## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

| | |
|---|---|
| **TITLE (PROVISIONAL)** | Reconsidering “minimal risk” to expand the repertoire of trials with waiver of informed consent for research |
| **AUTHORS** | Monach, Paul; Branch-Elliman, Westyn |

## VERSION 1 – REVIEW

| | |
|---|---|
| **REVIEWER** | Sheffield, Kristin<br>Eli Lilly and Co, Global Patient Outcomes and Real World Evidence |
| **REVIEW RETURNED** | 31-May-2021 |

| | |
|---|---|
| **GENERAL COMMENTS** | This paper extends the Anderson et al. 2015 paper on a similar topic (regulatory oversight of pragmatic clinical trials) by advocating for a concept of embedded trials that are integrated into clinical practice and adaptive. There are several points that could be clarified and improvements that could be made:<br><br>1. The EQuIPT acronym is a bit clunky and unnecessary. It would be better to discuss this concept descriptively rather than assign an acronym that won't resonate with readers.<br><br>2. The argument in the last paragraph (lines 54-55) on page 5 and continuing (lines 3-11) on page 6 needs more clarification or development. The point that you're trying to make is unclear, and some of the sentences seem contradictory.<br><br>3. Who is the intended audience for this paper? Regulatory policymakers? IRB reviewers? Related, what are the author's specific recommendations to address the issues raised, e.g. does FDA need to provide additional guidance?<br><br>4. Are there other regulatory or operational barriers besides the informed consent requirements that are limiting the use of pragmatic clinical trials? This paper devotes a lot of attention to informed consent; however, there may be other operational challenges worth noting. For example, the authors refer to informatics tools and pulling data directly from the EHR for study data collection. Will the tools and EHR be able to reliably provide baseline characteristics, AEs, and outcomes data necessary for a pragmatic trial conducted in a community care setting (outside of academic research environments with existing research infrastructure)?<br><br>5. It might be instructive to walk through a very specific proposed trial example and describe how it would be implemented. Alternately, the authors could expand more in-text about Figures 1 and 2. |

| | |
|---|---|
| | 6. Minor: page 3, line 34 – "Bartlett found.. that big data could feasibly replace only 15% ..." - missing words here – "of RCTs"? |

| | |
|---|---|
| **REVIEWER** | Curry, Leslie<br>Yale University School of Public Health, Health Policy and Administration |
| **REVIEW RETURNED** | 27-Jun-2021 |

| | |
|---|---|
| **GENERAL COMMENTS** | This manuscript presents a novel concept aimed at supporting rapid learning within health systems through embedded, quantified trials that mitigate some elements of regulatory burden while preserving core ethical obligations to the patient. The authors seek to address a highly relevant current challenge, which is closing the well-established, seemingly intractable Know-Do gap. While much is being written about the principles of learning health systems, there is a paucity of literature regarding the concrete methodological components of how systems can facilitate rapid embedded research that culminates in implementation of evidenced-based decision support tools. In this way, the paper is an important contribution to the literature for those interested in developing methods for prospective data collection leveraging the EHR to support robust learning health systems. In particular, the conceptualization of participation risk as occurring along a spectrum, with informed consent procedures tailored accordingly, is useful in elevating dialogue and debate in this area.<br><br>At the same time, there are several aspects of the manuscript which require attention in order to enhance the manuscript's suitability for publication in BMJ Open and accessibility for readers.<br><br>Rationale: The proposed model is well motivated, as authors present a compelling case for the need to maximize learning to improve quality and outcomes of care in clinical settings. One of the most compelling arguments is the current reality of inequities in access to RCTs, which are mostly limited to academic centers. Making trial participation more widely accessible begins to address the many elements of structural racism inherent in US-based clinical research.<br><br>Approach: The Commentary classification of the manuscript is appropriate, given the lack of empirical data being reported (though the case illustrations are useful). Nevertheless the piece would be more effective if the authors could provide more grounded assertions than 'in our opinion'. Is it possible to bring in concrete arguments from clinical experience?<br><br>In my reading, I see the core claim the authors are making as: "EQuIPT trial designs so closely resemble usual practice that they bring minimal incremental risk beyond what is encountered in everyday care." This basic argument is important; however it is lost/diluted in the manuscript as currently written. The manuscript is circuitous in places and lacks a clear organizing framework/roadmap to guide the reader and tie the sections together. I would suggest cutting all extraneous comments (e.g., 'we need to stop quoting Hippocrates') and adding a road map few sentences to help the reader. One suggestion is the break the manuscript in two parts to make it more accessible. The main commentary could focus on the core elements of the argument for |

| | |
|---|---|
| | this model and illustrations, and then a supplemental file could include related details (e.g., on regulations/privacy, informed consent for clinical trials/current approaches; adaptive designs, perhaps figure 2 as example of pilot).<br><br>Finally, while authors briefly touch on possible downsides to their proposed model, the piece would be more balanced if these limitations were clearly explained in their own paragraph, which rebuttals/strategies for mitigating these limitations included. This should also appear in the abstract.<br><br>The visuals are very well composed and easy to interpret. |

