PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Peer Reviewed Evaluation of Registered End-Points of Randomized Trials (the PRE-REPORT study): Protocol for a Stepped-Wedge, Cluster-Randomized Trial
AUTHORS	Jones, Christopher; Adams, Amanda; Weaver, Mark; Schroter, Sara; Misemer, Benjamin; Schriger, David; Platts-Mills, Timothy

VERSION 1 - REVIEW

REVIEWER	Ana Marusic University of Split School of Interest
REVIEW RETURNED	20-Jan-2019

GENERAL COMMENTS	This study will address an important problem in clinical trial research and hopefully contribute to the more complete and transparent reporting of outcomes from clinical trial. The proposed methodological approach (cluster-randomized, stepped wedged design) is rigorous and well planned. The primary and secondary outcomes planned are well defined and appropriate, as well as the planned analysis of data. The date for the start of the study is stated in the protocol. I have only two concerns: 1. There will be quite a lot of extractions of data before and during the study. While the assessment of the outcome of the study are well presented and are methodologically rigorous and appropriate, the extraction of the data from the registries prior to the study, to create the information for the reviewers, is not that clearly described. Will there be only one extractor/assessor of that data? How will the accuracy of the extracted information be checked? 2. I am also concerned about ethical approval. While the IRB gave the opinion that the study does not meet the regulatory definition for human subjects research. It may be so in the USA, but it may be different for participating journals in Europe if there are any (I understand the reasons for not disclosing the names of the participating journals at this stage). The General Data Protection Regulation in the EU may apply to this research, especially as the subject of research are peer reviewers, who will receive intervention (information about a trial).Will be reviewers be able to choose whether they will participate in the study or not? I think this issue needs to be addressed in more detail, with justification for not informing the reviewers about the participation in the study.

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REVIEWER	Roberta W Scherer Johns Hopkins Bloomberg School of Public Health, United States
REVIEW RETURNED	31-Jan-2019

GENERAL COMMENTS	This manuscript describes the protocol for a trial aimed to evaluate whether providing trial register information on the primary outcome to peer reviewers will affect the proportion of trials published with selective outcome reporting, i.e., where the primary outcome in the published report does not agree with the primary outcome reported in the trial publication. Overall, the design is innovative. If successful, this trial could move the field forward. I do have some comments and some concerns. 1. Zarin recently described a fully described outcome as having five aspects: domain, time frame, metric, method of measurement, and method of aggregation. In many cases, however, the primary outcome described in clinicaltrial.gov only includes domain and time frame or is even more broadly described (e.g., “safety and efficacy”). The authors acknowledge that the primary outcome in the register may not be clearly defined (page 12, end of paragraph under ‘Secondary outcomes”). How will these issues be handled when determining ‘agreement’ between outcomes described in the register and in the publication? 2. More detail with respect to the timing of the intervention should be provided in the protocol. It is not clear how long it will take to determine that a manuscript describes a randomized trial, find the register information, and prepare the email to the reviewer. We are told that the reviewer will be sent an email with the trial register information and the email says ‘You recently agreed…’ Most journals aim to reduce the time between journal submission and decision on publication with the general pathway including manuscript submission,initial editor review, decision to send out for peer review (or to an Associate Editor who then sends out to potential peer reviewers). Generally, once a peer reviewer accepts to peer review, the full manuscript becomes available to him or her. It would seem to be optimal to provide the register information to the peer reviewer at the same time or certainly within a day or two of receiving the manuscript, but exactly where in the sequence above is the manuscript received by the PRE=REPORT team and also where and when processed? What safeguards are in place to ensure that the PRE-REPORT team will be promptly notified by the journals about when manuscripts are submitted? Additionally, how will you handle the situation where the peer reviewer completes the review before receiving the information email if it is delayed beyond the reviewer receiving the register information? 3. Will the register information also be sent to the editors? On page 8, the authors mention there will be no change in the information is sent to ‘peer reviewers and editors” during the control phase (although it is not clear what information will be sent). This would imply that the register information will also be sent to the editors. If not, then some justification would be useful for why peer reviewers rather than editors were chosen to be the target of the intervention. If so, then there should be some thought/discussion as to how this could impact the outcome for this trial.

