Reviewer’s report

Title: WHAT'S THE UPTAKE? Pragmatic RCTs may be used to estimate uptake, and thereby population impact of interventions, but better reporting of trial recruitment processes is needed.

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Reviewer: Merrick Zwarenstein

Reviewer's report:

I have read the comments of previous reviewers and the authors responses to these comments. I agree with the reviewers that the problem the authors address is important, and the proposed solution ingenious and potentially useful. The authors' responses deal successfully with all of the comments raised by the reviewers, and so in this sense I think the paper should go forward for publication.

However, and this is pretty much inevitable, new eyes see new problems. I appreciate that the narrowing of the scope of this paper to encompass only pragmatic trials has successfully dealt with the previous reviewers objections; but in so doing I see that inverse problems have arisen. These relate to the lack of clarity around what is meant by "pragmatic trials".

The authors' definition of pragmatic trials is simplistic (including the full range of patients), and doesn't have references. The concept of pragmatism in RCT design is not new, and has been under discussion over the last decade or so, with hundreds of citations to the following potential sources (each with their own approach), any or all of which could be cited. These include the original paper and book by two French statisticians, Schwartz and Lellouch from 1967, Dave Sackett's text book on Evidence Based medicine, from about 2005, the Consort Statement extension for pragmatic trials from the BMJ (Zwarenstein et al) , the first PRECIS paper from the Jnl of Clin Epi (Thorpe et al), and the fairly recent PRECIS2 paper from the BMJ (Loudon et al). All of these include far more specific and extensive definitions, explanations and descriptions of the characteristics that contribute to pragmatism in the design of randomized trials. I think any of these would be a suitable source for a better description and definition of pragmatic trials, which the paper needs, since it rests so heavily on this category of randomized trials.

It is therefore important to select only pragmatic trials: if the trials are not pragmatic in character it is quite likely that the overall effect size estimate will not translate directly to real world circumstance, and so it will be insufficient simply to multiply the trial effect size by uptake to produce an estimate of population impact. If some of the trials are more explanatory, a much more complex formula will be needed, one which adjusts the efficacy estimate to bring it closer to a true effectiveness estimate, prior to multiplying it by the uptake. Its hard to see what scientific basis this could use.
With a more detailed set of criteria for these trials, perhaps with a table of individual trial characteristics, it will be easier to explain how the selected trials are pragmatic, how these selections were made, and how reliable they are. This is glossed over in the paper at present. So, for this reason I think a more formal selection of pragmatic trials is required.

**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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Yes

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Yes

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I have no competing interests, but I contributed to a number of papers in which the concept of pragmatism in randomized trials was explored and publicized. My recommendations on this paper are undoubtedly influenced by my views on pragmatic trials.

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