Reviewer’s report

Title: Real-world evidence: How pragmatic are randomized controlled trials labeled as pragmatic?

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Reviewer: Elaine Morrato

Reviewer’s report:

The authors raise an important debate - how pragmatic must a trial be to be labeled 'pragmatic' in its publication title? It is important so that we ensure standards are applied, otherwise it may lead to misleading interpretations about the generalizability of the findings.

I have a couple of minor, but essential edits, that I suggest.

Search methods. Please include the search time frame and parameters used in the text. I think the paragraph beginning line 110, page 6, would be a good place. It sounds like the search simply involved finding RCTs with the word "pragmatic" in the title.

Search strategy interpretation. Please also include discussion/limitation implications of this search strategy. Yes, it reflects how authors 'label' their study. However, it under-represents the number and type of pragmatic trials reported in the literature. For example, the term 'large simple trial' is another prevalent term to describe the same pragmatic trial concept. Also, authors may not have included 'pragmatic' in their title, when in fact the study would meet many of the PRECIS-2 criteria. I can think of several major comparative effectiveness trials that fit this area -- e.g., ALLHAT (hypertension), CATIE (schizophrenia), SMART (FDA mandated -Salmeterol Multicentre Asthma Research Trial (SMART) ). The label "pragmatic" is simply more in vogue in recent years.

I use/endorse the use of PRECIS-2. However, I disagree with the authors that a single-center RCT cannot be pragmatic. It is a spectrum of pragmatism. The PRECIS-2 authors acknowledge you don't need a 5 on all scales to be labeled 'pragmatic'. The outcome, analysis, flexibility in delivery, etc can all be accomplished in a single center. I agree the degree of heterogeneity, and greater generalizability offered, is better with more sites. However, the language in the debate makes it a more stark, black-white contrast when it really is a gradient. I agree with the authors' general point, but my recommendation is to soften this language so it is not so absolute.

I also used to be involved in drug development and disagree with the authors that a pragmatic drug trial can only occur once the drug is on the market. And thereby, drug trials conducted prior to market authorization and labeled 'pragmatic' are by definition incorrect. FDA's requirement for ITT analysis is by definition one of the PRECIS-2 definitions of pragmatism. With the movement of patient-centered drug development and real-world evidence, there is increasing emphasis being placed on outcome measures used in Phase 3 protocols that are more pragmatic, another PRECIS-2 domain area. In addition, Phase 3b trials begin prior to market authorization
and may provide supplemental comparison claims or information necessary for reimbursement decisions, and as a result are often more pragmatic in nature to reflect real world use. Again, I agree with the authors' general point that most pre-authorization studies are on the more explanatory side of the scale, but my recommendation is to soften this language so it is not so absolute.

Operationalizing the concepts. I agree with the authors' recommendations for operationalizing the use of PRECIS-2. I have some suggestions for their consideration to make the operationalizing even more explicit:

1) journals require the PRECIS-2 figure as an online supplement/figure for studies claiming they are pragmatic. Just like journals require the use of the CONSORT diagram. At its heart, PRECIS-2 is an extension of the CONSORT diagram.

2) Justification for being a pragmatic trial (and use of the PRECIS-2 figure) should also be required in Clinical Trials.gov, and other trial registry systems. That would prevent investigators from labeling a trial 'pragmatic' post hoc just because the term is now more in vogue. It needs to be 'baked into' the prospective design of the trial.

3) Journal editors should set a standard for what constitutes the use of "pragmatic" in a publications title. Must a certain scoring threshold be met (and justified) for all 9 constructs? 6 out of 9? etc. And also, what is the minimum threshold for each construct? A score of 4 or more out of 5? 3 or more?

One last comment that would be good for the authors to address: How can scoring be standardized - it really depends on the anchors used for a '1' vs. a '5' - and that will vary depending on the patient population, clinical setting and drug being tested. The standard CONSORT diagram is more self-explanatory and absolute (i.e., numbers screened, enrolled, etc.). Whereas, the use of PRECIS-2 is a more nuanced and relative assessment.

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I direct the Pragmatic Trials and Dissemination/Implementation Science unit for the Colorado Clinical and Translational Sciences Institute, one of 50+ institutions funded by NIH to promote translational research. We have developed a pragmatic trials training resource (www.CRISPeBooks.org) which uses PRECIS-2 as our framework (the focus of this debate paper).

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