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REVIEWER	Davina Ghersi NHMRC Australia
REVIEW RETURNED	11-Feb-2019

GENERAL COMMENTS	Thank you for asking me to review this protocol. I hope the authors find my comments useful. Page 4, opening paragraph: “randomized trials can help to establish causality between interventions and patient outcomes…” The convention is that RCTs in health can help to determine if one intervention is more (or less) effective than another in improving health outcomes. Causality is usually used when referring to the risk associated with exposure (eg to an environmental factor). Page 4, reference 3,6-9. Most of these references are quite old with the most recent being 2015. If the aim is to establish that selective reporting is still a problem then more recent references are required. Page 4, para 2. Reference 17 is to the WHO public disclosure policy, but the paragraph concerns requirements for prospective registration. I would suggest referencing FIFTY-EIGHTH WORLD HEALTH ASSEMBLY A58/22, Ministerial Summit on Health Research (http://apps.who.int/gb/archive/pdf_files/WHA58/A58_22) Page 4, para 3. Reference 6 was published in 2015 and supports the statement “selective outcome reporting remains common”. Is a more recent reference available? Page 4-5: references 7, 9, 21-37. Are all of these references necessary? Page 5, para 2: This paragraph is providing the main argument for doing the trial, but I find it a bit unconvincing. - In 2019 do we really believe that clinical trialists, journal editors and peer reviewers are unaware of the requirement to register clinical trials? - Are problems accessing the audit trail really a valid excuse? Eg I just went to ANZCTR and all I had to do was click on the clearly labelled button “view history”. It literally took seconds to access. - Does the blinded peer review argument hold? How many journals blind reviewers to authors? And what evidence is there that it makes a difference to the quality of a review? - The key issue, I believe, is whether journals have policies that ask/require peer reviewers to look at the registry record as part of the peer review process. If such policies exist, are they implemented? If so, how? If not, why not? Eg If a submission is made without a registration number do they just bounce it back to the authors and ask them to submit the number? Page 5-6, and page 9, para 1: it isn’t clear to me why data is being extracted from registries onto a form. Why not just send the registry record (and history). Page 6, para 1. I would suggest rewording the goal to something like “to determine whether providing a summary trial registration report at the time of peer review improves the peer review process and clinical trial reporting”.

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	Page 8, para 2: the control group appears to be standard practice, defined as the practice as it exists at each journal at the time they were included in the trial. This relates to the statement on page 7 under “journal selection” that says journals “could not have already implemented a robust process….”. It isn’t clear what a robust process is, or whether some eligible journals may have more or less robust processes (or even existing policies) than others. Some more information on this would be useful. Page 9, Registry data abstraction. This seems a bit complicated. Why not just ask the manuscript authors to provide the trial registration number? If they can’t (or won’t) provide a registration number then you immediately have an outcome. If the journal has signed up to the ICMJE statement then they shouldn’t be considering unregistered trials anyway. If they have registered then it should be very simple for them to submit the number. Page 10. Pare 1 data collection). Using the sample size to identify the primary outcome. Why is this necessary? Primary outcome is one of the key items in the trial registration data set. Investigators must provide this information for the trial to be registered. If a submitted trial was registered without the primary outcome then there is a problem with the registration. https://www.who.int/ictrp/network/trds/en/ Key secondary outcomes should also be registered. Page 11, para 2. I don’t really understand the ordering of pairs of registered and published outcomes to address the “potential for investigators to be influenced by the knowledge the manuscript submitted later during the trial are more likely to have received the intervention”. On page 7 it is mentioned that authors and peer reviewers would be blinded to the identities of participating journals, so why is this necessary?

VERSION 1 – AUTHOR RESPONSE

Responses to Reviewers

Reviewer: 1

This study will address an important problem in clinical trial research and hopefully contribute to the more complete and transparent reporting of outcomes from clinical trial. The proposed methodological approach (cluster-randomized, stepped wedged design) is rigorous and well planned. The primary and secondary outcomes planned are well defined and appropriate, as well as the planned analysis of data. The date for the start of the study is stated in the protocol.

