Author's response to reviews

Title: Deficiencies in the transfer and availability of clinical trials evidence: a survey of existing systems and standards

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Version: 4 Date: 2 June 2012

Author's response to reviews: see over
Response to reviewers

Summary of changes

Rewrote the background to more clearly present the motivation and goals of the study. Separated into "motivation", "systematic review", and "scope and objectives".

Moved description of systematic review from results to background.

Moved some of the text from methods to background or discussion.

Further compacted results section, removing redundant and/or distracting remarks. Length of the paper again reduced by a full page.

Minor changes to the discussion to further sharpen the argument.

Had the entire manuscript proofread by several colleagues to enhance readability.

Reviewer: Atle Fretheim

Despite having done a good job with shortening and narrowing the scope of their paper (I am happy with the choices they made about what to keep and what not to keep), the authors still fail to provide a clear and logically structured text. As pointed out before, this is my subjective assessment and may be due deficiencies on my side. But there is nothing I can do about that.

We are glad that you are now happy with the scope of the paper, and hope that the present revision also addresses your concerns regarding the presentation. If the subsections in the results section (3.*) are still a little disjointed, that is because this reflects the current situation in the
field. In fact this is the main point of the paper: there is much to be gained by unifying the handling of trials in these (currently) disparate processes.

My main problem, which I find very frustrating, is that I fail to grasp the logic that motivated the study. I believe an important reason for my confusion and frustration is the following:

I don't understand whether the authors are motivated by a) the need for making it easier and faster to conduct systematic reviews, or b) the need for policy makers to have access to individual trial data. In one sense this may be the same thing, i.e. you need study-data to conduct a systematic review, of course. But it is conceptually completely different to think of systematic reviews as simply a source of study-data (which seems to be the authors' view on systematic reviews, at least in several passages) or as a means for getting the full picture of the best and most relevant available evidence (which I see as the main reason why systematic reviews are important for decision makers).

You are correct in that the systematic review report itself provides value for decision makers by "getting the full picture", especially in informal decision making contexts. However, when moving over to a more formal or quantitative decision making processes, the report alone is not sufficient. For such decisions, the systematic review can be seen as a source of study data, i.e. the selection of studies is the most valuable part. The same viewpoint applies to updating or extending an existing systematic review (e.g. with trials submitted by a company). We have rewritten the background section to clarify this.

One interpretation I have of what motivated the current study is this:

1. Systematic review of relevant research findings is needed for evidence informed policy decisions

2. It takes too much time to prepare a new systematic for an issue at
hand, and an important reason for this is the difficulty of retrieving findings from all relevant studies

3. If trial information (design, inclusion criteria, intervention-description, study population characteristics, results etc.) were readily available, this would speed up the systematic review process

4. In order to assess the potential for making trial findings more readily available, the authors have gathered information of the systems currently in place where trial-data can be retrieved

The last para of the Introduction seems to communicate along these lines. However, the abstract and the remainder of the document seem to focus more on the need for access to clinical data and systematic reviews as one of several possible sources of that (e.g. the "Background" in the abstract does not even mention systematic reviews).

We agree with your interpretation, but feel that systematic review provides an important opportunity to introduce structure into the domain of the medical literature and clinical trials data, which could benefit both future reviews and decision making. Also see our response above.

If the interpretation above is correct, please structure the text accordingly. And please simplify wherever possible. Anything not directly relevant and/or important should be taken out, since the main problem with this text (for me) is to understand it. Added points or arguments without direct relevance add nothing but confusion, in my view.

We have (further) simplified the text in several places.

I would also like to add: If my interpretation is correct, I think this is an important and interesting topic, and therefore suggest that the authors make the effort needed to making the text publishable. In my view, serious editing is needed to achieve that.
I am reluctant to providing a comprehensive list of comments since there is a real risk that I have misunderstood the authors' objectives, in which case the remainder of the review will be a waste of time. However, in an attempt to be as constructive as possible I will provide some more specific comments on the first main parts of the manuscript (i.e not on the Discussion):

Abstract: I suggest complete re-write after finalizing suggested revision of main manuscript.

We have written a new abstract. The background and methods have changed considerably, whereas the results are virtually unchanged.

Introduction: I suggest full re-write of the Introduction, e.g. by using the four points I prepared above, and expanding on them (see also comment below on placement of section on Systematic reviews).

The background (introduction) has been rewritten, and is now organized in subsections: motivation, systematic review, scope and objectives.

The para about non-inferiority is not needed to motivate the study and can be deleted (serves mainly as source of confusion).

