Author's response to reviews

**Title:** Guidelines for randomized clinical trial protocol content: a systematic review

**Authors:**

Jennifer M Tetzlaff (jtetzlaff@ohri.ca)
An-Wen Chan (anwen.chan@utoronto.ca)
Jessica Kitchen (jessica.kitchen@wchospital.ca)
Margaret Sampson (msampson@cheo.ca)
Andrea Tricco (triccoa@smh.ca)
David Moher (dmoher@ohri.ca)

**Version:** 3  **Date:** 19 June 2012

**Author's response to reviews:** see over
Dear Dr. Kansagara,

RE: “Guidelines for randomized clinical trial protocol content: a systematic review”

Thank you very much for your email dated May 22nd, 2012 and the included peer review comments. We are pleased that *Systematic Reviews* is interested in publishing our manuscript.

We have carefully reviewed the comments submitted by you and the reviewers and we have revised the manuscript accordingly. Enclosed you will find a table with a point-by-point reply to the recommendations, indicating where changes have been made. The revised manuscript with tracked changes has been uploaded on your website, as requested in your email.

Thank you again for your interest in our manuscript. We look forward to hearing from you.

Best wishes,

Jennifer M. Tetzlaff  
Clinical Epidemiology Program,  
Ottawa Hospital Research Institute  
501 Smyth Rd., Ottawa, Ontario, K1H 8L6, Canada  
Telephone: 613-595-1959  
Email: jtetzlaff@ohri.ca
Editor and Reviewers’ Comments and Responses: “Guidelines for randomized clinical trial protocol content: a systematic review”

We thank the associate editor and reviewers for their time reviewing our paper and for their comments, which we have carefully reviewed. We have revised the manuscript accordingly. Our responses are outlined below and changes are noted in an amended version of the manuscript. Some minor changes suggested by the coauthors have also been incorporated in the main documents with changes noted.

<table>
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<th>Comment</th>
<th>Response</th>
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<td><strong>Associate Editor’s comments</strong></td>
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| 1. Lines 84-87: please make even more explicit the distinction between reporting trial protocols and research reports. One has to read the paragraph fairly carefully to catch the distinction, and readers unfamiliar with CONSORT may confuse it with the prior and subsequent discussions re: trial protocol reporting. | We agree and have modified the text as follows (lines 84-88):

Reporting guidelines have been developed to improve the transparency of other research documents such as reports of research findings for journal publication [19-26]. Indeed, the implementation and endorsement of some of these guidelines, including the CONSORT Statement (CONsolidated Standards Of Reporting Trials) [27] for reports of RCT findings, have been empirically shown to improve report quality [28-30]. |
| 2. Lines 157-160: As reviewer 1 suggests, the rationale for choosing this subset of guidelines to further analyze is not readily apparent. One can infer that you intended to examine the more rigorous and/or most actively used guidelines, but this should be stated explicitly. Also, please define what you mean by “institutional adoption”. | We agree and have modified the text as follows (lines 163-168):

We itemized guideline content to compare recommendations across guidelines. This analysis was limited to evidence-informed guidelines, those with explicitly described methodology and those with either explicit or probable endorsement of the guideline by a recognized institution or organization. This subset was chosen to select guidelines that were potentially more rigorously developed (i.e., those with methodology beyond the consensus of a few authors’ opinions) or more widely acknowledged. |
| 3. Lines 269 – 277 describe an ideal guideline reporting process. It might be useful to frame the paper using these constructs. Indeed, the results (table 2) are already seemingly organized with this framework in mind. Consider mentioning the guidance for reporting guidelines in the introduction, and also citing ref #31 as one organizing principle for synthesis of results (table 2). | We have mentioned existing guidance more explicitly in the introduction (lines 88-92):

“However, development methods of reporting guidelines vary, potentially impacting their utility to various stakeholders [19,31]. Some groups advocate that reporting guidelines should be developed using rigorous, systematic and transparent methodology [19,31] and recommendations for reporting guideline development have recently been proposed [31].”

Please note that this review was not organized based on this recent guidance, which was developed and published |
later than the development of our review (although the guidance originated from some of the same researchers who developed and informed the methodology of this review and thus was developed from the same viewpoint). Therefore, we have not cited this as an organizing principle for the synthesis of results. In the acknowledgements section, we refer to a survey of guideline developers completed by Dr. Iveta Simera and colleagues on which the data extraction process of the current review was based.

