Reviewer’s report

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

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Reviewer: Rieke Van Der Graaf

Reviewer’s report:

Dear editor,

The authors have written a well-reasoned paper and added a new perspective to the highly actual discussion on standard of care research. Since the SUPPORT study that is central in their paper is a highly controversial study and the authors seem to be defenders of this study, their arguments may be questionable to opponents of the study. However, for the purposes of this review, I have tried to confine my comments to the structure of the paper and the question whether there positions logically derive from their premises rather than whether one should be a proponent or opponent of the SUPPORT study. Where I do argue with the authors on their positions this is for reasons of clarification and not so much because I believe they incorrectly defend the SUPPORT study.

Although I do have several comments, most of these comments can be addressed by clarification and improving the structure. Therefore, I have classified this paper as "minor comments".

I have one main comment and several minor comments: a large part of their paper now focuses on the SUPPORT study. Instead of presenting another view on the SUPPORT study and adding to the debate whether this trial was justified, I think it is more interesting to emphasize what they write on pages 20-23 where they argue what the task of ERCs is in risk-benefit assessment. The mixture of SUPPORT and their clopidogrel case is also somewhat confusing since the cases are not entirely comparable (see minor comments below). I take their main message to be that ERCs should primarily assess "What is the basis of expert opinions?"; "How strong is the evidence appealed to?", "How can clinical trial monitoring affect the possible increased risk of a clinical trial participation" instead of performing an own risk-benefit assessment. This message could be further emphasized and I think also more elaborated on (thus not only in the context of CER), and then diminish the attention for SUPPORT.

Comments:

1. There are many definitions of comparative effectiveness research/standard of care research. In their paper they seem to focus primarily on established effective forms of research, but in the literature CER is even more broadly defined and used. The paper would benefit from a clear definition.

2. I would depersonalize the statement that "it is unknown" what the relative merits of the alternatives are. Oftentimes it is now explicitly related to an extract of a paper written by John
Lantos and colleagues. If it is a generic argument, as the authors claim in the background and the abstract, then there is little reason to single out John Lantos. More importantly, this form of argumentation sometimes leads to overinterpretation of the author. For instance, on page 10 they state "while the premise accepted by Lantos et al may be true for some trials, and it may be true for the SUPPORT trial in particular, it does not follow (my italics) that it is true for a large number of comparative effectiveness trials when there is disagreement among experts about what the evidence says about the benefits and risks of the various interventions in use." Lantos is not arguing in the paper cited that his claim is correct for all forms of CER.

3. I'm puzzled about the dilemma described. See the following comments:

a. Typo? Or more explanation needed: page 12 line 19: why was the proton pump inhibitor added to clopidogrel while the trial compared ASA + PPI to clopidogrel alone?

b. Page 12: "the case illustrates the dilemma": until line 31 there I do not understand what the dilemma is (there have been trials and a consensus statement that ASA + PPI is superior to clopidogrel).

c. Page 12, line 43: "experts who supported the ACC/AHA guidelines did actually criticize the trial by Chan et al", I'm puzzled since it is stated a few lines earlier that this guideline was based on the Chan 2005 study (lines 16/17).

4. Page 12: "this is clearly not a case where experts agreed that there was insufficient evidence". Why then choose this case when it differs from SUPPORT? I think that the authors should more clearly describe the positions in the standard of care debate and/or in the equipoise discussion. Accordingly they can then illustrate why they choose this case and not another describing another position.

a. To illustrate: Emily Evans and Alex London have written a paper that might be helpful: http://www.cmu.edu/dietrich/philosophy/docs/london/EvansLondon-Equipoise.pdf They argue that there is difference a between agnosticism and disagreement, agnosticism meaning that you don't know which of the 2 treatments is better and disagreement among experts, where some favor A over B and others B over A. The agnosticism as described by Evans/London is not entirely similar as the "is not known" situation which the authors describe. Actually, my interpretation of the fragment cited on page 6 is that there is also disagreement in the Lantos case, but what is described as the "is not known" situation is EITHER that experts do not know before the trial whether patients are better of inside or outside the trial OR that it is not known before the trial whether patients will do better in arm A versus arm B. It would be helpful if the authors clarify their position/interpretation with regard to "is not known" and the paper of Evans/London.

