Author’s response to reviews

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

Authors:

Nivantha Naidoo (nividanaidoo@gmail.com)
Van Thu (van.nguyen@clinicalepidemio.fr)
Philippe Ravaud (philippe.ravaud@aphp.fr)
Bridget Young (Bridget.Young@liverpool.ac.uk)
Philippe Amiel (philippe.amiel@inserm.fr)
Daniel Schanté (daniel.schante@gmail.com)
Mike Clarke (m.clarke@qub.ac.uk)
Isabelle BOUTRON (isabelle.boutron@aphp.fr)

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Author’s response to reviews:

Professor Isabelle Boutron
Equipe METHODS, CRESS UMR 1153
Hôpital Hôtel-Dieu
1 place du Parvis Notre-Dame
75004 Paris
France

Dear Editors,

Thank you for the opportunity to revise our manuscript entitled “The Research Burden of Randomized Controlled Trial Participation: A Systematic Thematic Synthesis of Qualitative Evidence”.

We have answered all the reviewers’ comments and modified the manuscript accordingly. Many thanks for your time and kind consideration.

Yours sincerely,
Professor Isabelle Boutron
RESPONSES TO REVIEWER 1 (Rachel Louise Shaw)

Please see our responses below your comments enumerated point by point.

“This is an excellent and necessary piece of work. The authors conducted a review of qualitative evidence exploring experiences of participating in randomised controlled trials. The review follows appropriate systematic review processes and the authors used both PRISMA and ENTREQ to manage transparency of their review. There are a few recommendations I would like to make which I think will provide a better context for this work and potentially boost its salience for readers.”

Thank you very much for your helpful feedback and insightful comments. They have certainly made an improvement to the manuscript.

1. “I think the objectives of the review are central to implementation science and the work could be framed within that context. Successful implementation of an intervention requires acceptability and feasibility assessments of the trial and key to those are participants' experiences of taking part. Poor recruitment and high rates of drop-off challenge the power of a trial and these are likely to be due to participant burden, as shown in this review. In short, the challenges of external validity noted in the review findings and conclusions are also challenges to implementation science. I'd like the authors to situate their review within this context to demonstrate that there are implications here for implementation science.”

Thank you for this recommendation.
We fully agree that trial participation and research burdens experienced have implications for implementation science.
We now add this concept in the introduction section:
“All these tasks could be responsible for important psychological, physical, and financial burdens for patients which may affect their willingness to begin and complete participation in a trial [1] and consequently have some implications for implementation science.”
And in the discussion section under heading Implications and subheading Impact of trial recruitment and retention:
“Our results have also some implication for implementation science. Indeed, successful intervention implementation requires that patients accept trial participation. Further, slow recruitment increases costs and delays the transposition of evidence into policy and practice. Furthermore, results are less reliable if the planned sample size is not achieved [2, 3] and a high refusal rate raises important concerns about the external validity. The extrapolation of the findings to the target population will not be guaranteed [4-9] and the financial investment in the research might be wasted.”

2. “The humanisation of healthcare framework (https://www.tandfonline.com/doi/pdf/10.1080/17482620802646204 and https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/the-humanising-care-project/) aims to re-humanise healthcare and I think several of the issues raised by this review require us to re-humanise the processes involved in recruiting
participants to trials. I think adding the humanisation framework as context to the work will boost its salience in conveying the need to do things differently in trials recruitment and management. A useful recommendation of this review would be to highlight the need to re-humanise healthcare research. This adds some weight to the argument of needing to carry out 'minimally disruptive clinical research'. As an aside, I think this label needs to be problematised a little - it downplays (possibly disrespects) the burden experienced by participants in a kind of de-humanising way.”

Thank you for highlighting this important concept.

We now emphasize the need to re-humanise healthcare research and reference the paper highlighted.

We would like to keep the wording “minimally disruptive clinical research” by reference to the concept of “minimally disruptive medicine”[10]. We clarify that although clinical trial participation will always be burdensome for patients, investigators should aim to reduce this burden as much as possible and move toward a minimally disruptive and compassionate clinical research.

“Toward minimally disruptive and compassionate clinical research
Funders, trialists and methodologists should rethink the planning and conduct of trials. First, they must minimize research burdens and should implement “minimally disruptive and compassionate clinical research”. Second, in the same way a framework has been developed for the humanization of healthcare[11], we need to move towards compassionate clinical research. Indeed, our results highlight that most of the burden experienced by participants are psychological burdens. While it is impossible to completely reduce this burden, trialists could implement interventions to favor compassionate and empathic support to patients. Such support has demonstrated its beneficial effect for healthcare.[12]”

3. “I also wonder if the authors would think it appropriate to call for a re-think in trial design, recruitment, statistical analyses etc. There are clearly (and necessarily, from a methodological rigour standpoint) strict guidelines in this kind of (pseudo-experimental) work, but threats to rigour should be weighed against the threats to external validity. It’s a bit like the precision-recall trade-off in doing a systematic review - is the loss of participants/power a worthy trade-off for creating a less-burdensome participant experience? Or should we rather be re-thinking the way we test interventions in a less burdensome ways from the outset, which may require significantly challenging the status of RCTs and systematic reviews of RCTs at the top of the evidence hierarchy. I am not asking the authors to do anything specific here other than to touch upon these wider issues related to the work they have undertaken and the future of clinical research.