4. Table 3: the purpose of this table is unclear. Much of the information is already presented in Table 2. The text (line 194) states that table 3 presents details for “specific guidelines”, but it is unclear how these specific guidelines were chosen for inclusion in the table. On the other hand, the title of the table suggests all 40 guidelines are represented here. In actuality, the table reiterates several points already revealed in Table 2: few guidelines described methods, none used a formal consensus process, and the number of contributors ranged widely. Please consider deleting Table 3 altogether and simply embedding in Table 2 the relevant citations applicable to each characteristic (i.e. next to methods described — Yes, enter the citations of the 8 studies). Alternatively, if you feel it is essential to retain the specific descriptions of these guidelines, consider limiting Table 3 to only those 8 guidelines that described their methods.

We agree that there is overlap in the content presented for Table 2 and Table 3. All guidelines are presented in Table 3 and this has been clarified in the text (lines 203-204).

We appreciate and support the view made in this comment and suggest that Table 3 be deleted from the manuscript but included as a supplemental file/web appendix for the following reasons:

The purpose of Table 3 was to avoid inadvertently masking those guidelines that describe some relatively systematic and robust methodology, something that aggregate presentation of the results of our review (as shown in Table 2) may have done. We chose a table to describe this information as it was more succinct and reader-friendly than describing exceptions in the main results or the discussion sections and we felt it enabled a more transparent presentation of any inferences made. Additionally, details of contributorship are not included in Table 2.

We have included citations in the text and in the supplemental file, and thus have not added them to Table 2.

5. Table 4: there is quite a bit of information in this table. As reviewer 1 suggests, please consider reformatting to make it easier to read, though I am unsure what specific formatting recommendations to offer. A few minor points: 1) it might be easier to follow the subheadings under 25-50% and < 25% if the order was the same and you placed the “design, safety/monitoring, ethical considerations, and dissemination” subheadings at the end of the 25-50% column, 2) if feasible, please consider using similar subheadings under the > 75% and 50-

We agree and previously experimented with various formats to try to have the table meet the journal’s requirements. We hope that the amended version (now Table 3, Page 27) is satisfactory.

1) This amendment has been made
2) This amendment has been made
3) Thank you. This has been changed to 5 guidelines.
75% categories, 3) “target population” under the 25% category was recommended in 6 guidelines which would make it 25-50% - please double check the number here and place into the appropriate column.

6. Table 5: please clarify either using a table footnote, or with more explanation in the Methods section how you defined “more likely to recommend”? Was this a gestalt impression of the content of one set of guidelines vs the other, or was this determination based on the Table 4 quartiles?

The groups were compared descriptively with consideration for small sample sizes (only large differences are noted). This has now been clarified in the text (lines 178 and 244-247) and in a footnote to the table.

7. Please further consider and describe the impact of funding subtype (government, industry) on results as suggested by reviewer 1.

In our study, a funding source for guideline development was only explicitly described in 6 guidelines and in all cases was from a non-profit source. Thus, an analysis of this nature is not possible. However, at the editor’s suggestion, we have conducted an exploratory post hoc analysis comparing results based on the following categories:

1) Guidelines explicitly or likely produced for or by a non-industry institution (n=19)
2) Guidelines explicitly or likely produced for or by an industry institution (n=3)
3) Guidelines not clearly produced for or by a specific institution (Note: authors could be from a specific institution but if not stated as produced for this institution, guidelines were placed in this category) (n=18)

From this analysis we note the following in comparing guidelines from industry to non-industry:

General characteristics:
- Guidelines explicitly or likely produced for or by an institution are less likely to credit authors than those not clearly produced for or by a specific institution (non-industry: 58% vs. industry: 0% vs. not reported 100%)
- Number of contributors (where reported) is greater for guidelines produced for or by a non-industry institution (Median [IQR] = 3 [2.5, 14.5]) than those that had no clear or probable institutional affiliation (1 [1, 2]). No guideline produced specifically by industry stated number of contributors.

Methods
- In our sample, guidelines produced by/for non-
industry organizations are more likely to be published (non-industry: 75%; industry: 0%; not reported: 83%)

Number of items/concepts:
- There was no difference in the number of included items or concepts between non-industry and industry affiliated guidelines. Both recommended more items than guidelines without a reported affiliation (non industry: Median [IQR] = 28 [20, 45]; industry: 26 [25, 40]; not reported: 16 [11, 23]). There was no difference in the number of recommended concepts

Content:
- Guidelines prepared by/for industry are more likely to recommend:
  - protocol title,
  - name of principal investigator,
  - description of investigational treatments (general)
  - publication plan (general)

Please note, that this additional analysis has not been added to the manuscript for the following reasons: The categories are not clearly defined. Many guidelines were not produced by or for a specific organization but rather for protocol authors in general. For guidelines that were produced for or by an organization, the organization is not always a funding source for trials or the guideline could be intended for trials sponsored, but not necessarily funded, by that organization. This is not stated. Similarly, the target ‘audience’ of many of the guidelines is not always explicit or specific (e.g. CIOMS, ICH E6 could presumably apply to both industry and non-industry funded trials).

