Author's response to reviews

Title: Developing Clinical Practice Guidelines: Types of evidence and outcomes; values and economics, synthesis, grading, and presentation and deriving recommendations

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

Thank you for the reviewers comments on our three linked articles:

MS: 2134316586562065. Developing Clinical Practice Guidelines: Target audiences, identifying topics for guidelines, guideline group composition and functioning and conflicts of interest. Martin Eccles, Jeremy Grimshaw, Paul Shekelle, Holger Schunemann and Steven Woolf

MS: 4444259685620621. Developing Clinical Practice Guidelines: Types of evidence and outcomes; values and economics, synthesis, grading, and presentation and deriving recommendations. Steven Woolf, Holger Schunemann, Martin Eccles, Jeremy Grimshaw and Paul Shekelle

MS: 1983721217561132. Developing Clinical Practice Guidelines: Reviewing, reporting, and publishing guidelines; updating guidelines; and the emerging issues of enhancing guideline implementability and accounting for comorbid conditions in guideline development. Paul Shekelle, Steven Woolf, Jeremy Grimshaw, Holger Schunemann and Martin Eccles

We have prepared a single response that covers all three articles and is uploaded with each of them.

You also asked us to justify the classification of the manuscripts as Methodology papers. Although we accept that the content of the manuscripts does not necessarily map well onto the indicative content of Methodology pieces in your Instructions to Authors we feel that the content is a presentation (and discussion) of methods and that, for a reader coming across them, they would have a better indication of their content from their being labelled as Methodology rather than as Debate. We would therefore like to keep them labelled as Methodology papers.

Reviewer 1 Brouwers

General Major Feedback for the Series

This series was a well written and easy to follow collection of papers related to guideline development. The general comments apply to each of the three papers in this series.

What Is The Gap?

While the three documents are well written, the most significant limitation with this series is whether another series or publication on the development of clinical practice guidelines is actually required. As referenced in this series, there are several publications of the "how-to" of guidelines by several guideline development groups and several research teams (examples include 2006 series in Health Research Policy Systems; 2008 BMJ GRADE methodology series; 2010 and 2011 IOM document and the Trustworthy Guideline work). Indeed, several of the authors in this series have contributed to these more current publications. In addition, and also as referenced by the authors, there are several on-line resources and manuals with both conceptual and practical elements to advance the guideline field including comprehensive procedure manuals by guideline development groups (examples include National Institute for Health and Clinical Excellence: Guidance [http://www.nice.org.uk/guidelinessmanual]; CMA Handbook on Clinical Practice Guidelines [http://www.cma.ca/multimedia/CMA/Content_Images/ClinicalResources/PDF/English/CPGHandbook.pdf]; Cancer Guidelines Resource Centre [http://www.cancerguidelines.ca/Guidelines/index.php]; and the IOM work described above).
Thus, while this series likely does update the original messages that authors provided in 1999, I am not convinced it provides an update for the field or advances our thinking in ways that are different from other recent publications and resources that are available and targeted to a range of stakeholders.

In general, this series would be strengthened by identifying more explicitly what gap(s) it is filling or perhaps a more critical analysis of how the field has evolved since 1999 or perhaps an analysis of some of the current controversies in the field or priority areas for development.

As an extension of the issues described above, it was surprising that some key papers or advancements in the guideline enterprise were not referenced. Some examples include:

- AGREE: Neither the original AGREE nor the AGREE II was mentioned (see agreetrust.org - but please note academic link this reviewer has with this work).
- Only some and not all of the 2006 Health Research Policy Systems series.
- CanIMPLEMENT (see http://www.cancerview.ca/portal/server.pt/community/initiatives_and_resources/473/cancer_guideline_adaptation_and_implementation_project)
- Guidelines International Network and its efforts around guideline methods, processes and the like (see http://www.g-i-n.net/).

Recognition of these works or a better understanding of why this work would not be included in the series is needed.

RESPONSE A number of considerations guided the writing of these articles. Firstly, despite the fact that our previous article on this topic was written in 1999 it is still being regularly cited. Under these circumstances we feel an update is important. Secondly, we were commissioned to write the supporting paper on developing guidelines to inform the most recent Institute of Medicine report. Whilst some of what we wrote appears in the report, not all of it does and we feel a more detailed treatment of these issues is justified. Thirdly, we are writing this for an interested general audience, rather than an audience of knowledgeable guideline developers such as the reviewer; we appreciate that we did not make this clear and have now amended the text of the introduction to reflect this.