b. In the CER/standard of care discussion several options have been described. It would be helpful to describe these options in more detail and to set out how they interpret SUPPORT according to one of these positions in the debate (or have a new view on the matter). For instance see the paper of Silverman and Dreyfuss 2015, page 23:
i. Experimental group versus unrestricted care as usual

ii. Experimental group versus protocolized care as usual

iii. Comparison between 2 protocolized strategies (SUPPORT), where protocolized care can be partially or fully fixed (SUPPORT)

5. Page 13: "how should ERCs in cases such as this one evaluate the risks and benefits of this trial". Please note that the focus of the paper is now changing from a more general discussion of "not knowing" and "disagreement" to risk-benefit assessment AND the role of the ERC in this approach. Several steps are missing here: 1. How exactly does the hitherto discussed epistemological part of the discussion precisely relate to risk-benefit assessment and 2. why ERCs are the only responsible stakeholders in making this assessment (i.e. why does this obligation not rest with the researchers, see also my comments below). Also from the clopidogrel case just presented it does not become clear that the ERC has a special role to play.

6. Page 13ff: the options for the ERC in evaluating the risks are interesting and also the fourth option they present. It remains however somewhat unclear whether these options are unique to CER research, or could be applied to any risk-benefit assessment. If the latter is the case, this will have substantial impact on the content thus far (pages 1-12).

7. Page 14ff: "in particular, an ERC should not assume,…that the researchers submitting a protocol for review, although they may be experts, fulfill our criterion of recognized experts". Exactly, but why don’t they have the same obligation as members of ERCs? Meaning that before they submit the protocol to an ERC, they should make the same evaluation as members of ERCs should do?

8. Page 20: to base recruitment on patient preferences is an interesting strategy, though not novel. It may help the reader to also discuss here some objections, such as increased risk of biases and circumstances that may prohibit self-selection (for instance, children in the SUPPORT study could not easily move to another hospital).

9. Page 21: "OHRP has placed great emphasis on the risks of interventions being studied in the research. This is a mistake." This is a questionable statement and also somewhat puzzling in structure:

a. The authors now return to SUPPORT, while they have left this case for a while concentrating on the clopidogrel case. So it cannot follow from their discussion that OHRP made a mistake.

b. Even if one would argue that the OHRP made a mistake, then in my opinion thus far the authors have not convincingly argued that a comparison of two arms where O2 is administered by means of fixed protocols that deviate from what physicians typically do (more centers were in practice using the higher dose than the lower) does not pose patients at an increased risk compared with the standard of care. Arguments set out by Silverman and Dreyfuss (page 26), such as being less flexible, working with pulse oximeters that were altered and the risk of
inaccurate oximeter readings are ignored in the paper. While there may have been no added risks in the clopidogrel case, as the authors argue (pg 21, line 10-12), the standard of care in the SUPPORT study deviated from what patients may have received outside the trial. Apart from SUPPORT and clopidogrel we may think of cases where it is both standard of care to conduct surgery and to give medication. Although both treatments may be accepted strategies risks of the one procedure clearly differ from the risks of the other procedure and may be differently appreciated by patients. Therefore, in my opinion the deviation in itself may be sufficient to disclose this information to patients and may as such form a risk. Whether or not this risk is eventually high or low and whether patients are eventually better off by being in the trial is partially a post hoc statement and partially something that will depend on risk mitigation strategies such as the increased monitoring that the authors suggest.

10. Page 21, line 24-26: I do not think it is realistic to expect that ERCs will ever do systematic reviews. Again, why can this not be left to researchers who submit the protocol and isn't the task of ERCs to check whether they agree with the outcomes of this review?

Discretionary comments:

1. Abstract, page 2 line 16: "a case" : the reader thinks that this is SUPPORT, while it becomes clear only on page 10ff that this case is the clopidogrel case.

2. Abstract and background are almost similar

3. Page 5, line 9ff: I would add a 1-2 lines why the OHRP regarded it as a more than minimal risk study since on page 4 it becomes clear for the reader why proponents think it is standard of care, but not why opponents (like OHRP) think that it is more than minimal risk/not standard of care.

4. Page 10, line 16: why indeed?

5. A term that they remarkably do not mention in their paper is (clinical) equipoise- and that even though it is a controversial concept - it highly relates to their discussion. I believe that those interested in equipoise would be interested in their paper, and hence it might be interesting to mention it somewhere and as a key term.

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If not, please specify what is required in your comments to the authors.

Yes

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