I have only two concerns:

1. There will be quite a lot of extractions of data before and during the study. While the assessment of the outcome of the study are well presented and are methodologically rigorous and appropriate, the extraction of the data from the registries prior to the study, to create the information for the reviewers, is not that clearly described. Will there be only one extractor/assessor of that data? How will the accuracy of the extracted information be checked?

**Thank you for raising this question. We will have two independent raters responsible for performing comparisons between registered and published outcomes, and we will test and report inter-rater

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agreement and kappa for these variables. We will also have two assessors complete registry searches for each trial before labeling a trial as being unregistered. We have updated the Methods to clarify this. Because of limited available resources, we are unable to utilize multiple individuals to duplicate each step in the data extraction process. However, we believe that the potential for significant errors is low based on the familiarity of both data extractors in working with trial registries and their extensive experience in performing trial registry data extraction.

2. I am also concerned about ethical approval. While the IRB gave the opinion that the study does not meet the regulatory definition for human subjects research. It may be so in the USA, but it may be different for participating journals in Europe if there are any (I understand the reasons for not disclosing the names of the participating journals at this stage). The General Data Protection Regulation in the EU may apply to this research, especially as the subject of research are peer reviewers, who will receive intervention (information about a trial).Will reviewers be able to choose whether they will participate in the study or not? I think this issue needs to be addressed in more detail, with justification for not informing the reviewers about the participation in the study.

**Thank you for this feedback. We do have participating journals based in Europe, and issues surrounding the General Data Protection Regulation were reviewed extensively by the editors and legal counsel from participating journals before they agreed to participate. Several participating journals requested that our investigators sign and abide by confidentiality agreements, which we have done, and we describe this process in the manuscript. We, those who are funding the study, and the editors of the participating journals think the study design is ethical from the perspective of reviewers for several reasons. First, our study team does not record names or other identifying characteristics from reviewers of the included trials. As such, this is more a study of the collective decision-making process of the editor and the reviewers than a study of individual reviewers. Second, as a stepped-wedge study, all participating journals will be receiving the intervention by the end of the trial and, if the data are supportive, may continue to use the intervention following completion of the study. In this sense, like many stepped-wedge studies, from the perspective of reviewers this is not different from a quality improvement project. Additionally, if journal editors judge necessary, participating journals will inform reviewers about the possibility that their reviews might be included in research involving the peer review process. We now provide more information in the Ethics and Dissemination section regarding the ethics of the study design.

Reviewer: 2

Reviewer Name: Roberta W Scherer

Institution and Country: Johns Hopkins Bloomberg School of Public Health, United States Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

This manuscript describes the protocol for a trial aimed to evaluate whether providing trial register information on the primary outcome to peer reviewers will affect the proportion of trials published with selective outcome reporting, i.e., where the primary outcome in the published report does not agree with the primary outcome reported in the trial publication. Overall, the design is innovative. If successful, this trial could move the field forward. I do have some comments and some concerns.

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1. Zarin recently described a fully described outcome as having five aspects: domain, time frame, metric, method of measurement, and method of aggregation. In many cases, however, the primary outcome described in clinicaltrial.gov only includes domain and time frame or is even more broadly described (e.g., “safety and efficacy”). The authors acknowledge that the primary outcome in the register may not be clearly defined (page 12, end of paragraph under ‘Secondary outcomes”). How will these issues be handled when determining ‘agreement’ between outcomes described in the register and in the publication?

**Thank you; we agree that this is a critically important issue, and have expanded on the section of our manuscript addressing the primary outcome definition. In order to classify a registered outcome as being specifically defined, we state that it should be described in enough detail to allow investigators designing another study to measure the same outcome parameter. In general, this usually requires a description of the outcome domain, specific measurement, and specific metric. While description of the method of aggregation should, in our opinion, be prospectively specified in the registry, as described in the Zarin article referenced by the reviewer (NEJM 2011, 364;9) this level of detail is often omitted from registry entries and credible arguments have been made that method of aggregation does not need to be prespecified, so we do not require it in order to consider an outcome as being specifically defined. We added the Zarin citation to the relevant section.

