Author's response to reviews

Title: Factors influencing the participation of gastroenterologists and hepatologists in clinical research

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Author's response to reviews: see over
BMC Health Services Research

To the Editors:

My colleagues and I are pleased to submit our revised manuscript entitled “Factors Influencing the Participation of Gastroenterologists and Hepatologists in Clinical Research” to *BMC Health Services Research*.

We are grateful for the opportunity to revise our manuscript in response to the reviewers’ many thoughtful comments. Accompanying this cover letter is our point-by-point response to the comments.

I will continue to serve as the corresponding author. Please do not hesitate to contact me by e-mail at mchut001@mc.duke.edu if you have any questions.

Sincerely,

John G. McHutchison, MD, FRACP

Professor of Medicine
Duke University School of Medicine
Responses to Reviewer: Merran Toerien

1. Choice of physician groups. The research compares gastroenterologists and hepatologists but provides no explanation for why either of these groups was chosen or why the comparison is of importance. This should be explained in the introduction.

We surveyed both gastroenterologists and hepatologists under the assumption that, while both might be involved in clinical gastrointestinal research, gastroenterologists tend to be more heavily involved in procedural care and hepatologists tend to focus on nonprocedural practice. We have added a statement to this effect to the introduction on page 4.

2. Literature. I thought the reference list was a little thin given the amount of previous work published in this area. For a useful review in relation to oncology, see: Fayter, D et al. (2006). Systematic review of barriers, modifiers and benefits involved in participation in cancer clinical trials. Centre for Reviews and Dissemination, University of York (see: http://www.york.ac.uk/inst/crd/pdf/crdreport31.pdf)

Additional published work has been reviewed and determined to be consistent with our previous statements. References to these additional papers (citations 4, 7-8, and 10-12 have been noted in the introduction on pages 3 and 4 and in the discussion on page 13.

3. Methods (i). These are appropriate and clearly described. However, it would be useful to know a little more about the exploratory questionnaire used to generate questions. Did this include open questions in an effort to ensure that unexpected factors affecting research participation were allowed to emerge?

Yes, our focus group did use an open-ended or free-response format, and responses to initial survey questions were used to generate the alternatives used in the questionnaire. This information has been added to the Methods section on page 5.

4. Methods (ii). The authors should specify how they defined those with and without clinical research experience (e.g. did participants have to indicate 0% in response to the item “research-clinical” in Question 8, or 0% to all three of the research items, etc.)

Clinical research participation was defined as spending at least 1% of time in clinical research activities (Q8). We have added this information to the Methods section on page 6. We also clarified that we are defining participation rather than experience, as the text read originally.

5. Methods (iii). Related to point 3 above, there appears to be some slippage between “clinical research” and “clinical trials” in the questionnaire and in the paper. As a whole, both the paper and the questionnaire focus on trials, yet some of the items in the questionnaire refer to types of research that do not necessarily involve a trial design. E.g. the question in item 11 refers to trials, but the fourth option lists epidemiological research, which is not necessarily conducted through a trial design. And the options of “Research-Basic; Research-Clinical and Research-Academic” do not necessarily involve trial research specifically. Towards the end of the methods section, the authors state: “Differences between... physicians with and without clinical research experience, and physicians with limited and extensive clinical trial experience were also
evaluated”. Were these two terms (“clinical research” and “clinical trial”) chosen deliberately? In other words, for those who were counted as having clinical research experience, was this necessarily trial experience?

We interpreted clinical trials as representing a (large) subset of the research that might be conducted under the heading “clinical research.” This was based on internal discussions during the development of the draft survey and confirmed during the pretest/focus group discussions. Since our pretest participants viewed clinical research as predominantly consisting of clinical trials, we generally did not distinguish between the two on the survey.

In the analysis, we defined clinical researchers based on the percent effort reported for research-clinical activities (question 8). Clinical trial experience was based on the number of trials as reported in question 9 (those reporting participation in 5 or more trials in the past 12 months were considered more trial experienced). This distinction was not made clear in the Methods section previously but has now been added (see page 6).