Whilst it is true that some content has not changed much over the intervening years we would argue that we have updated and extended the text considerably. In Paper 1 the consumer involvement section is updated and new (largely thanks to the reviewers comments) and the conflicts of interests section is new (in this context). The evidence grading content of paper 2 is new in this context (though it has, of course been written about extensively in its own right) as is the analytic framework text (in this context). Much of the content of paper three (updating, implementability, dealing with co-morbidities) is new. Finally, the context for guideline production has changed (with the advent of guideline clearing houses and, in the UK, the National Institute for Health and Clinical Excellence) and the papers reflect the impact of this evolving context.

In support of our position, whilst we agree with the reviewer that there are a range of publications and web based resources (some of which she identifies) they are either not applicable to guideline development (e.g. AGREE) or are not easy to find. A Google search does not identify the resources the reviewer offers but does identify our 1999 article. In addition, it is our experience that citing web links is problematic – a number offered by the other reviewer relating to the organization in which he worked...
did not produce what he suggested they would. However, we accept that we have not framed the changed landscape of guideline development and, in the background to the first paper we have now extended the text to include a broader description of the landscape including a number of the references/organizations that the reviewer mentions.

Since it was published, the methods of guideline development have progressed both in terms of methods and necessary procedures and the broad context for clinical practice guidelines has changed. To help users identify and choose guidelines there has been the emergence of guideline clearing houses (such as the AHRQ Guideline Clearing House (www.guideline.gov)) that identify and systematically characterize guidelines on a number of domains and the development of robust guideline appraisal instruments such as the AGREE tool (ref). There has been the appearance of large scale guideline production organisations both at a national level (such as the UK National Institute for Health and Clinical Excellence or Scottish Intercollegiate Guidelines Network) and a condition level (such as the Ontario Cancer Guideline Program). There have also been relevant reports (that some of us have participated in) for the World Health Organisation and professional societies (Schünemann HJ, Woodhead M, Anzueto A, Buist AS, MacNee W, Rabe KF, Heffner J. A guide for guidelines for professional societies and other developers of recommendations: an official American Thoracic Society (ATS) / European Respiratory Society (ERS) Workshop Report; forthcoming). Such organizations and those interested in producing and using guidelines now have a high profile society in the Guidelines International Network (http://www.g-i-n.net/). Against this background it seems timely to, in a series of three articles, update and extend our earlier paper on the methods of developing clinical practice guidelines.

**Positions and Support for Positions**

At times, the core references to support a position are those written by the authors of this series. This in itself is not a problem - these are very often important pieces that contributed to knowledge about guidelines. However, this series would be strengthened by considering additional points of view. Similarly, at time, the references are supported by seemingly dated references. And finally, at times, aspects of the methods or positions read as statements of fact or as a methodological standards rather than examples of good and reasonable strategies. Just a point of caution to the authors; as they note, for many steps and or components in the guideline enterprise, there are little data to support one position over another. Thus, the papers would be strengthened by addressing these issues and ensuring choice of language aligns with the evidence and the alternative positions available. Specific examples are provided in the feedback for the individual papers.

RESPONSE Thank you for this helpful comment. We have reviewed the wording throughout and addressed the specific issues as indicated in the point responses for the individual papers.

**Style.**

Given then is no page limit with IS, I would recommend the three independent papers be merged into 1. Backgrounds and abstracts are virtually the same. It is less
cohesive as three separate pieces. There are opportunities to make some sections considerably more succinct as some components that have been published at length elsewhere.

RESPONSE The reviewer is not correct in their assertion that Implementation Science has no length restrictions. The “About this journal” section sets out an indicative word limit of 6000 words per article. Accordingly, we have written three articles (linked by a common, short introduction) from our initial report, each of which fits within this word limit. However, in order to allow readers to see them together we have suggested to the handling editor that these are produced as an article series and so would be presented together.

We appreciate the need for being succinct and have, in writing these articles, halved the volume of text from the original report; however, we have again gone through the text to identify further areas where we could express ourselves more succinctly.

PAPER 1.  Target Audiences, etc...

This is nicely written document. It addresses many of the key elements related to these steps. In addition to general feedback described above, the following are issues for consideration specific to this paper in the series.

1. The authors underplay the more contemporary role of guidelines as a tool to direct policy. This has implications regarding who is the key audience, the methods used to create recommendations, the type of evidence (or strength of evidence) that is being considered and the tensions that ensue. This paper would be strengthened by a deeper consideration of the issues and an exploration of health care systems that have grappled with these challenges.

RESPONSE We have further highlighted the fact that policy makers are amongst the secondary audiences for guidelines.

