Reviewer’s report

Title: The ethical challenges raised in the design and conduct of pragmatic trials. An interview study with key stakeholders

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Reviewer: Rafael Dal-Re

Reviewer's report:

I thank the editor for giving me the opportunity to review this manuscript.

This is an interesting, well written manuscript in which the authors reported their findings after interviewing 45 individuals that have previously involved in pragmatic RCTs (pRCTs). These 45 individuals had different backgrounds and countries. It is a rather long manuscript, as are usually those reporting on qualitative research. However, I suggest to reduce its length to make it easier to read.

This report provides new information on the perception different stakeholders have on pRCTs, however, to fulfil the objective the authors should address 2 main issues:

a) All types of pRCT are considered as if there were no fundamental differences between them. So, in the manuscript there is no mention on the 2 types of pRCTs: participant-level RCTs and cluster RCTs (these latter are mentioned on page 25, Discussion). Readers should understand that all the text refers to both types of pRCT, although I believe that the work was focused mainly on participant-level pRCTs.

Also, assessing 2 marketed medicines that have been prescribed for a given indication for many years in a pRCT, has little to do with conducting a quality improvement pRCT. The differences are not clearly established along the manuscript. For instance, participants in a pRCT assessing medicines most likely had a very different experience than that of those individuals that participated in quality improvement pRCT. This should be commented in the manuscript.

b) Many interviewees believe pRCT have features that, from my perspective, are far from a true pRCT, that should resemble usual clinical practice, in a normal clinical encounter. Introducing non-usual elements will render the trial as (most likely) not pragmatic or with limited pragmatism. This is the most relevant issue I found in this work. A number of comments included in the text and in Table 2 hardly have any relation to what I believe a pRCT should be. This fact impacts on many messages of the report and will create some confusion on readers with limited knowledge on what pRCTs are (or should be).

Other comments:
In the EU, there is only one regulatory framework, that of medicines (and devices at a national level). Generally speaking, pRCTs assessing other types of interventions are not regulated — apart from the need to have the trial protocol approved by the relevant REC and the approvals needed for ensuring funding. If this scenario is different in Canada, authors should comment on this to help readers understand the Canadian 'regulatory environments'. This is relevant, since in the EU a 'regulator' could have experience only in regulated interventions (medicines, devices) pRCTs, but not when non-regulated interventions were assessed. In this report, 5 interviewees were regulators.

How were the pRCTs identified? Which were included? Why these were included? I strongly suggest to including a brief description (A Box or Table) of those pRCTs in which interviewees were involved. There is not the need to include all the pRCTs, but an example of different pRCTs assessing different types of interventions.

I am somewhat confused here. My understanding is that in a pRCT interventions are provided as in normal clinical practice. This means that if an intervention (let's say a medicine) has X risks (adverse events profile), this is the same whether the patient receives the medicine in a pRCT or outside the pRCT.

As McKinney et al (Clin Trials 2015, 12: 494) stated "The [US] Common Rule itself makes clear that the appropriate benchmark for assessing minimal risk is the degree of incremental risk added by participation in the study: In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). With this last point in mind, we believe that a reasonable interpretation of the regulations is that minimal-risk determinations should be made by assessing the degree of risk introduced by study participation over and above the risk that characterizes the person's life if he or she was not participating in the study."

In other words, I can hardly understand how any could think that patients participating in a (truly) pRCT could "be [in] a greater risk of an adverse outcome because of their participation in the trial" (Line 248). In Lines 259–60, the same idea is conveyed, something that I cannot agree with. I can be wrong, but I think that these two interviewees (those of quotes # 1.1 and 1.2) have a wrong interpretation of what a pRCT is. How can a pRCT could put participants "into a high-risk situation" (beyond the risks of the use of interventions outside the pRCT) (Quote 1.1). Similarly, "how people are affected because of the pRCT" (Quote 1.2), means that this ethicist has a different interpretation of what is a pRCT; people are minimally (if any) affected because of the pRCT; otherwise, it is not a pRCT but an explanatory RCT. I am not assuming that my interpretation is the correct one; but since many readers will be aligned with me in my interpretation of what a pRCT is, authors should comment on this, as they did in Lines 267–278 with regards to ethics review process.

If there is an "external research team", then the trial does not mimic usual clinical practice…Again, an issue regarding what interviewees think a pRCT is.
Lines 375─6. Here is an example of what I referred above: selection criteria should be based on what is included on the medicines' leaflets approved by the regulatory authorities or that supported by enough scientific evidence. When non-regulated interventions are assessed —so there are no 'approved leaflets'—, then the situation is different to that of a pRCT on marketed medicines: only scientific evidence could be claimed, and this could bring some issues into the discussion, for instance, when the quality of that evidence is not robust enough.

Lines 380─4. A pRCT with medicines should include the target population as per the approved leaflet. Excluding groups will reduce the degree of pragmatism, unless one is conducting a trial in a specific population (eg, children) with medicines that are approved for both children and adults. Of course, if the pRCT is conducted only in children, the generalizability of the results will only be to children of other settings.

Discussion

The discussion is too long. I would suggest to reduce its length in 2 pages or so (now it has 7).

However, my most important comment is that, from my perspective, authors should guide readers' reflection rather than commenting what interviewees have mentioned. Let me mention 3 examples:

a) Lines 552─6. I wonder what groups owe protections within a pRCT, if this must recruit participants that would have received the assessed interventions in usual practice. If, for instance, two psychotherapy treatments are well established for a given indication and some investigators want to conduct a comparative effectiveness pRCT, which are the groups to be identify that owe special protections? I am not sure if the authors would agree with me, but the critical point when discussing on pRCTs is that they should resemble usual practice. Only those 'groups' that owe protections in usual clinical practice should be protected in pRCTs. So, if those psychotherapy treatments are not used in children, then the pRCTs should exclude children.

b) Lines 572─6. Here what I do believe is interesting are the first 2 lines; the rest —when discussing that other studies have found patients to be excluded (...) for practical reasons— I suggest to delete it: a trial in which investigators are not behaving as in usual clinical practice is difficult to be correctly considered as pragmatic.

c) Lines 601─5. Once the authors have commented that the concept of usual care has different interpretations, what I would expect is that they discuss what should be the approach to be taken by investigators willing to design a pRCT.

One final comment. Why the authors referred to 'a usual care arm' (Line 608; Table 3, page 47). For me, and I would bet that for other readers, this is a typical explanatory trial wording: there is an 'experimental arm' and a 'usual care' arm. However, in a pRCT, both arms should be 'usual care arm'. This is the core of a pRCT: the comparative assessments of interventions that are already considered as usual clinical care.
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