Author’s response to reviews

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

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

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Trials
Response to reviewer comments:

Reviewer #1:

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.

Response: We thank the reviewer for the positive comments about our manuscript. As suggested, we have reduced the length of the manuscript, particularly the discussion and introduction.

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.

Response: Our larger project about ethical issues in pragmatic trials is not limited to a particular kind of trial design, but considers pragmatic trials more broadly. Accordingly, we did not limit our interviewees to a particular design of pRCT; participants were free to raise any ethical issues arising in trials they had experience with – regardless of design. We have now added in a paragraph within the introduction (lines 106-111), methods (lines 162-172) and at the start of the results section (lines 227-237) that makes it clear that pragmatic RCTs have diverse designs and attributes and the interviewees had a range of experiences (some covering different designs and some with different interventions). We have also added additional information in the methods to explain that we deliberately sought out participants with diverse experiences of different trial designs and interventions.

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).

Response: We agree with the reviewer that the interpretation of what constitutes a pragmatic RCT does vary. Indeed, as Califf and Sugarman note: “These terms [pragmatic (or practical) clinical trials] have been used by different experts to denote various concepts, resulting in ambiguity that can lead to miscommunication.” We agree that there likely is an underlying difference between the reviewer and some of our respondents as to what would constitute a pragmatic RCT. However, we believe that this reflects the reality of diversity of pragmatic RCT definitions, as evidenced in the literature:

Califf and Sugarman Clin Trials. 2015;12:436-441: “we propose three key attributes of PCTs: (1) an intent to inform decisionmakers (patients, clinicians, administrators, and policy makers), as opposed to elucidating a biological or social mechanism; (2) an intent to enroll a population relevant to the decision in practice and representative of the patients/populations and clinical settings for whom the decision is relevant; and (3) either an intent to (a) streamline procedures and data collection so that the trial can focus on adequate power for informing the clinical and policy decisions targeted by the trial or (b) measure a broad range of outcomes.” (emphasis added)

Anderson et al Clin Trials. 2015;12:511-519: “In contrast to explanatory clinical trials, pragmatic clinical trials (PCTs) are designed to evaluate the comparative effectiveness of interventions within routine clinical settings.”

Concannon et al Clin Transl Sci. 2014;7:164-171: (citing the CTSA consortium definition): “A pragmatic clinical trial is a prospective comparison of a community-, clinical-, or system-level intervention and a relevant comparator in participants who are similar to those affected by the condition(s) under study and in settings that are similar to those in which the condition is typically treated.” (emphasis added)

Others have used the term Early pragmatic trials (EPTs) to refer to RCTs comparing new interventions with existing standards. Moreover, “In pragmatic research, existing treatments can be tested against one another for their comparative effectiveness in real life, or new treatments are compared with (a variety of) usual care for a specific condition.” Kalkman et al. Trials. 2016;17:419. doi:10.1186/s13063-016-1546-3.

In the present study we did not impose a specific definition of what a pragmatic RCT was. As noted in the interview guide, we asked interviewees (with the exception of patient partners or community members) “When you think of a trial that is more pragmatic, what comes to mind?” This was further probed to explore typical features etc.

Some participants identified pragmatic RCTs with respect to key design features, while others were flexible with respect to design features but were in keeping with Tunis et al (JAMA. 2003;290:1624-1632) insofar as it was a trial in which the study was designed to generate
information to make a decision. The analysis of these responses will be reported in a future manuscript.

Other comments:

Line 158. 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.

Response: This line was meant simply as a descriptive term to refer to the different legislation, regulatory bodies, or research governance structures that interviewees could be exposed to and was, in effect, synonymous with jurisdiction in its usage. This text has been revised in line with its intended use (lines 162-164) to state:

“Interviewees were purposively sampled based on their role and jurisdiction (to capture different experiences with trials conducted under different governance structures, such as varying ethics guidelines).”

Line 165. 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.

Response: Individuals were not necessarily identified or interviewed on the basis of a single trial (although this was the case for the majority of patient partner or community members).

Trials involving patient partners or community members were identified through a keyword search of funder sites, such as the PCORI portfolio of projects https://www.pcori.org/research-results?f%5B0%5D=field_project_type%3A298 and the Canadian Institutes of Health Research (CIHR) Funding database; http://www.cihr-irsc.gc.ca/e/38021.html as well as through our investigator team and through a literature search for self-identified pragmatic RCTs that mention a patient advisory board or similar.

