Reviewer’s report

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

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Reviewer: Shaun Treweek

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Real world evidence: How pragmatic are randomized controlled trials tagged as pragmatic?

General

I have an immediate conflict to highlight, which is that I am one of the developers of PRECIS-2.

I like this paper and agree with the suggestions; indeed we have discussed similar ideas within the PRECIS-2 development team. It is very pleasing to see that a group independent of the development team are making these suggestions. Like them, I am sure that many trials labelled pragmatic are not very pragmatic at all and there is a danger with allowing any old trial to be called pragmatic on a whim. I do have a few comments though and these are listed below.

Compulsory Revisions

General

1. The authors say, essentially, that trials done in single centres, are placebo controlled, or are pre-licensing trials (or any combination) can never rightly be described as pragmatic. PRECIS-2 assumes usual care as the comparator and says explicitly that trials in single centres will pull the trial towards explanatory. So there I agree. I’m much less convinced about the pre-licensing argument though. Indeed, licensing trials designed with a genuinely pragmatic approach to design decisions and compared to the best alternative or alternatives sounds like a pretty good idea to me rather than an explanatory trial followed, perhaps but maybe not, a trial taking a more pragmatic approach. Payers certainly (as the authors state) are interested in whether something works in their actual patient populations, not some highly selected subgroup tested in very non-routine circumstances. Complex interventions are definitely tested 'pre-licensing' in pragmatic trials so that evidence can be gathered to convince payers that the intervention is worth investing in. Testing medicines ought to be the same I think, although it may be regulators, not trial teams, who force designs to be less than pragmatic (those placebos for example may be more due to regulators than trialists).

It would be good if the authors could clarify whether they think pre-licensing is can never be pragmatic, or whether, perhaps, they could be if the regulatory regime wasn't sending trial teams in the direction of explanatory designs by its requirements.
Background

p4, line 61-63. This bit of text suggests that there is a trade-off between internal and external validity, with explanatory valuing internal validity, pragmatic external validity. I don't think this is true (indeed, when we have looked, we have found no link between internal validity as measured using the Cochrane Risk of Bias tool and PRECIS-2 scores. Unhelpfully, we have not yet published this). Essentially what we believe is that all trials need to aim for high internal validity; those that aim to be pragmatic need to also aim for high external validity. Kirsty Loudon wrote a good rapid response to a BMJ article on this point: http://www.bmj.com/content/349/bmj.g6694/rapid-responses It would be good if the authors had a look at their text and checked to see if they really meant to say that there is a trade-off to be made.

Minor Essential Revisions

Abstract

1. p2, line 26/27. I'd reword 'Pragnmatic RCTs assess...' since they don't only assess medicines, they can assess treatments in general. Also, I don't think the medicines have to be available, the pre-licensing point I make above. The authors should have a think about the wording and adjust it, if they consider it appropriate, after considering the pre-licensing point above.

Background

1. p4, line 58/59. Schwartz and Lellouch talked about 'laboratory conditions' and 'normal conditions' for explanatory and pragmatic trials, respectively. I think this is an easier distinction than is currently given: essentially do you create an artificial testbed to tease out a bit of causal understanding, or do you test the treatment in normal conditions, as it would be used more generally. Dave Sackett made it even simpler: can it work in ideal circumstances vs does it work in routine care? The authors might want to tweak their sentence a bit to make the distinction clearer.

2. p4, line 66/67. I'm not sure I agree with the typical pragmatic trial paradigm presented here, at least in part because of the pre-licensing point I mentioned earlier. That said, it's a paradigm not absolute truth so if the authors don't feel it needs to change after considering my pre-licensing point, that's ok.

3. p5, line 82. I think the PRECIS-2 tool can be used to tag a trial as to where it sits on the explanatory - pragmatic spectrum rather than only whether it is pragmatic or not. I guess the way I'd see this working is there is a PRECIS-2 wheel, a line such as 'The X trial scored 4 or 5 on three domains, 1 or 2 on 5 domains and 3 on one domain. based on these scores, the Y journal considers this trial to be explanatory in its design approach. See Z for more details.' What would be great would be if many journals (and funders, ethics etc) what scoring rules were to be found at Z. We'd then all know what we were getting. Could the authors considering adding
something about explanatory too just to be clear that its about placing the trial on a spectrum of design approach?

Argument

1. p 5, line 93/94. Depending on the setting, I think trial could be applicable to only the setting it was done in and still be highly pragmatic. If the setting is a single hospital this is clearly not the case. But if the setting was, say, cancer prevention delivered by a charity at leisure centres across Scotland (a trial I'm involved with now) then I think that trial will be applicable to its own setting but not necessarily generalisable beyond Scotland. In other words, I think the authors need to be a bit clearer about what they mean by setting. Trialists can't always design trials to work in healthcare settings they don't know but the point is that if rolled out in the setting in which the treatment was evaluated, you expect the routine result to be similar to the trial result if that trial was pragmatic. This may be far from the case if it was explanatory.

2. p6, line 107/108. I don't think pragmatic trials should set out to avoid blinding. It is often not possible and then we rely on the assessor blinding that the authors mention but I still don't think the aim should be to avoid blinding because it risks adversely affecting internal validity. Kirsty Loudon touches on blinding in the BMJ link I give above. If the authors don't want to change the text, can they acknowledge that others disagree (Kirsty and I certainly..) and then say why they are right and we are wrong. I'm fine with that, the text just needs an acknowledgement of the debate and a bit more of a justification.

Publication of protocols and results of pragmatic RCTs

p9, line188-191. One thing to note here is that some interventions aim to change, say, care organisation, or the flexibility of delivery, meaning they may be explanatory one domain but highly pragmatic on all the others. Where this happens we (the PRECIS-2 development team) tend to put a not on the wheel saying that, say, organisation change is the point of the intervention and that is why the domain is explanatory and everything else is more pragmatic. This is mentioned on p6 of the BMJ PRECIS-2 article and it would be good to acknowledge this possibility here.

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I am one of the developers of the PRECIS-2 tool that the authors discuss and recommend for further use.

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