2. As described in the general feedback section, there are areas in which positions or support for the positions should be thought through a wee bit more. An example in this paper would be the patient involvement section. With the exception of the 2006 Eccles citation, most of them are late 1990s. The paper could be strengthened by considering
   (i) some more recent advancements or examples such as:
       • Cochrane review by Nilsen 2006
       • Impending results of the review by Légaré et al Implement Sci. 2009 Jun 4;4:30.

   (ii) alternative methods of thinking about patient involvement
       • integrating existing research articulating patient preferences for specific care options in lieu of (or in addition to) direct patient involvement
       • the broader public engagement literature and its potential role in practice guideline development

RESPONSE Thank you for this helpful comment and the suggested references. We have substantially re-written the first half of the current text on consumer involvement. Specifically, the identified Legare protocol has now resulted in a published review which we have used to support the text in a number of places. The update of the Nilson systematic review is also used to (briefly) identify the broader issue of consumer involvement in healthcare decision making.

PAPER 2. Types of Evidence, etc...

1. As in paper 1, this is nicely written document, again addressing many of the key elements related to these steps. One of the most interesting elements in the entire series (and unique) and something that I believe may be less understood by guideline developers and researchers if the analytic framework. This was nicely positioned.

RESPONSE Thank you; no response needed.

2. The section on economic considerations was well done. However, at the end, I was not quite certain on the position of the authors in reconciling the IOM recommendation that “every clinical practice guideline should include information on the cost implications” associated with implementation from later descriptions recognizing varying methods of guideline development and varying roles and responsibilities of guideline developers (versus policy makers). This would have been an example of interesting debate (see general feedback above) that could be have been explored a wee bit further.

RESPONSE We have made some edits in response to this helpful comment. Firstly we have highlighted the fact that the IoM recommendation was aspirational and made in the knowledge that this was going to be, at best, very difficult and at worst impossible. Secondly we have added the following text immediately after in order to better contextualise this area of guideline development.

Although there is emerging practical experience this position has not really changed. In addition, it has also become recognized that issues of cost are much more likely to be health system specific (as compared to other areas of guideline development) and so, unless explicitly mandated (like the UK National Institute for Health and Clinical Excellence (NICE)), many guideline developers do not do this.

3. So too would have been the issue of language/wording of guidelines. Here, a deeper debate about contemporary challenges would have been welcome. For example, in the cancer field, there is a lot of guideline activity and many documents have been produced for issues in which good evidence exists. The challenge is where evidence is sparse and/or of poor quality and yet where advice (policy or clinical) is required. Is there a role for “weasel” words here so as to not overstate the definitiveness of the recommended action? How can language (or should language) be used to express the varied reasons behind why recommendations may be weak. This would be a really interesting debate.
RESPONSE Thank you for this comment. We agree with the issue and think we have addressed this in the current text. However, we have made some minor edits to try and highlight the issue.

4. The section on evaluation and grading is (again) very well written. It profiled the GRADE approach almost exclusively; this methodology has been written about extensively elsewhere. I believe this profile could be made considerably more succinct (with reference to these other publications). And I think this section would benefit from other models or examples of critical appraisal and grading, some of the controversies in this area, and some of the varying opinions on this matter.

RESPONSE Thank you for this comment. We had chosen to address the issue of other methods of grading evidence within the process cited by references 44 and 45 to which the interested reader can go. We have left this unchanged.

PAPER 3. Reviewing and reporting....

1. Again, this is a very nicely written paper.

RESPONSE Thank you; no response needed.

2. Like the analytical framework section in Paper 2, the accounting for comorbidities section in this paper was one of the more unique and interesting elements of the series and something that has not been fully considered or embraced in the guideline community (my impressions). More attention to this issue would have been welcome.

RESPONSE Thank you. We agree but we don’t think there has been anything more written about this. Under these circumstances we have tried to avoid going beyond presenting what has been published, though we have identified a forthcoming report offering some practical guidance for guideline developers (Fabbri LF, BoydC, Boschetto P, Rabe KF, Buist AS, Yawn B, Leff B, Kent DM, Schünemann HJ. How to integrate multiple comorbidities in guideline development: An official ATS/ERS Workshop Report. Forthcoming).

3. Also, while I realize a full analysis of strategies to facilitate implementation of guidelines was out of scope (versus, making guidelines more implementable) is out of scope, there may be value in referencing Cochrane’s EPOC group or some of the key systematic reviews on interventions in the section where the authors recommend development of relationships with those responsible for guideline dissemination and implementing evidence-based uptake strategies are required. Those are not listed in Table 3.

