Reviewer's report

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

**Version:** 0 **Date:** 28 Aug 2019

**Reviewer:** Shona Kalkman

**Reviewer's report:**

This paper constitutes a qualitative interview study among a range of stakeholders to identify ethical issues of pragmatic trials. These issues help to shape the particular guidance required for the design, conduct and oversight of pragmatic trials. The importance of ethical guidance relates to the fact that in recent years pragmatic trials have been acknowledged as an important source of evidence for decision-making (real world evidence, comparative effectiveness) and that as a result, more and more pragmatic trials are now being conducted. Pragmatic trials raise distinct ethical questions due to their design and setting. As the authors correctly point out, pragmatic trials resolve some ethical issues, but at the same time introduce others. Over the past 5 to 7 years many papers have been published on the topic of ethics and pragmatic trials (regarding risk, consent, usual care, etc.). Even empirical studies on the matter have been published. Nevertheless, I think this study provides relevant new insights as--compared to older interview studies--many more stakeholders are now familiar with pragmatic trials and in fact have actual experience with their design and conduct (perceived challenges vs. experienced challenges). With respect to study methodology, recruitment of respondents, inclusion and analysis appear sufficient and are well-described. The results are presented in a clear and understandable manner and show considerable overlap with previous work. In the discussion, the authors indicate that their study highlights both well-known as well as new ethical issues.

Overall, my view is that this study is timely, well-executed and offers helpful leads to establish adequate 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. 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.

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