<table>
<thead>
<tr>
<th>8. Please include the review protocol as an appendix.</th>
<th>The review protocol has now been included as an appendix to the review (Appendix A). This was intended to be uploaded with the original submission. Thank you.</th>
</tr>
</thead>
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<tr>
<td>9. Please conduct an updated search and amend the manuscript accordingly.</td>
<td>While we appreciate the reason for this request we regret that we do not have the resources to complete an update of this review at this time.</td>
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</table>

**Reviewer 1**

| 10. My recommendation is to consider the proportion of RCTs funded by the various sources identified. Some of the funding sources most likely represent the majority (e.g. industry and government) while others are relatively minor players. I cannot see | This is an interesting suggestion; however, we feel this is not possible due to the reasons outlined above (#7). |
that this has been taken into account either in the introduction or in the analysis and discussion. I would like to see an evaluation of the results stratified by industry vs government sponsored guidance as these are, in my mind, the most common funders of trials in terms of both numbers of trials and money spent. In the introduction, I found myself thinking about the different motivations behind protocol guidelines depending on the source. Likewise, the accessibility of guidance may vary by source.

11. Because industry typically interacts with the FDA, their decisions on protocol guidance likely overlaps with FDA guidance. This could be evaluated.

This may be interesting for future research. We feel it is too specific for our review.

12. In Method, subsection ‘Guideline content’. This section is unclear. It is difficult to tell why this was done, what is the purpose based on the text, and how or why the subset was selected. Similarly, the results for this subsection are somewhat opaque.

We have now clarified our methodology and the rationale in the methods section (lines 163-175):

We itemized guideline content to compare recommendations across guidelines. This analysis was limited to evidence-informed guidelines, those with explicitly described methodology and those with either explicit or probable endorsement of the guideline by a recognized institution or organization. This subset was chosen to select guidelines that were potentially more rigorously developed (i.e., those with methodology beyond the consensus of a few authors’ opinions) or more widely recognized. To aid in this comparison, we referred to the 2005 version [37] of CDISC’s (Clinical Data Interchange Standards Consortium) Protocol Representation Model [38], which aims to comprehensively list potential protocol concepts (to support the interchange of protocol information).

Guideline content was mapped, where possible, to one of 264 concepts included in this model. Where no suitable concept existed or where the concept had a different level of granularity than the CDISC concepts, a new category was created. Content mapping was conducted by one reviewer (JT) and verified in full by a second reviewer (JK).

We have also modified this section of the results (lines 237-42):

We extracted content from a subset of 23 guidelines. The recommended content varied substantially between the guidelines (Table 4). Over 380 concepts were recommended (median [IQR] = 31 [24, 80] concepts per
13. The discussion could go into more detail on the author’s thoughts on the downsides to their findings earlier.  

We have added this more explicitly to the discussion (lines 273-275):

If not properly developed, guidelines could potentially ultimately be of limited use and may not improve the reporting of elements that are important to key users of protocols.

14. In the discussion it is noted that there recently has been recommendations on guideline development reporting. I would think these should be also mentioned in the introduction.

Please see note 3. The recent recommendations have been noted in the introduction.

15. In the discussion, paragraph 6, the sentence “Given the evidence or protocol deficiencies…” needs citations to support these statements. I do not know that those statements are true, or what they entail off the top of my head so would like to be able to refer to the original research.

Thank you. References have been added to this statement.

16. Table 1 should include the % of guidance from each of the types of funders

Table 1 lists the % of guidance based on funding source. We have not added the % of guidance from each of the types of funders to Table 1 as suggested due to the reasons stated previously (#7)

17. Table 4 is difficult to read as formatted.

Please see point 5 above.

**Reviewer 1 additional comments (notes in text)**

18. Line 98: “(available upon request)” - Not clear what is available.

This statement referred to the protocol being available upon request. This has been amended to “(Appendix A)” where the protocol to the initial version of the review has now been appended.