2. More detail with respect to the timing of the intervention should be provided in the protocol. It is not clear how long it will take to determine that a manuscript describes a randomized trial, find the registry information, and prepare the email to the reviewer. We are told that the reviewer will be sent an email with the trial register information and the email says ‘You recently agreed…’ Most journals aim to reduce the time between journal submission and decision on publication with the general pathway including manuscript submission, initial editor review, decision to send out for peer review (or to an Associate Editor who then sends out to potential peer reviewers). Generally, once a peer reviewer accepts to peer review, the full manuscript becomes available to him or her. It would seem to be optimal to provide the register information to the peer reviewer at the same time or certainly within a day or two of receiving the manuscript, but exactly where in the sequence above is the manuscript received by the PRE=REPORT team and also where and when processed? What safeguards are in place to ensure that the PRE-REPORT team will be promptly notified by the journals about when manuscripts are submitted? Additionally, how will you handle the situation where the peer reviewer completes the review before receiving the information email if it is delayed beyond the reviewer receiving the register information?

**We agree that these are also important issues. The specific methods and timing of screening potentially eligible manuscripts and distributing the registry information to reviewers differs between the participating journals in order to allow integration of the study into the existing editorial and peer review processes at the participating journals. While there are disadvantages to this approach, it was necessary in order to secure cooperation from the participating journal editors. Additionally, this approach provides a pragmatic assessment of the effects that our intervention has when adopted by a group of journals with heterogeneous editorial and peer review practices. In some cases reviewers will receive the registry information at the same time that they agree to perform the review and are given access to the manuscript, and in some cases they will receive an email from the journal staff containing this information after they have already agreed to review. For the latter group, our goal is to provide the registry information to reviewers within 24 hours of their acceptance of the reviewer assignment. Based on our discussions with the participating editors, this will give the reviewers the opportunity to take the registry information into consideration before finalizing their reviews in the vast

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majority of cases. All of the participating journals routinely obtain reviews for the manuscripts in question from multiple individuals, making it very unlikely that all reviewers for a particular manuscript will complete their reviews before the registry information is made available to them. We plan to analyze our included manuscripts on an intention-to-treat basis, such that included manuscripts sent for review from journals that have crossed over into the intervention condition will be analyzed in the intervention group even if the reviewers complete their reviews before the registry information is provided to them. We have expanded the “Manuscript Eligibility” and “Intervention Phase” sections of our submission to address some of these issues.

3. Will the register information also be sent to the editors? On page 8, the authors mention there will be no change in the information is sent to ‘peer reviewers and editors” during the control phase (although it is not clear what information will be sent). This would imply that the register information will also be sent to the editors. If not, then some justification would be useful for why peer reviewers rather than editors were chosen to be the target of the intervention. If so, then there should be some thought/discussion as to how this could impact the outcome for this trial.

**The intent of our study is to make the registry information available to peer reviewers, and we have edited the sentence in question to clarify this. We have also edited the “Intervention Phase” section to address why reviewers are the main targets of our intervention. Although one could argue that this information should also be provided to editors, because reviewers are directly responsible for the rigorous evaluation of study design, including the assessment of outcomes, we think reviewers are the most appropriate target of this intervention. As described above, and in the manuscript, the specific methods by which this information will be provided to the reviewers differ based on the established editorial practices at each participating journal; in some cases the journal editor in chief will distribute the data sheet to the selected reviewers, and therefore will have direct access to the information. In other cases the editors will have access to the registry information through the online editorial platform which records emails from the editorial staff to reviewers, but they will not receive these emails directly. We anticipate that editors will be exposed to the registry information when they review comments from reviewers who have received the data sheets. These differences in information flow are in keeping with the pragmatic design of our study. While there would be both advantages and disadvantages to establishing a strict single process for each participating journal, the editors of our participating journals were justifiably anxious not to implement processes that would disrupt their previously established work flows, and in order to obtain cooperation from a sufficient number of journals we had to adopt individualized approaches to data sharing for the participating journals.

Reviewer: 3

Reviewer Name: Davina Ghersi

Institution and Country: NHMRC - Australia Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below Thank you for asking me to review this protocol. I hope the authors find my comments useful.