| | |
|---|---|
| **REVIEWER** | Manda-Taylor, Lucinda<br>University of Malawi, College of Medicine |
| **REVIEW RETURNED** | 07-Jul-2021 |

| | |
|---|---|
| **GENERAL COMMENTS** | 1. Major: How do the authors think that the EQUIPT design would be transferable to other settings, particularly, low-middle-income settings where concerns around consent (with illiterate, primarily unquestioning patients) may be recommended by the care provider to enter into clinical research) can be challenging? In addition the EQUIPT design requires access to an EHR platform. Electronic data capturing is not as robust in LMIC - there are omissions and possible errors in reporting that could possibly mean that access to a patient's health information may be incorrect. Can the authors problematize these issues in the commentary.<br>2. Please can the authors make sure that the line spacing in the text is consistent. |

## VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Kristin Sheffield, Eli Lilly and Co
Comments to the Author:
This paper extends the Anderson et al. 2015 paper on a similar topic (regulatory oversight of pragmatic clinical trials) by advocating for a concept of embedded trials that are integrated into clinical practice and adaptive. There are several points that could be clarified and improvements that could be made:

1. The EQuIPT acronym is a bit clunky and unnecessary. It would be better to discuss this concept descriptively rather than assign an acronym that won't resonate with readers.

We would like to keep “EQuIPT” in the paper, because we think some abbreviation is needed, and the alternatives we came up with were far more clunky. However, we have de-emphasized it, taking it out of the title and abstract and no longer promoting it for widespread use.

2. The argument in the last paragraph (lines 54-55) on page 5 and continuing (lines 3-11) on page 6 needs more clarification or development. The point that you're trying to make is unclear, and some of the sentences seem contradictory.

We have changed this paragraph and hope that the point is now clear, and free of contradictions and redundancies.

3. Who is the intended audience for this paper? Regulatory policymakers? IRB reviewers? Related, what are the author's specific recommendations to address the issues raised, e.g. does FDA need to provide additional guidance?

We have added text on page 5 indicating that the key audience is IRBs, but that interest from physicians, patients, and institutional leaders will also be essential. In contrast, we argue that statutory and regulatory changes are not needed in the US, which is a point that we think strengthens the paper.

4. Are there other regulatory or operational barriers besides the informed consent requirements that are limiting the use of pragmatic clinical trials? This paper devotes a lot of attention to informed consent; however, there may be other operational challenges worth noting. For example, the authors refer to informatics tools and pulling data directly from the EHR for study data collection. Will the tools and EHR be able to reliably provide baseline characteristics, AEs, and outcomes data necessary for a pragmatic trial conducted in a community care setting (outside of academic research environments with existing research infrastructure)?

The new Limitations section acknowledges operational barriers based on EHRs, differing privacy laws, and the need for providers and patients to accept to value of enrollment in such studies. We agree that informatics tools will only be useful for certain eligibility criteria and outcomes, and we now discuss those in the Limitations section and in the detailed example of a proposed trial.

5. It might be instructive to walk through a very specific proposed trial example and describe how it would be implemented. Alternately, the authors could expand more in-text about Figures 1 and 2.

We have added an example (colchicine for primary prevention in cardiovascular disease) in detail in the Supplementary text. This example also gives an opportunity to acknowledge that the informatics tools must be accurate in assessing eligibility criteria and outcomes.

6. Minor: page 3, line 34 – "Bartlett found.. that big data could feasibly replace only 15% ..." - missing words here – "of RCTs"?

Thank you for identifying this error, which we have corrected.

Reviewer: 2
Dr. Leslie Curry, Yale University School of Public Health, Yale University School of Medicine
Comments to the Author:
This manuscript presents a novel concept aimed at supporting rapid learning within health systems through embedded, quantified trials that mitigate some elements of regulatory burden while preserving core ethical obligations to the patient. The authors seek to address a highly relevant current challenge, which is closing the well-established, seemingly intractable Know-Do gap. While much is being written about the principles of learning health systems, there is a paucity of literature regarding the concrete methodological components of how systems can facilitate rapid embedded research that culminates in implementation of evidenced-based decision support tools. In this way, the paper is an important contribution to the literature for those interested in developing methods for prospective data collection leveraging the EHR to support robust learning health systems. In particular, the conceptualization of participation risk as occurring along a spectrum, with informed consent procedures tailored accordingly, is useful in elevating dialogue and debate in this area.

We appreciate your assessment that our paper adds something novel and important to the discussion about developing learning health systems.

At the same time, there are several aspects of the manuscript which require attention in order to enhance the manuscript's suitability for publication in BMJ Open and accessibility for readers.

Rationale: The proposed model is well motivated, as authors present a compelling case for the need to maximize learning to improve quality and outcomes of care in clinical settings. One of the most compelling arguments is the current reality of inequities in access to RCTs, which are mostly limited to academic centers. Making trial participation more widely accessible begins to address the many elements of structural racism inherent in US-based clinical research.

We are grateful to receive support in this assertion. The new Limitations section does note that absence of an EHR will perpetuate inequities.