RESPONSE Thank you for this comment; we have taken the opportunity to add the text below to the preamble section dealing with implementability.

Strategies to promote the implementation of guidelines are beyond the scope of this paper but the interested reader is directed to the work of the Cochrane Collaboration Effective Practice and Organisation of Care Review Group in the Cochrane Library (www.thecochranelibrary.com).
4. The issues outlined in the general feedback are more relevant for this paper. In particular, what is the gap this paper is trying to fill?

RESPONSE See earlier response.

Reviewer 2: Tim Stokes
PAPER 1
1. This is the first of three papers that together constitute an overview of clinical guideline development that is both very timely and important. The authors are collectively the international leaders in the field of guideline development methodology and their work in the 1990s and subsequently has been very influential in forming the methods of national guideline developers such as NICE in the UK. There is a need to update the original work of these authors (BMJ 1999) and the paper uses relevant more recent publications to update key aspects of guideline development methods.

2. This specific paper clearly summarises its four areas. The comments below constitute discretionary revisions.

RESPONSE Thank you for these comments; they need no response.

3. Consumer involvement in guideline development (pp. 8-9). It is implicit in this section that patients can offer key questions the Guideline Development Group wish to review and also add their preferences in terms of what health outcomes are important to patients and need to be considered in the analysis. This is dealt with in paper 2 in the series but it would be useful to flag this point more explicitly here.

RESPONSE Thank you for flagging this. We have enhanced the text at the top of p9 as follows:

“Second, patients in general and lay people in particular bring a perspective to practice guidelines that clinicians and scientists may lack. They can offer key questions that a Guideline Development Group may need to review and also add their preferences in terms of what health outcomes are important to patients and need to be considered in the analysis. Their sensitivity to the concerns that matter most to those afflicted by a disease provides important context for decisions about the balance of benefits and harms and the importance of gaps in the scientific evidence.”

4. Managing conflicts of interest (pp. 15-17). It is accepted that there has to date been little published on how COI influence guideline development. Nonetheless, a number of national guideline developers, notably NICE in the UK, have considerable experience of handling these during guideline development and NICE publish a detailed policy on who such conflicts should be handled in terms of GDG chair and members that could be referenced here (see: http://www.nice.org.uk/aboutnice/whoweare/policiesandprocedures/policiesandprocedures.jsp?domedia)

RESPONSE Thank you for this comment. NICE, like many guideline developers, will have policies dealing with COI. Rather than preference a single guideline producer we
have left the text unchanged. The offered link went to NICE’s general policies as an organisation rather than to a specific document (though if we had to guess we’d have gone to the Managing guidance consultation comments – which seemed a little constrained for our context).

PAPER 2
1. This is the second of three papers that together constitute an overview of clinical guideline development that is both very timely and important. The authors are collectively the international leaders in the field of guideline development methodology and their work in the 1990s and subsequently has been very influential in forming the methods of national guideline developers such as NICE in the UK. There is a need to update the original work of these authors (BMJ 1999) and the paper uses relevant more recent publications to update key aspects of guideline development methods. It is aimed at a general readership and is at an appropriate level of detail.
2. This specific paper clearly summarises its key areas. The comments below constitute discretionary revisions (except 5 - minor essential).

RESPONSE Thank you for these comments; they need no response.

3. p. 6 intermediate outcomes, surrogate outcomes and surrogate measures. In the text only intermediate outcome and surrogate measure are explicitly defined. It would be useful to have a definition of surrogate outcome as well. It might be useful to reference this to standard epidemiological definitions here such as those of the IEA (e.g., Last, Dictionary of Epidemiology).

RESPONSE We think that this confusion has arisen from our slightly loose use of the words outcome and measure interchangeably. We have appropriately replaced measure with outcome (and surrogate outcome is defined) and hope that there is no longer any confusion here.

4. Incorporating economic considerations in guideline development. p.15-16. One major national guideline developer - NICE - does require that its Guideline Development Groups are required to make decisions based on the best available evidence of both clinical and cost effectiveness. It is noted that NICE clinical guidelines do routinely conduct de novo health economic modelling of key questions as well as review the existing cost effectiveness literature. It notes that "only rarely will the health economic literature be comprehensive enough and conclusive enough that no further analysis is required. Additional economic analyses will usually be needed (NICE Guidelines Manual 2009 7.1.3 - http://www.nice.org.uk/media/68D29/The_guidelines_manual_2009_-_Chapter_7_Assessing_cost_It would be helpful if this point was referenced.