Based on this comment and one by Referee 2, this statement has been amended to (lines 110-112):

“Tools were excluded if they recommended content intended solely to guide protocols of a to a narrow health care research area (e.g. disease stage based on a specific classification system), as we intended to focus on guidelines that could be generalized to other
<table>
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<th>Line</th>
<th>Original Text</th>
<th>Revised Text</th>
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<tr>
<td>20.</td>
<td>“Books were eligible, a sample of which were identified by reference lists and by local library portals and the Internet (Amazon.com [34], WorldCat.org [35] using the search terms ‘protocols’ or ‘clinical trials’.”</td>
<td>“A sample of books were also reviewed for relevant guidelines, and were identified, based on book title, by reference lists and searching Amazon.com [34], WorldCat.org [35] and local library portals using the search terms ‘protocols’ or ‘clinical trials’.”</td>
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<tr>
<td>21.</td>
<td>“representing one of six countries previously identified as the top “health-related publication producers” [36]: Do you mean the you identified them previously, a priori?</td>
<td>“representing one of six countries identified by the cited paper as the top ‘health-related publication producers’. The word ‘previously’ was included as this citation is from research published in 2005.</td>
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<tr>
<td>22.</td>
<td>“clinical trial funding agencies.” organizations, maybe? Would accomodate the industry ones better, I think.</td>
<td>Thank you. This has been changed as suggested.</td>
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<td>23.</td>
<td>“…from 1991 to present (n=24; 60%)…”</td>
<td>“The majority of guidelines were published as journal articles (n=22; 55%); most were completed/published from 1991 to present (n=24; 60%); and most were presented as checklists, tables or bullet lists (n = 27; 68%), some with additional explanatory text.”</td>
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<td>24.</td>
<td>“We extracted content from a subset of 23 guidelines that provided a description of development methods, use of evidence to support their recommendations, or institutional adoption.”</td>
<td>“The majority of guidelines were published as journal articles (n=22; 55%); most were completed/published from 1991 to present (n=24; 60%); and most were presented as checklists, tables or bullet lists (n = 27; 68%), some with additional explanatory text.”</td>
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<td>25.</td>
<td>“We extracted content from a subset of 23 guidelines that provided a description of development methods, use of evidence to support their recommendations, or institutional adoption.” I think you identified these because you thought they represented better guidance - can you say that here as you describe them? Might make things more clear.</td>
<td>Please see the response above (#12).</td>
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<td>Subgroup comparisons Clearly, your ability to make any meaningful comments here is limited by the small sample size. May need to note that somewhere.</td>
<td>Thank you for this suggestion. We have now stated (244-248): Few differences were noted between pre-specified subgroups by scope, development methods, and funding source. The number of guidelines in each subgroup was small, limiting our ability to make definitive conclusions. Table 5 presents the most notable differences between the subgroups.</td>
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<td>Revised Text</td>
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<td>26.</td>
<td>“For example, only half of the more recent guidelines [61,72,73,76,82,83,85] included an item recommending that primary outcomes be stated, despite preceding research showing biased modifications throughout trials [3,5,11].”</td>
<td>Thank you. This has been changed to (lines 258-260): For example, only half of the more recent guidelines [61,72,73,76,82,83,85] included an item recommending that primary outcomes be stated, despite preceding research showing biased modifications of primary outcomes throughout trials [3,5,11].”</td>
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<td>27.</td>
<td>“Of the eight that did detail methodology, four seem relatively comprehensive (e.g. [44,48,61,72]); yet even between these guidelines, although some elements were present in all, the recommended content differed considerably” Confusing sentence.</td>
<td>This has been amended to (lines 275-277): “Of the eight that did detail methodology, four seem relatively comprehensive (e.g. [44,48,61,72]); yet even between these guidelines, although some elements were present in all, the recommended content differed considerably.” Although these four shared many common elements, considerable variation in recommended content was also present.</td>
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<td>28.</td>
<td>“None described using formal consensus methods or a systematic consideration of empirical research to inform guideline content.” Restating results. Not clear until next paragraph why you are saying this again here.</td>
<td>This statement has now been removed from this paragraph.</td>
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<td>29.</td>
<td>“Reporting guideline development requires substantial resources and time [36] and the conduct of this review is…” I do not understand the use of this word [Reporting] here. It seems like the sentence should start with Guideline?</td>
<td>This sentence refers specifically to the development of reporting guidelines as opposed to guidelines more generally. Although the first phrase of this sentence could apply to guidelines in general, the second is specific to reporting guidelines. This sentence has now been amended to: “Development of reporting guidelines requires…”</td>
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**Reviewer 2**

30. | Why did authors exclude a tool if it contained content specific to a narrower health care research area? It is understood that this study may not intend to focus on a specific area. But it is not clear enough in the report. | Please see the amendment to this sentence in response to comment 19 above. |
31. | Since this study has stated the importance of transparency of protocol, it may be desirable to include the protocol of its own as an appendix (rather than "available upon request"). | We agree. As stated above (point 8), the review protocol has now been included as an appendix to the review (Appendix A). |