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.

As the comment from Reviewer 1 is common to all three we respond to that first and then give a point by point response to Reviewer 2’s comments on each of the three papers in order.

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
This was an exceptionally difficult series to evaluate. On the one hand, the papers themselves are well written and perfectly reasonable descriptions of practice guideline development issues. However, there is virtually nothing new. The series reflects a repeat of messages one can find in many other peer review publications, in guideline manuals, and on-line resources. There is no apparent gap that is being filled.

We are glad that this reviewer found the papers “well written and perfectly reasonable descriptions of practice guideline development issues”. We would contrast this reviewer’s overall comment with the opening comment of Reviewer 2 who states “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.”

We believe that we have done this and it is novel, drawn together into one place and presented for a general readership.

Whilst it is true that some of the content has not changed much over the intervening years we would argue that much of the content of paper three (updating, implementability, dealing with co-morbidities) is new. The evidence grading content of paper 2 is also new in this context (though it has, of course been written about extensively in its own right). 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 response to this we have amended both the Abstract and Background paragraphs to read as follows (“it” refers to an immediately preceding reference to our 1999 paper)

Since it was published, the methods of guideline development have progressed both in terms of methods and necessary procedures and the context for guideline development has changed with the emergence of guideline clearing houses and large scale guideline production organisations (such as the UK National Institute for Health and Clinical Excellence).

**PAPER 1**
**Reviewer 2:** Tim Stokes

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/68D/29/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 co-morbidity).

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.ncchta.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.