RESPONSE We have amended the text of this section to read as follows:

Some guideline development organizations (e.g. the UK National Institute for Health and Clinical Excellence (NICE)) advocate the review of appropriate cost-effectiveness studies alongside the review of the clinical evidence, though, in their guideline development manual, they note that "only rarely will the health economic literature be comprehensive enough and conclusive enough that no further analysis is required. Additional economic analyses will
usually be needed.” The available “economic evidence” may be limited in terms of general applicability to the specific context of the clinical guideline but can be useful in framing the general bounds of cost-effectiveness of management options for a clinical condition and providing an explicit source for some of the assumptions that may have to be made.

In terms of the authors’ statement (p. 15) that "there is no clear role for a multi-disciplinary guideline development group in deriving recommendations around the clinical decision - the 'right decision' is produced by the model" this is debatable. NICE would argue that there is a clear role for the GDG in terms of deriving recommendations around the clinical decision and makes clear recommendations as to how to involve the GDG in this process (see 7.2.1 NICE GM 2009).

RESPONSE Thank you for clarifying this issue. We had focussed on the output side of the use of decision analysis and appeared to ignore the input side and the role of a guideline development group in this. We have amended the text to read:

For guidelines focused on a single decision it may be possible to incorporate economic data into a formal decision analysis framework. Traditionally, it is the province of health economics to model (combine, adjust, extrapolate, represent) intermediate clinical outcome data and data from other sources to explore the overall costs and consequences of treatment alternatives. In principle, it is possible to map clinical data onto generic quality of life scores, model the advancement of disease and produce cost per QALY estimates for each treatment decision. However, such a process contrasts with the above methods in a number of ways. Firstly, although they may have a role in informing the questions, values and assumptions that go into a model, there is no clear role for a multi-disciplinary guideline development group in deriving recommendations around the clinical decision - the ‘right decision’ is produced by the model.

5. wording recommendations. McDonald reference - not cited.

RESPONSE Thank you for flagging this; we have added the citation.

PAPER 3
1. This is the third of three papers that together constitute an overview of clinical guideline development that is both very timely and important. The authors are collectively the international leaders in the field of guideline development methodology and their work in the 1990s and subsequently has been very influential in forming the methods of national guideline developers such as NICE in the UK. There is a need to update the original work of these authors (BMJ 1999) and the paper uses relevant more recent publications to update key aspects of guideline development methods. It is aimed at a general readership and is at an appropriate level of detail.
2. This paper specifically addresses three timely issues (reviewing, updating and comorbidity).
3. The comments presented here constitute discretionary revisions.

RESPONSE Thank you for these comments; they need no response.
4. The section on peer review and consultation could benefit from some minor restructuring so as to separate out the process of asking for detailed comments from named individuals and professional societies and formal public consultation with all relevant stakeholders. It would also benefit from reference to appropriate guideline methods manual (e.g., NICE) that set out in detail their procedures here.

5. A number of national guideline developers, including NICE, put great stress on contestibility as a core principle of their work - and an important way of achieving this is a process for consulting with stakeholders. NICE relies on consultation with stakeholders (with an expectation that experts in the field will register through their organisation as stakeholders and comment) and external statistical and health economic peer review by an independent third party (NCCHTA www.nchta.org). Only occasionally, and when specifically indicated, does it seek additional external expert review from named individuals. Such individuals may be conflicted in terms of their interests - which will need to be declared. Reference could be made here to paper 1 and its discussion of COI.

RESPONSE Thank you for this helpful observation. We have edited the start of this section to read:

Only so many experts and perspectives can be represented on a guideline group. The review process provides an opportunity to elicit input from broader and important perspectives that the group itself cannot encompass but have important insights into the evidence (and its contestability) or the challenges of adopting recommendations. This can be divided into the two steps of invited peer review, where the reviewers are identified by the guideline developers on the basis of their perceived ability to contribute, and public consultation, where the document is open to comment from any interested party.

We have introduced the sub-headings “Invited review”, “Public Consultation” and “Dealing with peer review” and made minor adjustments to the text to correspond with these headings.

We have introduced the phrase “contestability” into the text (see above).

We have edited the text of the end of the section on “Invited review” to read:

The group’s procedures for selecting reviewers should pay attention to this consideration in choosing harsh critics who can articulate their scientific or clinical reasoning. It should also take note of the need to be explicit about conflicts of interest (as discussed in the first paper in this series). Inviting criticism from provider groups and specialty societies who are expected to be critical is also important.

We hope that we have satisfactorily dealt with the reviewers’ comments and the manuscripts are now suitable for publication.

Yours sincerely,

Martin Eccles & Paul Shekelle on behalf of all authors.