Author’s response to reviews

Title: Pragmatic Clinical Trials Embedded in Healthcare Systems: Generalizable Lessons from the NIH Collaboratory

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Author’s response to reviews:

Dear Dr. Rutten,

Thank you very much for your careful review of "Pragmatic Clinical Trials Embedded in Healthcare Systems: Generalizable Lessons from the NIH Collaboratory" (BMRM-D-17-00250). Your suggestions have made this a stronger manuscript, and we are grateful for it.

We’ve revised the manuscript as you suggested, and have provided responses to reviewer comments below. For your convenience, we uploaded a tracked-changes version of the manuscript as supplementary material.

Sincerely,

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Editor Comments:

The summary of lessons learned from the demonstration projects of the NIH Collaboratory will make a useful contribution to the literature and will be of interest to BMC Medical Research Methodology readership. Please consider the reviewers’ comments as follows:

1. Offer a few sentences to clarify the structure and funding of the Collaboratory to address the first comment by Reviewer 1.

In lines 233 to 235, we added this sentence: To date, the Collaboratory has funded the ten demonstration projects described here and worked with the Project Principal Investigators (PIs)
to overcome challenges and barriers to in designing, conducting, and disseminating results from their PCTs. In addition, an NIH funding opportunity announcement (RFA-RM-16-019) was developed as a part of the Common Fund initiative to support ten more projects over the next several years.

2. Clarification of the purpose of the manuscript building upon prior relevant publications (per Review 2) will address the concerns raised by Reviewer 1 about the value of this contribution.

After describing the publication (see #3) we modified lines 246 to 250 to read as follows:

“Although there have been numerous publications describing nuanced challenges and solutions encountered in the conduct of specific Demonstration Projects, this is the first to widen the focus and describe the NIH Collaboratory more generally. In this paper, we build on the knowledge created by the cores to review important generalizable lessons learned over the first four years since the Collaboratory was established. We also discuss the remaining opportunities and challenges for the Collaboratory and its forthcoming projects, and for the medical community more broadly regarding PCTs to power a learning health system.”

3. Include in your introduction a bit more discussion with relevant citations of the value of pragmatic trials to address the comments of Reviewer 1 about the PCTs.

We added the highlighted sentence to lines 217-225 and a citation from NEJM on PCTs.

“Pragmatic clinical trials (PCTs) are trials that use data collected in the electronic health record as part of routine care, or are “embedded” in routine care, and are a foundational component of such a system. By their nature, PCTs are designed to show real-word effectiveness in broad, generalizable patient groups (as opposed to the more restricted protocols and populations found in exploratory randomized trials) [12]. These PCTs have the potential to significantly decrease the evidence gap and inform real-world practice with digital health data collected at the point of care. They involve critical partnerships between health care systems and academic investigators to embed clinically meaningful research questions into the infrastructure of the health system to generate real-world generalizable results in an efficient manner.”

We also added some citations from the Collaboratory. We can remove some if necessary (There are over 100 Collaboratory publications.) We summarize these as follows:

“Members of the Collaboratory Core Groups (described in more detail below) worked with the PIs to facilitate the PCTs and have reported on solutions to the challenges encountered. These include a special issue on the ethics of research in usual care settings [16,17], a special issue on
the ethical and regulatory complexities of pragmatic clinical trials [14,18–28], journal articles on initiating and implementing patient-reported outcomes measures [29], electronic health records, phenotyping, and informatics [30–32], stakeholder engagement and health care systems interactions [33–36], as well as biostatistical lessons learned on cluster and constrained randomization [37,38]. Members of the Collaboratory have also developed a Living Textbook on the design, conduct, and dissemination of PCTs.”

4. Include additional details in your methods section (Reviewer 2)

We added additional methods in lines 319 to 323, as follows:

“The information regarding lessons learned was gleaned from a number of sources. The Collaboratory held yearly Steering Committee meetings (Bethesda, MD, 2012 – 2107) in which all the Principal Investigators (PIs) gather to share their experience and knowledge through interviews and presentations. Members of the Coordinating Center interview each of the PIs at these meetings to gather lessons learned, and each PI presents lessons learned at a general session followed by an opportunity for discussion. Leaders of each of the Cores also attend the meetings and hold monthly calls with the PIs and their teams to discuss problems and explore solutions, and these lessons are gathered as a part of minutes from the call. In addition, all the PIs and some members of their teams are authors on this paper.”