Page 4, opening paragraph: “randomized trials can help to establish causality between interventions and patient outcomes…” The convention is that RCTs in health can help to determine if one

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intervention is more (or less) effective than another in improving health outcomes. Causality is usually used when referring to the risk associated with exposure (eg to an environmental factor).

**Thank you; we have edited the sentence in question to clarify this issue.

Page 4, reference 3,6-9. Most of these references are quite old with the most recent being 2015. If the aim is to establish that selective reporting is still a problem then more recent references are required.

**Thank you for this suggestion; we have added several more recent references.

Page 4, para 2. Reference 17 is to the WHO public disclosure policy, but the paragraph concerns requirements for prospective registration. I would suggest referencing FIFTY-EIGHTH WORLD HEALTH ASSEMBLY A58/22, Ministerial Summit on Health Research (http://apps.who.int/gb/archive/pdf_files/WHA58/A58_22)

**We have included the recommended citation; thank you.

Page 4, para 3. Reference 6 was published in 2015 and supports the statement “selective outcome reporting remains common”. Is a more recent reference available?

**We have included two additional more recent references. Please note that the initial work in this field involved the evaluation of trials with broad clinical relevance, while more recent publications have tended to address selective outcome reporting within specialized medical fields. Because our study involves journals that are relevant to a wide range of medical specialties, we have preferentially cited many of these broadly applicable publications.

Page 4-5: references 7, 9, 21-37. Are all of these references necessary?

**We have deleted several of the references in question.

Page 5, para 2: This paragraph is providing the main argument for doing the trial, but I find it a bit unconvincing.

- In 2019 do we really believe that clinical trialists, journal editors and peer reviewers are unaware of the requirement to register clinical trials?

- Are problems accessing the audit trail really a valid excuse? Eg I just went to ANZCTR and all I had to do was click on the clearly labelled button “view history”. It literally took seconds to access.

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- Does the blinded peer review argument hold? How many journals blind reviewers to authors? And what evidence is there that it makes a difference to the quality of a review?

- The key issue, I believe, is whether journals have policies that ask/require peer reviewers to look at the registry record as part of the peer review process. If such policies exist, are they implemented? If so, how? If not, why not? Eg If a submission is made without a registration number do they just bounce it back to the authors and ask them to submit the number?

**While we agree that awareness of the requirements relevant to trial registration have probably improved over time, we are unaware of any data showing that clinical trial data are now effectively intergrated into the review process. We have cited the two manuscripts that we are aware of that best address this issue, one from 2013 and one from 2015. Regarding the issue of viewing audit trails for registered trials, we understand that many experts in peer review and editorial practices will be familiar with these resources. However, our systematic review published in 2015 found that the majority of published manuscripts aimed specifically at describing the problem of registered and published outcome discrepancies failed to utilize these audit trails. (BMC Med. 2015; 13:282) Furthermore, because these manuscripts were published, we can conclude that the reviewers and editors assessing them either were not aware that these audit trail should have been utilized or they didn't feel that their use was important enough to preclude publication. We also agree that the role of blinded peer review is controversial, but discussing the pros and cons of this issue is beyond the scope of our study. The fact remains that many journals utilize blinded peer review, and asking peer reviewers to access registry entries is not consistent with blinded peer review for those journals that have decided that this approach is preferable. Our proposed intervention addresses each of these issues. Importantly it also addresses the reviewer's suggestion that the root cause of the persistent problem of discrepant outcome reporting might lie in either the absence or disregard of policies clearly delineating responsibility for registry review.

Page 5-6, and page 9, para 1: it isn't clear to me why data is being extracted from registries onto a form. Why not just send the registry record (and history).

**In many cases the registry records for the eligible clinical trials are quite lengthy. In an attempt to make it as easy as possible for reviewers to access what we consider to be the most important information from the registry databases we have decided to focus on providing information relevant to the timing of registration and the description of prospectively defined outcomes.

Page 6, para 1. I would suggest rewording the goal to something like "to determine whether providing a summary trial registration report at the time of peer review improves the peer review process and clinical trial reporting".