We have now included further examples of details regarding the types of experiences of the interviewees. The approved consent form also indicated that they would not be identified or be identifiable from their comments. For this reason, we have not included details of the specific trials as this may be potentially identifying of individuals. The text has now been revised (lines 164-174)
Line 244—5. 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.

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.

Response: We thank the reviewer for pointing out that some of the quotes about risk can cause confusion. We would like to clarify that pragmatic RCTs were referred to in ways that include comparative effectiveness research on approved drugs, but also the effectiveness of new interventions compared to standard practice, particularly in comments from those conducting behaviour change trials. However, some of this confusion may also have arisen due to an attempt at being more efficient with the quotes.

Quote 1.1, for example, was truncated for expediency. We have clarified this intended usage of the quote in the text [LINES 269-271] which now reads:

“Interviewees commented on the benefits of pragmatic RCTS and drew distinctions between those patients who may be at higher risk of adverse outcomes irrespective of the intervention at hand and those that may be at a higher risk because of the intervention (see Quote 1.1). This was noted due to the perception that many pragmatic trials would be trials of interventions deemed to be low or minimal risk yet may be employed in populations that may be of poor health.”

However, we do note (as per quote 1.2) that the interpretation of risk was not universal and may not be straightforward with respect to overall assessments of participant welfare.

We have revised the text to clarify the context of quote 1.2 (and expanded the quote in Table 2) as well as adding further comment, as per the reviewer’s request (see lines 282-286), with the text now reading:

“Others suggested that head-to-head trials of two interventions in standard use didn’t necessarily mean that there was no risk to being in the trial and rather it depended on whether participating in the trial created a change in the participants welfare (Quote 1.2). This fed back into broader
questions of what should be considered a risk and the comfort with conducting RCTs in contexts where patients had a poor prognosis.”

Line 302. 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.

Response: This sentence has now been revised to read: “While recruitment of trial participants by their treating clinician is not a unique issue in pragmatic RCTs, it was flagged as potentially being more pronounced in pragmatic RCTs due to the closer integration of research and clinical care.” (lines 323-325)

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—as 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.

Response: We note that interviewees represented a broad range of trial types, all within the scope of pragmatic RCTs. We have now clarified the context of the perceived broader range of participants, noting that the type of trial (such as health system or health policy trials) may generate different or additional concerns (lines 399-406). The text now reads:

“Interviewees discussed how pragmatic RCTs may include a broader range of patients than explanatory trials which might only have included a subset of a clinical population, and that this raised challenges of identifying the extent to which particular groups or individuals may be affected by the trial and the protections owed to them. Others discussed how pragmatic RCTs of health systems or health policy trials may have an impact on individuals not traditionally considered to be research participants and raised questions regarding how responsible parties should respond. This was not just in relation to who may be affected in a material sense, but also those who may expect to have legitimate claims of those conducting the trial.”

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.

Response: The intent of the text here was to identify a strength of pragmatic RCTs emphasizing that they are ethically advantageous to explanatory RCTs. The exclusions of patients with co-morbidities was an example used by participants to highlight a group that were systematically excluded in explanatory trials and which led to inequities in care. We have revised this text to clarify this point (lines 408-412). Specifically, we state that:

“One particular area of concern was equity and justice in relation to the participants who were recruited within trials. Interviewees raised concerns about groups, such as pregnant women,
children, and those patients with co-morbidities, being excluded from explanatory trials and how pragmatic RCTs may be beneficial in this regard because they were more inclusive of the range of patients who would be seen in usual practice (Quote 4.1).”

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.

Response: In line with the reviewer comments we have shortened the discussion by focusing on placing the themes within the broader context of the literature, as opposed to restating the issues that were discussed. The discussion has been shortened by several pages.

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.

Response: The reviewers comments relate to a passage regarding vulnerable populations. Given the degree to which vulnerable participants has been discussed in the literature, this text has now been removed to shorten the discussion. Now the text begins with the discussion of direct and indirect participants of research.

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.

