGEAC, did not feel that ADAPTE and
PGEAC have quite merged yet. Until this has happened we have left this as a speculation citing this reviewer. We ask the reviewer to confirm that this is fine.

**Major Compulsory Revisions**

The paper answers three questions: 1) should WHO develop international recommendations, 2) what should be done centrally and locally, 3) how should recommendations be adapted. Q 1 and 2 are quite normative and can not be easily answered by findings from literature. The literature review predominantly concerns Q 3. However, it is not clear in the paper how the findings from literature were used in the answers.

RESPONSE: In regards to questions 1 and 2 we searched literature for evidence against issuing international recommendations and for examples of international recommendations that have been successfully used. We provided these examples. The reviewer is quiet right that we have not made it clear how the findings were used. We have modified the methods section to describe this better. The modified section reads:

The methods used to prepare this review are described in the introduction to this series [27]. For this review we analyzed existing guidelines for guidelines of national or international organizations to identify processes that these organizations use to adapt guidelines locally beyond what was known for existing organizations as described in the background section. We also searched PubMed using “guideline” AND “adaptation OR applicability OR template OR transferability” (MESH headings/keywords) for studies and systematic reviews comparing different strategies to increase adaptation, acceptance and transferability (we identified 637 citations of which 203 citations were identified as systematic reviews using the clinical queries filter for systematic reviews). We reviewed the titles of all citations and retrieved abstracts and full text articles if the citations appeared relevant to the topic. We checked the reference lists of articles relevant to the questions and used snowballing as a technique to obtain additional information. We also searched the Cochrane Library and Google for articles and methods related to guideline adaptation (“guideline adaptation”). In addition, we searched databases maintained by the Agency for Healthcare Research and Quality (AHRQ, [28]) and the Guidelines International Network (GIN, [29]). The answers to the questions are our conclusions based on the available evidence, consideration of what WHO and other organisations are doing and logical arguments.

Moreover, the number of individual studies found (p. 11) nor the selection process is described. Thus, this is not a systematic literature review. Studies found were used as illustrations/examples and not as empirical evidence. I do not object to this approach, but the authors should avoid the suggestion that this is a literature review. I would suggest to provide the number of selected papers in addition to the number of citations (p. 10) OR to leave these all out.

RESPONSE: We agree that we should have provided this information and that we did not perform a “Cochrane style” systematic review and have not identified this paper as such. We provided the details in our answer to the prior comment.

Furthermore, the headings ‘Findings’ and ‘Discussion’ are misleading as there is no clear cutoff between these. I would suggest to leave out the heading ‘Findings’ and to change the heading ‘Discussion’ in ‘What should the WHO do?’ The latter could also include ‘Further work’.

RESPONSE: As this paper is part of a series of reviews, we have not changed the headings but have made the structure clearer. The revised section reads:

**Findings**

We did not identify systematic reviews addressing the key questions specifically. We found individual studies and projects published in the peer reviewed literature and on the Internet that we will use to illustrate the responses to the key questions.

**Minor Essential Revisions**

p. 5: the term ‘health interventions’ should be specified. These could include diagnostic procedures, drugs, surgical interventions and psychosocial techniques which require specific
professional education and skills. Therefore, this is not only an economic issue. Resources include costs, materials as well as skilled professionals. These should be available locally.

RESPONSE: Thank you. We inserted the following text:

This requires explicit recognition that resources to provide health interventions (including diagnostic procedures, pharmaceuticals, surgical interventions and psychosocial techniques) are limited.

p. 7: it is not clear how the authors selected the organizations (SIGN, NZGG, USPSTF). I agree with this selection but why these? Why not NICE? The selection should be motivated.

RESPONSE: The selection was motivated by specifics that were available and were most relevant to the question. We inserted the text:

In this background section we provide selected examples of organizations that have specifically provided information relevant to the key questions we posed although the WHO is unique in that its mandate includes the more complex task of providing international guidance.

p. 7: the AGREE Instrument does not contain questions but items that can be scored using a four-point Likert scale. The domain ‘applicability’ only includes three items. However, the other domains also have items linked to applicability. For instance, ‘The target users of the guideline are clearly defined’ and ‘The guideline has been piloted among target users’ in the domain ‘Stakeholder Involvement’, ‘The health benefits, side effects and risks have been considered in formulating the recommendation’ in the domain ‘Methodology’ and ‘The guideline is supported with tools for application’ in the domain ‘Clarity and Presentation’. The grouping of the items in the domains was determined based on the results of factor analysis, but this classification is arguable.

RESPONSE: We changed “questions” to “items”.

We modified the section to:

The items that are part of the instrument of the AGREE collaboration [14] include the following three items most relevant for the assessment of guideline applicability:

- The potential organisational barriers in applying the recommendations should be discussed.
- The potential cost implications of applying the recommendations should be considered.
- The guideline should present key review criteria for monitoring and audit purposes

p. 8: I would remove ‘(objective)’ because the assessment of quality cannot be fully objective. That’s why two independent reviewers are preferred in systematic reviews.

RESPONSE: We agree. We replaced objective with transparent.

Discretionary Revisions
p. 4: reasons for not adopting publishing guidelines: ‘lack of ownership’ could be added

RESPONSE: We only cited the main reasons based on that publication.

p. 7-10: subtitles may help the reader (e.g. SIGN, NZGG, USPSTF)
p. 8: ref 20: I would refer to SIGN 50: A guideline developers’ handbook.
RESPONSE: We included these two suggestions

p. 8: the concept of implementability of guidelines has been elaborated by Shiffman et al. (Shiffman RN, Dixon J, Brandt C, Essaihi A, Hsiao A, Michel G, O’Connell R. The GuideLine Implementability Appraisal (GLIA): development of an instrument to identify obstacles to guideline implementation. BMC Med Inform Decis Mak 2005 Jul 27;5:23.) This article can also be used elsewhere in the text.

RESPONSE: We cited this reference. Implementation is dealt with in another review of this series.