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

Please consider our revised manuscript, "Deficiencies in the transfer and availability of clinical trials evidence: a survey of existing systems and standards" for publication in BMC Medical Informatics and Decision Making.

We have taken the reviewers' recommendation to reduce the length and scope of the manuscript to heart, and believe the revised manuscript presents a more focussed and comprehensible argument. Specifics are in the attached summary of changes and response to reviews. We think that given the enhanced focus, the article should be considered a research article. If you strongly feel that this is not the case, publishing as a "debate" article is also acceptable to us.

We still feel that a review of the complete system for the dissemination of aggregate results of clinical trials is currently lacking in the literature, and that our manuscript is needed to fill that gap.

Yours sincerely,

Gert van Valkenhoef
Response to reviewers

Summary of changes

• Drastically cut down manuscript: removed systems and standard in operational management and industry data warehousing, details on FDA submission, sections on medicinal product information and clinical practice. Also removed several tables and figures. Reduced text on remaining standards and controlled terminologies, and removed the "summary" sub-sections from systems and standards. Manuscript reduced from 25 to 14 pages.

• Added a short section on publication of trials in scientific journals (in part moving material from the systematic review section).

• Re-organized the remaining results sections to improve flow.

• Background rewritten from scratch to better reflect purpose of paper.

• Update table of trial registries: number of registered trials, and add new ICTRP primary registries.

• ClinicalTrials.gov has results XML available since Dec. 2011.

• Removed reference to PhRMA repository, since it doesn't exist anymore.

• Updated discussion where appropriate (mainly removing mention of systems that are no longer discussed).

Reviewer: Atle Fretheim

The authors have prepared a comprehensive, very long report (around 10,000 words) on a complex subject. Their stated objective is to “provide an overview of the existing systems and standards supporting the various processes in which, directly or indirectly, evidence from clinical trials is used”. This is an extremely ambitious goal – too ambitious in my view. The authors will need to make several important changes – I think – to turn this into a manuscript that is publishable in the traditional peer-reviewed scientific literature.

• Thank you for this long and insightful review. We agree with your assessment concerning the scope of the paper, and have used your comments to drastically reduce the length of the paper.

I have not numbered of categorised my comments into "major or minor compulsory revisions", since my feed-back at this stage is very general and indeed "major".

Firstly, the document is not organized in a way that makes it an easy read. Clearly this is a subjective point of view (mine), but after having started reading the document 5-6 times without being able to grasp its logic or direction (and therefore starting over after reading only a couple of pages, time and time again), I strongly feel that the authors should be obliged to make an effort at presenting a) their reasoning for preparing the report, and b) their findings, in a more accessible way. My trouble with the manuscript may partly be due to my limited insights in drug-regulatory processes (and/or stupidity), but I know enough about the field to belong to what I would think is the target audience.
• We hope that (1) the reduced scope, (2) the rewritten background and (3) the reorganized results section will make the revised manuscript an easier read.

The first problem is: What IS the problem? Why this report? The authors argue reasonably well for the need to improve the accessibility of key information "on past decisions and clinical trials" to facilitate the process of market authorization, in particular to reduce the problem of late-stage failures in drug development (supposedly to avoid waste of time and money). I understand this and I was curious to learn more about the information used by regulatory agencies in their processes, and the authors’ analysis of how this could be improved.

• We re-oriented the stated scope of the paper to be policy decision making based on aggregated results from clinical trials, since we feel that the relevance to late-stage failures was perhaps not fully substantiated in the text (though we do believe it is real).

However, the authors expand on the scope and include information systems for dealing with data-collection during the conduct of trials (not directly relevant to drug-regulatory agencies, I would think) and to the flow of information to clinicians and patients (not relevant to regulatory agencies). These are huge, complex areas by themselves and even in the current mega-length report (for a research paper, that is), these topics cannot be more than superficially explored. Also, the authors do not present an argument for why these topics are important – are there major problems with the current handling of information during the conduct of trials? Are there major problems with how trial-findings are communicated to clinicians and patients? I am sure there are, but the authors have not presented arguments for this in the introductory parts of the manuscript, and therefore their decision to include practically all aspects of use of clinical trials information seems a bit strange.

• We have eliminated these subsections (which we decided to publish as a separate research report). This allowed us to focus on accessibility of the key information (aggregate data from clinical trials) to decision makers.

An illustration of the problem with the current document: The main information channel for clinical findings to the public (especially clinicians) has traditionally been "research articles" in peer-reviewed medical journals. This "system" for supporting the use of clinical trials findings is barely mentioned in the current manuscript - likely to confuse many readers. A description of this "system" is a big task in itself, and the problems with basing dissemination of trial-findings on publication in journals are many - probably enough to fill several separate manuscripts.

• Indeed, the literature was briefly mentioned in some places and discussed in more detail in the section on systematic review. We introduced a separate section in which we briefly describe the practice of publishing trials in the scientific literature as well as the abstract databases. We feel this greatly improves the readability of the paper.