5. In the discussion, expand upon how lessons learned will inform future work.

We revised lines 476 through 483 as follows:

“As the first round of demonstration projects approach completion, the Collaboratory will continue to identify challenges and lessons learned regarding health care systems interactions, data analysis, interpretation, reporting, and dissemination to inform the next set of demonstration projects and PCTs in general. These lessons will inform other national evidence generation efforts that are underway, such as the Patient-Centered Outcomes Research Network (PCORnet). To understand the full potential of PCTs to advance healthcare, additional knowledge is needed about research designs that were not a part of the first phase of Collaboratory, but may be a part of the second phase:”

6. Revise conclusions to align with lessons learned.

We deleted a paragraph about PCTs and revised lines 553 through 564 as follows:
“The NIH Collaboratory is an important part of the overall effort to improve the national capacity to generate evidence to inform healthcare decisions by patients, providers, and payers. Even before the demonstration projects have completed their work, much has been learned. Planning activities are substantial and should be supported as part of a phased approach, such as the planning and implementation phases used by NIH for the Collaboratory. New challenges frequently arise during execution; change is the only constant, and because of this, early and ongoing engagement with all stakeholders is critical. As the new demonstration projects begin, we hope to learn from these lessons and generate others, as there remain opportunities for additional learning in order to make intelligent investments in PCTs. There is also the need to train a new clinical trials workforce, to train reviewers for PCTs, and align interests for all stakeholders to contribute to a national evidence generation system.”

We also changed the conclusion line in the abstract: “Conclusion: A planning phase is critical, and even with careful planning, new challenges arise during execution; comparisons between arms can be complicated by unanticipated changes. Early and ongoing engagement with both health care system leaders and front-line clinicians is critical for success. There is also marked uncertainty when applying existing ethical and regulatory frameworks to PCTs, and using existing electronic health records for data capture adds complexity.”

BMC Medical Research Methodology operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.

Reviewer reports:

Vance W Berger, Ph.D. (Reviewer 1):

Thank you for your comments.

I found it a bit odd that while this is hailed as an NIH collaborative, and though there is no shortage of authors, not a single one lists the NIH as an affiliation. Is the NIH actually involved in this collaborative?

See lines 233 to 236 where we clarify the role of the NIH as a funder of the NIH Collaboratory. We also note that the NIH is actively involved in our steering committee meetings. Because this paper presents recommendations for future Collaboratory funding, it could not be authored by any NIH representative (i.e., NIH staff cannot publish things calling upon themselves to fund something).
The conclusions do not follow from the report. In fact, one might even question whether what appear as conclusions are actually conclusions at all. It seems more of an objective to conduct these trials in such a way that they provide the right kind of evidence. What, then, are the conclusions of the study? For that matter, do we actually have a study here? This is not a criticism of the effort, but what is gained by having it published, above and beyond what is gained by disseminating just the trials that grow out of this effort?

We agree that the Conclusion could follow the lessons learned more closely and have revised accordingly. Specifically, we deleted a paragraph about PCTs and revised lines 553 through 564 as follows:

“The NIH Collaboratory is an important part of the overall effort to improve the national capacity to generate evidence to inform healthcare decisions by patients, providers, and payers. Even before the demonstration projects have completed their work, much has been learned. Planning activities are substantial and should be supported as part of a phased approach, such as the planning and implementation phases used by NIH for the Collaboratory. New challenges frequently arise during execution; change is the only constant, and because of this, early and ongoing engagement with all stakeholders is critical. As the new demonstration projects begin, we hope to learn from these lessons and generate others, as there remain opportunities for additional learning in order to make intelligent investments in PCTs. There is also the need to train a new clinical trials workforce, to train reviewers for PCTs, and align interests for all stakeholders to contribute to a national evidence generation system.”

Unfortunately, your focus on cluster randomization undermines your effort at providing reliable and unbiased evidence. I certainly understand that it is much easier, logistically, but this is more than offset by the fact that there is then confounding between the interventions and the center effects. And while we can all pretend that these effects can be separated with suitable covariate adjustment, in fact they cannot, and, in this context, "suitable covariate adjustment" is a misnomer, since there will always be center attributes that are not measured. I did see that one trial that made it to the table had individual randomization, so clearly this does fall within the realm of possibility. Why not just do it right all the time?

Certainly cluster randomized trials are vulnerable to methodological limitations, as are all designs. Significant advances have been made, however, in our understanding of how best to randomize clusters in such a way that balance in key covariates is achieved. The concern that there might be remaining imbalance in unmeasured factors is a concern for any kind of design. The following might be useful references for the effective use of cluster randomized designs:


Lila Finney Rutten (Reviewer 2): The authors provide a useful overview of lessons learned from the NIH Collaboratory demonstration projects.

Thank you for your comments.

The introduction could be strengthened by building upon previously published literature on the NIH Collaboratory with a clarification of what this manuscript adds in terms of lessons learned. Consider including the following references:


In lines 237 to 244, we added some references from the Collaboratory. It is possible that we added a few to many, and are happy to remove some if needed. As mentioned above, we clarified what this manuscript adds in lines 262 to 267.

The Methods section is lacking detail in terms of the specific processes used to obtain the information summarized in the lessons learned.
In lines 314 to 321 we added information regarding the methods.

The discussion could be strengthened by including more specific thoughts on how the lessons learned will inform/guide future work in the Collaboratory and perhaps other similar national infrastructure (e.g. PCORnet).

See revision in lines 473 through 481.

The Conclusions should be more focused on lessons learned and next steps rather than on the value of PCTs.

See revision lines 548 to 558 and to the conclusion section of the abstract (lines 188 to 193).