Reviewer’s report

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

Version: 1 Date: 02 Jan 2018

Reviewer: Merrick Zwarenstein

Reviewer’s report:

This is a well written and well designed study of an important and topical problem in the area of research integrity. As the authors correctly identify and demonstrate, an increasing number of randomized trials are self labelling as pragmatic, without evidence that they are indeed pragmatic, even, in my experience without any description or reference as to what they mean by pragmatic.

It is therefore very timely that the authors have decided to investigate whether self labelled pragmatic trials are actually pragmatic, using a widely accepted criteria set - the PRECIS 2 tool.

(note of methodological conflict of interest- i am probably not entirely objective about this paper as i am was centrally involved in development of the PRECIS 1 and 2 criteria set and led the movement to give renewed attention to the work of Schwartz and Lellouch, the original authors of the concept of the pragmatic/explanatory continuum).

The authors conduct a simple and elegant study to test this idea, by reviewing all recent RCTs, extracting a set devoted to evaluation of medicines, and assessing these rcts according to a number of fundamental characteristics without which, they argue, no trial should be labelled pragmatic. Although they do not include data for each trial, nor evidence that their evaluation of each of the criteria was consistent, and although they do not deeply explain why they selected the specific criteria that they did select, I think that their paper is intended as an argument, rather than an empirical paper, and so this initial relatively light (methodologically speaking) approach to their question (how pragmatic are self proclaimed pragmatic trials) is appropriate. I would largely agree with the criteria they use to distinguish pragmatic trials (with one partial exception that i describe below). I agree that a placebo controlled trial, as they eloquently explain, cannot be said to be a pragmatic trial and I agree that a single centre trial is too restricted in its generalizability to be counted as a pragmatic trial.

However, I disagree with the authors' assertion that a new intervention (note that I am not saying 'pharmaceutical intervention") cannot ever be evaluated in a pragmatic RCT. The authors argue that the existing GCP and other equivalent regulations for pharmaceutical or biologic registration preclude the possibility that the recruitment path, flexibility, adherence and follow up approaches can be compatible with pragmatic designs. I agree with this assertion of non pragmatism for new drug interventions, but I do not think it is true for non-pharmaceutical interventions, which, given their lack of requirement for GCP regulations, could in fact be evaluated in an RCT with a
pragmatic design, i.e. a trial that closely mimics really world approaches to recruitment, adherence, flexibility and follow up.

This creates a quandary for me: while I accept that RCTs of pre preregistration drugs are likely to be explanatory on the larger set of PRECIS 2 criteria of recruitment path, adherence and flexibility, I do not accept that this applies to non pharmaceutical interventions. For this reason, I think that the paper needs a small amount of editing to clarify this, so that it avoids making this statement too broad, i.e., extrapolating beyond medicines trials onto non medicines trials of psychotherapy, behavioural interventions, and service delivery interventions.

At present the authors write:

64 :When assessing medicines (drugs or biologics), the typical paradigm of an explanatory RCT is 65 the double-blind, placebo-controlled trial assessing efficacy of a new medicine or indication 66 before licensing [8]. Conversely, the typical paradigm of a pragmatic medicine RCT assesses 67 effectiveness of two commercially available medicines that are prescribed in routine care [9].

I would suggest the following:

64 :When assessing new medicines (drugs or biologics) or new indications prior to licensing, the typical RCT is highly explanatory (double-blind, placebo-controlled) Conversely, the typical paradigm of a real world, comparative effectiveness medicines trial is highly pragmatic, and most often compares the 67 effectiveness of two commercially available medicines that are already widely prescribed in routine care but have not previously been compared to eachother [9].

I would also change the following text:

The authors currently write:

Consequently, in principle, 95 pragmatic RCTs of medicines should assess already marketed medicines (rather than those still 96 in clinical development before licensing) and should be done in several sites providing care to 97 heterogeneous populations. Moreover, when they compare different medicines head-to-head, 98 using multiple placebos for blinding is a substantial deviation from usual clinical practice; e.g. 99 taking two masked medicines, one active and one placebo, is a very different patient 100 experience than having to take only one medicine. Also, RCTs that compare a single active 101 medicine versus a single placebo can hardly be pragmatic. Uncertainty about whether the 102 active medicine will be assigned would affect what patients interested to participate and may 103 also affect therapeutic response compared with real life. Furthermore, the patient instead of going to his/her usual pharmacy to acquire (with or without co-payment or full-payment) the 105 drug, would typically go to a specific pharmacy where he/she will be given (free of charge) 106 assigned packages of drug or placebo.
All this could produce the Hawthorne effect in many participants. Therefore, pragmatic trials should avoid blinding (except for blinding assessors of 108 outcomes, whenever possible).

I suggest a version which continues to makes clear that most preregistration drug trials are going to be of necessity, explanatory, but which explicitly allows that this phenomenon may not be a problem in rcts of new interventions that are non drugs/bioligics.

Consequently, in principle, in order to be defined as 95 pragmatic, an RCT of a medicine should be done in several sites providing care to 97 heterogeneous populations. Moreover, when they compare different medicines head-to-head, 98 using placebos for blinding is not desirable as it is a substantial deviation from usual clinical practice; e.g. 99 taking two masked medicines, one active and one placebo, is a very different patient 100 experience than having to take only one medicine. Also, RCTs that compare a single active 101 medicine versus a single placebo can hardly be pragmatic, since uncertainty about whether the 102 active medicine will be assigned would affect which patients participate and may 103 also affect therapeutic response compared with real life. Furthermore, the patient instead of going to his/her usual pharmacy to acquire (with or without co-payment or full-payment) the 105 drug, would typically go to a specific pharmacy where he/she will be given (free of charge) 106 assigned packages of drug or placebo. All this could produce the Hawthorne effect in many participants. Therefore, pragmatic trials should avoid blinding (except for blinding assessors of 108 outcomes, whenever possible).

(and I suggest adding here a copy of a section from later in the paper- lines 158 onwards).

Finally, the question of whether preregistration medicines can be evaluated in pragmatic trials:

158 RCTs on medicines before they are licensed could hardly be pragmatic since they have to comply with clinical trials regulations that 160 have no resemblance to their subsequent application in routine care (reference needed for this statement).

The 'recruitment', 'organisation', 'flexibility: delivery', 'flexibility: adherence' and 'follow-up' domain scores in the PRECIS-2 would therefore be assessed at 1 or close to the explanatory extreme for RCTs of such preregistration medicines.

This of course may not apply to RCTs of new (but non medicinal) interventions, e.g. surgical or services delivery interventions that are not covered under GCP regulations, which may be designed to be more pragmatic.

And finally I suggest deleting the following text:

However, similar considerations could

174 apply to trials of other types of interventions. For example, in our sample of RTCs that were 175 tagged as pragmatic (Box), we found more trials on care management (n=164) than on medicines and ..... and .... on psychotherapy. However, 177 the mere requirement to participate in
a controlled clinical experiment already poses substantial distance from everyday life experiences for interventions such as cognitive behavior, diet, exercise or acupuncture. Therefore, probably many of these trials are not genuinely pragmatic, but this is difficult to judge without in depth knowledge of their exact....

I suggest replacing this text with the following:

While we are confident that our finding applies to RCTs of medicines, it remains to be evaluated whether these findings apply to trials of other, non-medicines interventions.

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