Reviewer’s report

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

Version: 0 Date: 16 Oct 2019

Reviewer: Rachel Louise Shaw

Reviewer's report:

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.

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.

The humanisation of healthcare framework (https://www.tandfonline.com/doi/pdf/10.1080/17482620802646204 and https://www.hra.nhs.uk/planning-and-improving-research/applicationsummaries/researchsummaries/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.

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.

I noticed a few typos in need of correction:

line 76, 81 patient's should be patients'
line 256 quit - think it should be quite
line 291 insert "treatment" after cancer
line 323 reference required for 'minimally disruptive clinical research'
line 324 implement - not implements

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

**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?**
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Not applicable

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