Response: We believe that emphasizing the potential discrepancy between eligibility on paper and the actual participants is an issue that is especially relevant to pragmatic RCTs precisely because trials that recruit only a subset of eligible patients should not be considered representative of the clinical population. Moreover, such a finding would directly contravene the goals of the learning healthcare system as proposed by Faden et al., and where the reduction of social inequalities is a key goal. As such, we have revised this text to clarify the intent of the point and that while a trial may, according to the protocol, be viewed as pragmatic the implementation will also be key (as recently demonstrated by Johnson et al. Trials. 2016;17:32) we have revised this text to state (lines 582-590):
“A particular concern relating to trial participants was justice and equity. This emphasis on justice aligns well to the importance placed on including participants in pragmatic RCTs that reflect typical clinical populations [59], but also concerns expressed within previous studies of trial recruitment that found patients may be excluded by clinical researchers for practical reasons such as ability to travel or level of education rather than clinically relevant eligibility criteria [60]. Recent work by Johnson et al., recently indicated that the degree of pragmatism of an RCT may be perceived to change over time between design and implementation [61]. While such changes may reflect practical constraints or changes that need to be made, vigilance should be maintained with regard to equity considerations if changes potentially affect the trial population.”

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.

Response: Our goal for this manuscript is not to prescribe a single definition or practically implementable approach to the question of what would constitute usual care. We have now added that consistent with Zwarenstein “the definition of usual care (or the chosen comparator) is the responsibility of the trial team, as is the design of the intervention arm(s), and we do not presume to direct the trial team on what they should select as the comparator.” (Zwarenstein et al J Clin Epidemiol. 2017;84:27-29. doi:10.1016/j.jclinepi.2016.10.010). Such would require a greater degree of explication, and would thus necessitate much more space than is feasible here. Rather, we leave it open as to what the most appropriate approach would be. We have revised the text to reflect this (lines 617-625). In particular we state that:

“A final area of discussion was the concept of usual (or standard) care, a topic which has been a key point of discussion within recent trial controversies [47, 48, 50, 68]. As per Zwarenstein et al [69] we do not wish to prescribe a specific definition of usual care. Rather we note that it is the responsibility of the trial team to determine, and appropriately describe, what usual care constitutes. However, consistent with the CONSORT extension for pragmatic trials [43] and TIDieR guidelines [70], describing control interventions or co-interventions as ‘usual care’ is not sufficient and they should be described in the same level of detail as the intervention arm. Notwithstanding the presence of these reporting guidelines, there is a paucity of research evaluating the extent to which the reporting of pragmatic RCTs meet recommendations.”

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.

Response: An RCT will always be designed to test one or more study arms against one or more comparators. It could be a head to head comparison of different interventions of interest, or an intervention of interest (e.g., a new model of health service delivery) versus some comparator (e.g., non-protocolized usual care). As such, we have used the term intervention arm and
comparator arm as a way to illustrate that there will be an intervention of interest and an alternate against which the comparison is being made (the comparator). We do not believe that this is inconsistent with either or both arms being deemed to be usual care. Rather the intent here (and in the final row of table 3), is to illustrate the potential for usual care to be heterogenous. To inform a decision, as pragmatic RCTs should, then usual care needs to be clearly defined and described (lines 617-625).

Reviewer #2:

Overall, my view is that this study is timely, well-executed and offers helpful leads to establish adquate guidance. In fact, I have very few remarks for improvement. The only thing I would ask the authors is whether they were able to differentiate perceived/experienced issues per stakeholder group.

The "new" issues raised relate to public trust, the social license, and special protections of a broader range of participants who might be affected by the trial. I would be interested in the particular views of patients/patient representatives as these new issues require input from this stakeholder group.

Response: We thank the reviewer for the kind remarks on our study. We have reviewed the themes and where there may be nuances that were more readily or differently expressed between stakeholder groups, we have more clearly noted this (for example, while waiver of consent was a common issue raised, issues of public trust were almost exclusively raised by the ethics or legal stakeholders) (lines 357-362).

Also, considering these new issues, do the authors envision a role for patient and public involvement in the establishment of guidance? I assume that if public trust and social license are important for ethical guidance, we would need to understand the expectations people have when it comes to pragmatic trials.

Response: Indeed we do. As part of the project team we have included two patient or community partners (as indicated in the appendix of team members) who have experience of clinical research. They have been involved throughout the project and attend team meetings where project development and progress is discussed. In addition, we anticipate that at the end of the project we will hold a consensus meeting and consultation on proposed guidance (as detailed in Taljaard M, Weijer C, Grimshaw JM, Ali A, Brehaut JC, Campbell MK et al. Developing a framework for the ethical design and conduct of pragmatic trials in healthcare: a mixed methods research protocol. Trials. 2018;19:525. doi:10.1186/s13063-018-2895-x.).