Reviewer’s report

Title: The Research Burden of Randomized Controlled Trial Participation: A Systematic Thematic Synthesis of Qualitative Evidence

Version: 0 Date: 21 Oct 2019

Reviewer: Joseph Unger

Reviewer's report:

In this paper, the reviewers have conducted a systematic review in order to compile qualitative data on patient burden in trial participation.

My main question pertains to the relevance of a systematic review with respect to qualitative data. In contrast to a systematic review and meta-analysis, which seeks to quantify and establish an average effect (which is important for understanding the magnitude of effects), here the authors have applied a systematic review to qualitative findings, which essentially generates an amalgamation of all identifiable qualitative reasons patients have given in included studies. Although the systematic review process provides an underlying rigor to the study identification process, it could end up excluding studies that provided qualitative findings that are no less pertinent (since any reason provided by a patient about research burden is implicitly valid), suggesting the exclusion of the studies under a rigorous systematic review framework ends up being a bit arbitrary.

Background, lines 73-74: This would seem to need to be substantiated with a reference or two rather than just asserted.

Line 75: The authors indicated, "However, despite hundreds of thousands of RCTs, relatively few studies have considered the burden of research participation on patients." To clarify, do they mean, "within the context of the trial itself"?

Line 80: For clarity, I would recommend adding "patient" at line 80, "… however no review yet has specifically explored patient research burden."

The inclusion of patient benefits in this study is given little emphasis and reads like an afterthought. For instance, it was not mentioned in the abstract, and was only first mentioned in the paper at line 80, and never in the Methods section.

Line 113: The authors indicated that early phase studies were excluded… this would seem to require a bit more explanation, insofar as phase II is considered early phase but can be randomized.

Methods: The listing of Appendix tables in the text is a bit jumbled. The first appendix listed is Appendix 5 rather than Appendix 1. Line 93. Then appendix 6 is listed on line 124, followed by
Appendix 2 on line 129. I would suggest that the authors recheck the references to all tables/figures.

Figure 2 is the key representation of the results, and it would be helpful if the Results section was partitioned to reflect the key themes in Figure 2, that is, Factors Related to Burden, Burdensome Impacts and Consequences, and Psychological Impacts.

Line 207: The introduction to this new paragraph begins, "We also found that time consumed by trial participation…" as though this was a new theme, yet time had just been discussed at the end of the prior paragraph.

Lines 220-221: The authors wrote, "We further discerned factors related to research burden, which we differentiated into patient factors and trial factors (Figure 2; Appendix 4)." It is not clear how this is reflected in Figure 2, although I surmise it is encoded by the green and blue colors, yet there is not legend or description I could find in the manuscript indicating this.

Lines 316-319: The authors indicated, "Nevertheless, it appears that research burden is currently not considered by regulatory agencies, which mainly focus on the direct risk induced by the interventions and data collection. This burden is also rarely considered by researchers who are more interested in the comprehensiveness, quality and appropriate standardization of the data collected." These provocative assertions require some substantiation with references to published literature. In my experience, researchers consistently consider patient burden in the design of trials. As one example, researchers generally limit the use of patient reported outcomes to about 20 minutes to account for patient burden (see, Basch et al., JCO, 2012). Having said that, I agree with their subsequent statement that more can be done.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

No

Are the conclusions drawn adequately supported by the data shown?
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Yes
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?  
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Not relevant to this manuscript

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