**Thank you; we have changed this sentence to more specifically define the study intervention.

Page 8, para 2: the control group appears to be standard practice, defined as the practice as it exists at each journal at the time they were included in the trial. This relates to the statement on page 7 under "journal selection" that says journals "could not have already implemented a robust process….".

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It isn't clear what a robust process is, or whether some eligible journals may have more or less robust processes (or even existing policies) than others. Some more information on this would be useful.

**As the reviewer points out, it is not surprising that the journals we approached about participating in the study had a wide range of characteristics and processes (or the lack thereof) in place that were relevant to their performance on this issue. Because of this existing heterogeneity, it was not possible to screen journals for participation based on many of these potentially relevant factors. We communicated extensively prior to beginning the study with the editors in chief and with other key members of the editorial team at each journal that ended up participating. In all cases, and as a condition of their participation, the editors of the participating journals felt that this was an area within their peer review process that had potential for improvement. Journals were excluded if the editors felt that their existing policies were adequate such that the intervention was unlikely to be helpful. We have updated the methods to clarify that this was largely based on judgement of the journal editors in chief.

Page 9, Registry data abstraction. This seems a bit complicated. Why not just ask the manuscript authors to provide the trial registration number? If they can't (or won't) provide a registration number then you immediately have an outcome. If the journal has signed up to the ICMJE statement then they shouldn't be considering unregistered trials anyway. If they have registered then it should be very simple for them to submit the number.

**We agree that this approach would be ideal in many ways. And in fact, for the majority of submissions a registry number is included in the abstract or methods of the manuscript in question and the process is as simple as that described by the reviewer. In this section of the manuscript we describe the steps that are taken in the minority of cases for which identifying a matching registry entry is not so straightforward. Unfortunately, many journals, including a number of the journals that were interested in participating, do not collect the registration number as a discrete field during the submission process, and changing this process was not possible within a feasible timeframe.

Page 10. Pare 1 data collection). Using the sample size to identify the primary outcome. Why is this necessary? Primary outcome is one of the key items in the trial registration data set. Investigators must provide this information for the trial to be registered. If a submitted trial was registered without the primary outcome then there is a problem with the registration.
https://www.who.int/ictrp/network/trds/en/ Key secondary outcomes should also be registered.

**The use of sample size calculations to identify the primary outcome is relevant for abstracting the primary outcome from the manuscript, rather than the registry entry. We have edited this paragraph to clarify this issue. While this should not be necessary, as obviously a manuscript describing results from a clinical trial should clearly identify the primary trial outcome, in reality a significant number of manuscripts fail to do so.

Page 11, para 2. I don't really understand the ordering of pairs of registered and published outcomes to address the "potential for investigators to be influenced by the knowledge the manuscript submitted

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later during the trial are more likely to have received the intervention". On page 7 it is mentioned that authors and peer reviewers would be blinded to the identities of participating journals, so why is this necessary?

**Comparing the registered and published outcomes to determine whether or not these are consistent requires some judgement. We are blinding our outcome assessors so that they will not be aware of whether included manuscripts were in the control arm or the intervention arm, so that this knowledge doesn't bias their assessments. Because of our stepped wedge study design, trials enrolled at the beginning of the study period are far more likely to be in the control arm than trials enrolled at the end of the study period, so if our outcome assessors evaluated the included trials in the order they were enrolled they could make educated guesses as to whether some of the trials they assessed were in the control arm or the intervention arm. Randomizing the list of paired outcomes before providing this list to the outcome assessors prevents this potential source of unblinding. This is a relatively minor point, but we felt it was worth describing as it addresses a potential source of bias within our study design.

VERSION 2 – REVIEW

REVIEWER	Ana Marusic University of Split School of Medicine
REVIEW RETURNED	18-Mar-2019

GENERAL COMMENTS	The authors have adequately addressed my comments, and I think that the revised version of the manuscript is now significantly improved.

REVIEWER	Roberta W Scherer Johns Hopkins Bloomberg School of Public Health United States
REVIEW RETURNED	13-Mar-2019

GENERAL COMMENTS	All of my concerns have been addressed. Thank you for allowing me to review this paper

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