6. Limitations of the work. The authors do provide a clear statement of some of the limitations of the study. However, their paragraph considering the possibility of bias in their sample is oddly worded (see second page of the Discussion). They rightly acknowledge that there would have been a risk of bias if they had limited their study to physicians with current or previous participation in clinical research. However, they do not seem to consider that, by drawing all participants from the American Association for the study of liver diseases, they may still have a sample that is biased in favour of research activity (since physicians with no interest in research may be less likely to be members). Given the focus on barriers to research, this risk of bias should also be mentioned – particularly as it may partly account for the relatively high numbers of participants who reported being research active.

This is an excellent point on several fronts. We have rephrased the limitations section to better account for both types of bias (see pages 13 and 14).

7. Figures. The results section would be easier to follow if the authors made it clearer which sections relate to which figures. Also, the current reference to Figure 3 (under the heading “Factors influencing patient enrolment in clinical research) appears to be in the wrong place as the figure shows no comparison but the preceding sentence compares gastroenterologists and hepatologists.

Thank you for noting the incorrect placement of the reference to Figure 3. We have also removed some of the figures, which we believe should help with the flow of the paper.

8. Discussion. The discussion should include some consideration of the implications of the findings regarding differences between gastroenterologists and hepatologists. As this was central to the research design, the absence of this in the discussion is notable.

We have added several paragraphs in the discussion (pages 12-13) that highlight some of the differences between the two groups and discuss possible factors that may explain those differences. We thank the reviewer for bringing this to our attention.
9. Conclusion. The conclusion refers to concerns regarding relationships with sponsors, especially regarding publication, which I could not find reported in the results.

The statement in the conclusion refers to an item in question 16 (barriers to clinical research), which is written as “concern about sponsor control of trial decision making, data, publication, etc.” We have made edits to the Results section (page 9) and moved and clarified the statement originally in the conclusion to the Discussion section (page 13) so that the text better reflects the wording in the survey.
Responses to Reviewer: Armin Weinberg

1. The first centers on the purpose of the paper itself. While I can imagine from the survey questions the intent of the study it is oddly difficult to find it clearly stated in either the abstract or the paper itself. Obviously they are trying to ascertain the factors that currently are influencing participation, weighing the impact of various barriers to participation, considering the factors related to patient enrollment, types of clinical research and or phase of trial, physician experience and training, and yes, even general demographics of the physician respondent pool. Indeed they seem to have had an acceptable response rate and should have ample data upon which to draw certain conclusions. Yet the data is really not clearly related to their conclusion which states “Critical gaps in the clinical research infrastructure in the United States limit hepatologists’ and gastroenterologists’ participation in research activities.” Sure the data describes barriers, preferences, experiences, but how are these converted into gaps in the infrastructure of the clinical trial enterprise? Bottom line: Needs work.

We have clarified the purpose of the study in the introduction (page 4) and reemphasized it in both the discussion (page 10) and conclusion (page 14). In particular, we have strengthened the chain of reasoning from participants’ responses regarding barriers to research to our conclusion regarding gaps in the infrastructure of clinical research.

2. The second area of concern centers on a lines that may raise a flag about the level of basic understanding of clinical trials enterprise or the inability to distinguish between fact, analysis and opinion. This starts with the first sentence of the introduction that reads, “….and have opportunities to offer their patients cutting-edge therapies.” Or as in the discussion section, “…describes some worrisome trends in terms of an appropriate research infrastructure to address pressing needs for insight into optimal clinical strategies.” Or as in the conclusion, “…this study highlights some of the critical gaps in the clinical research infrastructure in the United States that limit the expansion of evidence-based clinical practice and translational research.” Let me give a few a concrete example, the authors state at “Researchers in gastroenterology and hepatology will not be immune to this trend and may be forced to choose between conducting research that explores scientific questions with limited commercial value and those that serve primarily commercial interests.” I guess I am just confused by this type of statement. Are they saying that government funded research is less likely to produce findings of commercial value? I hope not.

The original statement has been reworded to clarify the intended distinction between investigator-initiated and industry-sponsored research—namely, that commercial interests may not be sufficient to support the investigation of many important clinical questions. For example, industry sponsors are unlikely to fund long-term comparative effectiveness studies for a variety of reasons (cost and marketing considerations, to name two). Comparative studies are highly valued among clinicians but generally will not be sponsored by industry. We hope this point is better made with the revised wording on page 4.
Preceding this is a line that states “Recent research also indicates that academic-industry relationships…” However, the article referenced here is TWELVE (12) years old. I hardly consider that recent! Lastly, I’ll back up to the statement that, “Funding for biomedical research has traditionally come from government sources and academic institutions.” which just belies my concern that they are well intentioned in the survey and may have useful data but are not really knowledgeable about the realities of clinical research. The latest stats put the government funding levels at probably 20-25%.