Approach: The Commentary classification of the manuscript is appropriate, given the lack of empirical data being reported (though the case illustrations are useful). Nevertheless the piece would be more effective if the authors could provide more grounded assertions than 'in our opinion'. Is it possible to bring in concrete arguments from clinical experience?

We have added a Personal Perspective section near the beginning. We hope we have understood correctly that this is what you are suggesting by "concrete arguments from clinical experience," rather than literature. This new section is long, in order to provide the examples of our having contended with difficulty in enrolling patients in trials, and in our dependence on making clinical decisions in the absence of good evidence – with little prospect of such evidence being sought through conventional RCTs. We could certainly move (elsewhere in the main text, or supplementary), shorten, or remove this section if desired.

In my reading, I see the core claim the authors are making as: "EQuIPT trial designs so closely resemble usual practice that they bring minimal incremental risk beyond what is encountered in everyday care." This basic argument is important; however it is lost/diluted in the manuscript as currently written. The manuscript is circuitous in places and lacks a clear organizing framework/roadmap to guide the reader and tie the sections together. I would suggest cutting all extraneous comments (e.g., 'we need to stop quoting Hippocrates') and adding a road map fw sentences to help the reader. One suggestion is the break the manuscript in two parts to make it more accessible. The main commentary could focus on the core elements of the argument for this model and illustrations, and then a supplemental file could include related details (e.g., on regulations/privacy, informed consent for clinical trials/current approaches; adaptive designs, perhaps figure 2 as example of pilot).

We have added text on page 6 that summarizes the argument that will follow, and we have shortened the individual sections by moving much of the text to a supplementary file as recommended. Although some of the new text is long (the overall length of the main text is slightly shorter than it was), we think the presentation of the main argument proceeds much more effectively, and we appreciate the suggestion.

Finally, while authors briefly touch on possible downsides to their proposed model, the piece would be more balanced if these limitations were clearly explained in their own paragraph, which rebuttals/strategies for mitigating these limitations included. This should also appear in the abstract.

We have added a Limitations section right before the Conclusion, in which we have also attempted to address comments made by the other reviewers.

The visuals are very well composed and easy to interpret.

Thanks, we are glad you think so.

Reviewer: 3
Dr. Lucinda Manda-Taylor, University of Malawi
Comments to the Author:
1. Major: How do the authors think that the EQUIPT design would be transferable to other settings, particularly, low-middle-income settings where concerns around consent (with illiterate, primarily unquestioning patients) may be recommended by the care provider to enter into clinical research) can be challenging? In addition the EQUIPT design requires access to an EHR platform. Electronic data capturing is not as robust in LMIC - there are omissions and possible errors in reporting that could possibly mean that access to a patient's health information may be incorrect. Can the authors problematize these issues in the commentary.

Much of the new Limitations section acknowledges that our paper is focused on the US, and that maximum benefit from EQuIPT designs may not be achievable elsewhere, especially in LMIC. We have added in the "summary of the argument" on page 6 that embedding is not essential for designating a trial as minimal risk, but in some countries may be essential to comply with privacy laws. Regarding poor literacy and different doctor-patient relationships, we argue that since an EQuIPT study does not add risk over the usual risk inherent in clinical care, it is appropriate to conduct with a wide range of providers and patients. A physician who communicates poorly or a patient who understands poorly is going to be an impediment to discussion of risks and benefits in usual care as well. The major risk of poor health literacy would come with traditional trial designs, where unapproved drugs are used or enrollment in the trial places limits on other treatments or health-related behaviors (the highest-risk category in our "spectrum" model).

2. Please can the authors make sure that the line spacing in the text is consistent.

Thank you for pointing out this error, which we have made an effort to correct.

**VERSION 2 – REVIEW**

| | |
|---|---|
| **REVIEWER** | Sheffield, Kristin<br>Eli Lilly and Co, Global Patient Outcomes and Real World Evidence |
| **REVIEW RETURNED** | 06-Aug-2021 |

| | |
|---|---|
| **GENERAL COMMENTS** | The authors have adequately addressed my original comments.<br><br>Minor suggestions:<br>The sentence where EQuIPT is introduced can be shortened, removing the 'whether the acronym catches on or not'.<br><br>The personal perspective section could be shortened. |

| | |
|---|---|
| **REVIEWER** | Curry, Leslie<br>Yale University School of Public Health, Health Policy and Administration |
| **REVIEW RETURNED** | 06-Aug-2021 |

| | |
|---|---|
| **GENERAL COMMENTS** | The authors have made important revisions that improve the readability of the paper and its utility for those interested in novel approaches to trials. I think the removal of several pieces into supplemental files works well. I personally like the addition of the personal experience section but defer to the editor if it feels too choppy. |

| | |
|---|---|
| **REVIEWER** | Manda-Taylor, Lucinda<br>University of Malawi, College of Medicine |
| **REVIEW RETURNED** | 03-Aug-2021 |

| | |
|---|---|
| **GENERAL COMMENTS** | Thank you to the authors for attending to my concern and clearly noting the applicability of the EQUIPT design in LMICs. I am therefore satisfied with the response highlighted in the limitations of the paper. |