Thank you for this comment.
Although we agree there is a trade-off between internal and external validity, we also strongly believe that we can considerably reduce research burden in trials without any impact on the internal validity. There is some evidence that trialists are collecting too much data and are requesting too many more visits than needed.
Nevertheless, we agree that other study designs should be explored such as trials embedded in routinely collected data or observational studies. These issues are now highlighted in the discussion section: “Further, we need to explore other study designs that could reduce burden and improve external validity such as trials embedded in registries, cohort [13] but also observational studies and use of routinely collected data.”

4. “I noticed a few typos in need of correction:”
   4.1 “line 76, 81 patient's should be patients”
   4.2 “line 256 quit - think it should be quite”
   4.3 “line 291 insert "treatment" after cancer”
   4.4 “line 323 reference required for 'minimally disruptive clinical research’”
   4.5 “line 324 implement - not implements”

We apologize for these oversights and thank you for your careful inspection. All the modifications have been made.

5. “The tables are really useful. And I really like the figure representing the themes generated in the synthesis.”

Thank you very much.

RESPONSES TO REVIEWER 2 (Joseph Unger)

Thank you for your kind and helpful feedback and comments. Please see our responses below your comments enumerated point by point.

1. “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.”
Thank you for your comment.
Qualitative research is increasingly important for clinical research policy and practice[14] and the patient voice has long been acknowledge as neglected[15, 16] yet is essential to improve the quality and value of research[17].
Systematic reviews of qualitative research provide essential information and are widely recognized as such. It is not an “amalgamation” of all qualitative data but a synthesis performed following well recognized processes[18]. In the context of this project, the synthesis of all qualitative studies exploring the burden allows for a better understanding of this concept. Indeed, each study was performed in a different context involving a limited number of participants. Synthesizing all this information provide very valuable information. As for all systematic reviews (even when a qualitative synthesis is provided), we defined inclusion and exclusion criteria. Here our eligibility criteria were large which allowed identifying a large number of reports.

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

Thank you for this comment. We have added a reference: [1]

3. “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"?"

Thank you. This has been clarified as requested: “However, despite hundreds of thousands of RCTs, relatively few studies have considered the burden of research participation on patients within the context of the trial itself.”

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

Thank you. We have added your recommendation.

5. “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.”

Thank you for your comment. We fully agree and now mention these results in abstract and methods section.
6. “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.”

Thank you for your comment. We agree that early phase trials can be randomized. They were nevertheless excluded in the context of this review as we believe they might raise specific issues and we wanted to mainly focus on phase III trials. This is now reported and a limitation has been added.

7. “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.”

Thank you for this comment. We have duly double checked the references to all tables and figures. To improve coherence of the paper the appendices have been re-ordered so that they are called in the same numerical order in the manuscript as in the appendix.

8. “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”

Thank you for this comment. We would like to clarify that the theme “Burdensome Impacts and Consequences” contains 3 subthemes “Psychological impact”, “Physical impact”, and “Cost impacts”. We modified the figure to avoid any misunderstanding. We also now added subheadings to the results section to clarify the different themes as requested.

9. 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”

Thank you for this comment. We agree and move this sentence above.

10. “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”

Thank you for your comment. We have corrected this error in the manuscript text as it was supposed to have read: “We further discerned factors related to research burden, which we differentiated into patients’ interpretation and trial logistics” This has been corrected and is now coherent with the text in the figure.
11. “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”

Thank you for this interesting comment. We agree that it was stated too strongly and that progress has been made in this respect however more needs to be done. We have rephrased the text to reduce the tone.
“Nevertheless, research burden is probably insufficiently considered by regulatory agencies, which mainly focus on the direct risk induced by the interventions and data collection. This burden is also inadequately considered by researchers who may be too busy focusing on the comprehensiveness, quality and appropriate standardization of the data collected.”

RESPONSES TO EDITORS' ENCOURAGEMENT AND REQUESTS

“In addition to the reviewers' comments, we encourage you to highlight the novelty of this study's result, compared to what is already available in the literature.”

Thank you for this comment. This is now highlighted in the discussion.

We have added the figure legends and additional file subsection as requested.


4. Rothwell PM: External validity of randomised controlled trials: "to whom do the results of this trial apply?". Lancet 2005, 365(9453):82-93.