Thus, my first proposal is to limit the current report to the specific issue related to information flow to regulatory agencies, for two main reasons: 1) The authors have explained quite well why this is an area where there is need for enquiry, and 2) This is a manageable scope for both the authors and the readers (and would likely make it easier to prepare a report with a more logical composition). I do believe that this could be a valuable contribution – it is unclear to many (of us) on exactly what basis drug regulatory decisions are being made, and a review and constructive critique of the information sources currently available to these agencies, is indeed welcome.

• As explained above, we felt it would be more appropriate to focus on the availability of aggregate data from clinical trials to policy decision makers of all kinds. To focus on regulatory decision making would imply an analysis of the contents of the dossier, which would take the manuscript in a radically different direction.
I am not sure the current approach qualifies as “science”. There is no clear, practical definition of what constitutes a scientific paper, but a purely descriptive report on the currently available information systems seems to me to be on the outer margins of what I would consider “science”. I would have expected this to be published as a "working paper" or "report" from the researchers' institution or those funding them rather than as a scientific article. However, if the authors “focus” their manuscript as I have suggested, and strengthen their analytical component, I guess it would be easier to see this (a little bit more) as "science". Whether this is "science" or not isn't necessarily a big deal, and the editors can also propose to publish this as a “Debate”-article instead of “Research”-article, for example – if in the end considered publishable.

- We hope that the refocussed and reduced manuscript presents a clearer and stronger argument -- and thus can be published as a research article. We have moved some of the material to a technical report.

I have looked more or less randomly at some of the references, and I suggest that the authors double check to ensure that the statements in the text are in fact backed by the articles/documents that are being referred to (e.g. is reference 8 the most relevant regarding the “insufficient communication of important information to patients and professionals”? – perhaps, but it is definitively not a major theme of the referenced text).

- We have checked the references. Indeed there were some problems with the old background section, probably because of its long evolution. This section has been completely rewritten, and we believe the references are correct for the current version.

If the authors decline my suggestion, I propose a thorough critical review on their part on how they can present both 1) why their work is important and 2) their thinking and findings in a more easily accessed way – with the aim of having the reader follow the step by step logic of the text as it is being read.

- We rewrote the background to address (1) and restructured and reduced the results to address (2).

However, I strongly believe that this manuscript would be hugely improved if the authors take the unpleasant decision of cutting it down dramatically, and to focus only on what seems to be the main issue: What are the current systems that are being used to access clinical trial-findings for drug regulatory agencies, and how (i.e. analysis) can these be improved? Could be a great article – perhaps not a research article (or perhaps it could be), but at least an informative, useful debate/commentary paper.

- Your suggestions (though we did not follow all of them) helped us to reduce the manuscript from 25 to 14 pages (the main body of the text from 14 to 8)

**Reviewer: Tatyana Shamliyan**

The paper presents a tremendous amount of work collecting information about existing standards for drug development and informed decision making in clinical settings. The topic is very important and I would not argue with author's conclusions that existing clinical research policy does not guarantee valid evidence for unbiased decision making.

However, the presentation of the methods and results is a mixture of very different approaches to describe and evaluate regulatory policy regarding marketing and comparative effectiveness research, compliance with the policy, information systems to collect and analyze the evidence, and various factors influencing decision making in clinical settings.

- In accordance with the other reviewer's comments, we have drastically reduced the scope of the manuscript. The revised manuscript should more clearly reflect the focus on accessibility of aggregate data from clinical trials for policy decision makers.
Since the authors conducted a systematic survey of the existing systems and standards, following PRISMA recommendations would help to appreciate all efforts in collecting and appraising information regarding policy, evidence collection, analysis, and translation to the decision making.

- Indeed, we followed the PRISMA checklist in describing our methods. We now mention this in the methods section.

Since the authors evaluated drug information systems and standards and data methods, a clear description of the evaluation criteria would help to identify the deficiencies and areas of improvement in regulatory policy vs. technical requirements for the shared databases.

- We have reduced the emphasis on regulatory policy, and focus on availability and accessibility of the evidence.

The manuscript should address problems (if any) in underlined business model for drug approval and marketing process including coverage decision and motivations for most-marketing studies and comparative effectiveness research.

- These are indeed important topics, but outside of the scope of the (revised) manuscript.

The proposed research directions look very general and relevant only to systematic reviews of the published articles rather than all stages in the process.

- You are correct that the directions are relevant only to the dissemination, availability, and use of aggregated data from clinical trials, and e.g. not directly relevant to drug development. Therefore, we have removed these non-relevant areas from the manuscript (and published these as a separate research report).

The proposed direction regarding policy decisions should be clarified with more details: “Computer supported decision models for policy decision making based on clinical trials”.

- We have clarified the intent of this direction.

Minor issues: the Pharmaceutical Research and Manufacturers of America (PhRMA) repository does not exist anymore.

- Thank you, this had escaped our notice. This is a quickly moving field, and we have also had to update the manuscript for several developments since the original submission to BMC (EU-CTR joining ICTRP, results XML from ClinicalTrials.gov, etc.)

“For a brief overview of drug information systems that considers the entire drug information life cycle, we refer to [9].” Please describe in details your previous work (ref 9) reviewing drug information systems.

- This reference has been removed -- though we do cite our new research report containing most of the material that was removed in this revision.