The statement regarding funding sources has been clarified and a more recent reference added (see page 3).

3. The third concern does relate to the presentation of the data. For this example I’ll use the following, “One-fourth of the respondents reported that ethical considerations completely prevented them from participating in clinical trials, and nearly half (49.1%) said they were concerned about trial ethics. “ Which one-fourth is it that they are referring to? Hepatologists? Gastroenterologists? Those who did or did not choose to participate in clinical research? Young ones or older ones? This is obviously not a very clear presentation of the results. Perhaps seeing some data in the table would help others but frankly it only made it more disappointing to not know where statements like this actually came from. Or yet another “As might be expected, physicians were most concerned about the inferiority of study medications compared to standards of care.” Excuse me but most concerned compared to what? This apparently comes from survey question #16 where the choice of “Inferior trial medication(s) compared to standard therapy” that is one of ten items that are offered up as items that prevent the respondent from participating in clinical trials. Yet I see nothing in the data, figures, tables, or narrative frankly that warrants this type of statement. Maybe they really didn’t mean “most physicians?”

As the reviewer notes, several of the results were not clearly stated, possibly resulting in misinterpretation by readers. In addition to addressing the specific statements referenced above (see page 9), we carefully reviewed the entire Results section to ensure that each statement clearly reflected both the survey question and the response to that question referenced by the statement.

4. Although we presume the physicians surveyed are well aware of the different phases of clinical research and designs used in the survey questionnaire I would like to know that this was at least confirmed in the pilot test phase or development of the survey instrument. Obviously, without some knowledge of this one can and one should question the validity of results especially related the respondents’ level of interest or experience in types of trials. Again, it would be helpful to know more about the group that was used to develop the survey questions and instrument. In fact, since they described their efforts to increase face and content validity by using different question to elicit the same information I would think sharing more about their instrument development methodology should be relatively easy.

We have added information in the Methods section (page 5) that better describes the development of the survey. The eight physicians who served as a pretest were all experienced researchers (not necessarily in gastroenterology), and their responses indicated an understanding of the survey questions commensurate with the questions’ intent. In addition, definitions of each clinical trial phase were provided in the survey (see question 18).

5. It might also be of interest to have them discuss the potential impact of enrollment experience vs. self declared participation experience in a set number of trials by the respondents. For example, it is possible to have agreed to participate in a study but fail to accrue. It is also
possible to have had more success in fewer with more positive outcomes or feeling about participation in trials in the future. Anyway, this is a potentially important distinction to the categories used in the current survey.

The reviewer raises a good point, which we have noted in the discussion on page 14.
Responses to Reviewer: Mattijs E Numans

1. I would prefer the authors to be more concise, especially in results and discussion session: please stay with the major findings and start the discussion with a short summary of the most important findings answering the research question posed in the introduction.

See response to item 9, below.

6. I wouldn't primarily conclude that there is a gap in US research structure as the authors do, this cannot be derived from the data directly. And this conclusion is not the most interesting kind of conclusion for readers in other parts of the world. What is worrying is that physicians rather consequently seem to decide on the level of payment (although it is being presented as a means to being able to arrange research support) instead of judgment of clinical relevance. It confirms the mechanism that pharmaceutical companies will go on determining the research agenda, because they are in the position to pay more. I would have liked the authors to elaborate a bit more on that aspect - establishing a research structure is only one of the solutions that can be thought of.

See response to item 9, below.

8. I don't think this manuscript is really on attitudes, more directly it is on determinants of participation.

The title and abstract have been modified to better reflect the focus of the survey on factors influencing participation.

9. I would prefer the authors to shorten methods and results section and elaborate on the discussion.

We have added some material to the Methods section in response to comments from the other reviewers. However, we did edit the Results section in an effort to shorten it, replacing some text and figures with tables (see new Tables 3 and 4), and the discussion has been expanded to include the observation noted in item 5, above, and comments from the other reviewers.