Author's response to reviews

Title: Comparative effectiveness research: what to do when experts disagree about risks

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Author’s response to reviews:

Comments by editor

1. We have deleted large parts of the background on the SUPPORT trial to make it clear that the paper is not about this trial. We now only use the debate after the SUPPORT trial to motivate the need to attend to disagreements about risks among experts. We have not indicated the deleted and moved sections in this part by tracked changes, as this would make the manuscript unreadable. Tracked changes have been indicated for the other changes made in the paper.

2. We have also rewritten the last part of the paper to emphasize that the ERC should not take the place of an independent expert. It needs to make sure that the views of all relevant experts have been assessed. We have also emphasized that the researchers need to assess the risks adequately in their protocols, as is also typically done today.

Comments by reviewer 1

1. We have defined “comparative effectiveness research” as research on accepted standards of care, which is the same definition that OHRP uses.

2. We have removed most of the references to the position of Lantos in the paper, and simply referred to the general position “that there is agreement among experts”.

3. We have clarified the dilemma, and clarified more fully that there are three different ACC/AHA guidelines in the time period discussed.
4. We have explicitly referred to the paper by Evans and London and clarified how our position differs from the one presented in their paper. Since we no longer discuss the merits of the arguments for or against the SUPPORT trial, we have not addressed the various options that might have been used by the SUPPORT researchers.

5. We have tried to link the discussion so far to the discussion about the ERC responsibility.

6. We have not attempted to make a general point to cover all research, specifically not research that investigates an intervention that is not in general use. Such research raises a lot of additional issues and it would be beyond the scope of this paper.

7. We have tried to say make it more clear what we think are researcher obligations and what are the obligations of the ERC.

8. We recognize that basing recruitment based on patient preferences is not novel, but we only mention this as a means of reducing risk, in addition to others. It would go beyond the scope of the paper to discuss advantages and disadvantages of the various strategies.

9. We have removed this reference to OHRP.

10. We have clarified what we mean by “systematic reviews” in our paper.

Discretionary comments

1. We have clarified the reference to the case.

2. Yes, intentionally so.

3. We do not discuss OHRP’s position any more in this paper.

4. We have added equipoise as a key term.

Reviewer 2

1. We do not think that the work of Collins and Evans is directly relevant for our paper, as we do not discuss the important issue of how to identify relevant experts. It would go beyond the scope of the paper to add this important element to our discussion.

2. We have attempted to clarify that we also see an important role for the researchers in the risk assessment.

Reviewer 3
1. We have placed much less emphasis on the SUPPORT study, and made clear that we only use it to motivate the importance of attending to expert disagreement.

2. We have clarified the role of researchers versus ERCs