Removed.

Methods: Although it is fine in principle to adhere to the PRISMA-setup, it comes across as confusing here (and I am not sure how applicable it is). The first sentence in the Methods is utterly confusing: The authors have been writing about systematic reviews in the preceding paragraphs in the Introduction, and now they are -- suddenly, out of the blue -- referring to their own study as a systematic review. I don't think many readers will "get" this.

We thought it was best to mention PRISMA explicitly, but if this leads to confusion, we are happy to remove it.

"Aggregate level" -- I don't understand why sources of individual patient data
are not of interest. Also need to specify what is meant by "aggregate level".

Added to the background.

"The aim of this paper..." belongs in the Intro (by convention). The remainder of this para illustrates the constraints the authors are facing by adhering to the PRISMA-setup in their reporting: It makes absolutely no sense to argue why their findings, in this case, are summarized qualitatively (as opposed to in a meta-analysis).

Both the editor and the other reviewer asked us to adhere to the PRISMA statement for the methods section. However, as you point out, it is not a perfect fit. We have been struggling to find best way to apply the PRISMA checklist to our work. We agree that some of the points are better omitted, and have removed those. We also moved the text about the aim of the paper to the new "scope and objectives" subsection.

The last para ("As with any review paper...") belongs in the Discussion (by convention).

Moved (new "limitations" subsection in the discussion).

Results:

ALLHAT-trial is one, but not necessarily the best example (and "on the prevention of heart failure" is not an accurate description of that study). I don't think you need to present an example (my suggested rule of thumb is to try and keep it simple), but if you insist, perhaps the LIFE-study ("Losartan Intervention For Endpoint Reduction in Hypertension Study") is an even better example -- 100+ publications at the moment (and no results reported in clinicaltrials.gov...)

Removed.

I find the second half of the first para badly worded and not very clear. The
essence of the para can be made in a sentence or two (e.g. "In addition to the difficulties with identifying clinical trial reports in the scientific literature, the published reports may suffer from several deficiencies, such as...")

Restructured and shortened.

"The registration of clinical trials is now a well-established practice and has become a key tool in addressing some of Evidence-Based-Medicine (EBM)'s challenges [31]" -- is an example of a redundant remark, and an annoying one since the authors seem to expect the reader to look up reference 31 to understand what they are talking about. This is an example of unnecessary text that has no additional value, and adds to the confusion.

Removed.

The "Systematic review"-section is problematic, conceptually. It makes sense if the objective is to look for sources of trial-data, but not if the objective is to find sources of trial data that can speed up the conduct of systematic reviews. At least not in the way this section is presented now. Again: the authors need to think about and communicate more clearly what they are trying to do. My suggestion, in light of my 4-point interpretation of the motivation behind the study (above) is to compress this section to one fifth of its current length, or so, and include in the Background section. I realize that a case can be made for using existing systematic reviews as a source of clinical trial data for new systematic reviews, but it is not clear that this is what the authors have in mind. Anyway, the broad and lengthy general description of systematic reviews seems totally misplaced under "Results".

Most of the "general" material has been shortened and moved to the background. However, as motivated above (and in the rewritten background) we decided to keep our discussion of the systems that support systematic review.

Under "Standards and data models": "...their various standards to a shared view of semantics of the domain of protocol-drives research and its
associated regulatory artifacts [67]". I don't have the faintest idea what you are talking about, and I refuse to have to look up references 67 to make sense of your text.

Simplified to "... the common elements of their various standards into a complete data model for clinical trials [55]" (the reference is the same, but the number has changed).

Conclusion: A major revision of the text is needed to make this a worthwhile read - but the needed revision only involves editing, i.e. improving the presentation (I do not expect additional analytical work). Thus, this should be doable with a few days of work. I would also suggest asking a colleague or two to read through before submitting again - and ask specifically for feedback about clarity and readability.

We thank for the thorough and insightful review. We hope the revised manuscript meets your expectations in terms of the presentation. After completing the main revisions, we have sought feedback from several colleagues in the two weeks prior to re-submission.

**Reviewer: Tatyana Shamliyan**

The authors revised the manuscript following the recommendations from the peer reviewers. I think that this revised version is much better and close to the point. The authors outlined the concepts and flaws in shared decision making based on aggregate clinical trials results. Research directions would benefit from exact operational definitions of the proposed policy and data management changes. However, such details may be more suitable for a grant proposal rather than a research paper. Considering the importance of the topic and tremendous author's efforts I recommend this manuscript for the publication.