Author's response to reviews

Title: Alternation as a Form of Allocation for Quality Improvement Studies in Primary Health Care Settings: the on-off study design

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Author's response to reviews: see over
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Doug Altman, Curt Furberg and Jeremy Grimshaw  
Editors-in-Chief  
Trials

Re: 1686126222133275 - Alternation as a Form of Allocation for Quality Improvement Studies in Primary Health Care Settings: the on-off study design

Dear Drs Altman, Furberg and Grimshaw

Thank you for the invaluable comments by the reviewers that have enabled us to improve this manuscript. We are grateful for the opportunity to resubmit. Below is a detailed response to the reviewers, in addition we highlighted all changes in the text of the manuscript in red.

Regards,

Jeffrey A. Johnson, Ph.D.
Response to Reviewer Merrick Zwarenstein

Major comments
1) ……….The authors use of the term pragmatic trials, and indeed of the entire concept of pragmatic trials is not in accordance with either the original definitions of pragmatic trials…….. if the paper does remove all mention of pragmatic trials (which are invariably randomized) then I think it should be published largely as is.

Response: Thank you for this comment, in light of this suggestion we have removed the word “pragmatic” and describe the trial simply as “controlled”

Minor comments
1) I think alternation raises the same problems as randomization and so, given the excellent qualitative interview information included in the study, one could argue that it would have been no more difficult to randomize these patients than it was to alternate them. so i suggest that it is worth clarifying how much easier it is LOGISTICALLY to alternate patients by period of recruitment than it would be to individually randomize them; and then reduce the amount of material saying how resistant staff were to alternation, and simply deal with this by saying that this was resistance to evaluating in a local context something for which there was already non-local evidence.

Response: Thank you for this comment. We agree and have made the following statement in the Discussion:
The degree of dissatisfaction seemed exacerbated by 1) the patient population involved (e.g. patient population viewed as high-risk (e.g., depressed or suicidal)), 2) conducting assessments without taking action (e.g., administering the PHQ-9 and not acting on the results), and 3) the (non-blinded) allocation process. It is noteworthy, however, that all of the concerns expressed by PCN staff would be equally applicable to a patient-level or even cluster-randomized trial. Alternate designs, such as the stepped wedge design [24], with a staggered rollout of a new treatment strategy may not evoke the same perceptions.

Response to Reviewer Andrew Vickers

Major comment
1) First, there is no reason why the proposed design needs to be seen as an alternative to randomization; it can be just a different type of randomized trial. For instance, the following sentence is misplaced: “However, random allocation is not acceptable in some cases, and alternative designs can be implemented, such as the on-off design described here”.

Response: Thank you for this observation. The sentence has been reworded (also in response to Dr. Zwarenstein related comment above) and now reads as follows:
However, random allocation of patients as seen in classic RCTs may not be acceptable in some cases, such as where front-line health care providers object to participation in RCT designs, and alternative forms of random allocation can be implemented, such as the on-off design described here.
Comment: The authors have to be much more specific about what specific aspects of typical randomized trials are problematic and how their new design addresses those specific aspects.

We believe this point is addressed in the “features of the on-off design”. Here we show that the key feature distinguishing feature of the on-off design compared to other designs including (RCT, cross-over or step wedge) is the allocation of patients to control or intervention by alternating time periods.

Comment 2) Second, it is not clear to me why the alternation design has to involve:

a) investigator specified order rather than randomized (e.g. why do the control group first and then treatment? Why not decide at random?)

Response: Indeed there is no reason why the alternation periods cannot be decided at random. To clarify this point we have added the following sentence to the description of the features of the on-off design:

….Eligible participants from a recruitment pool (or defined population) are allocated to intervention or control groups in sequential clusters. The sequence of the clusters can be determined at random. Recruitment to clusters is on an alternating defined time frame (e.g., one month), until the required sample size is obtained or the time for identification expiries…..

Comment b) only a single crossover (e.g. why not do first month control, second treatment, third treatment, fourth control etc. etc.)?

Response: Indeed there is more than one crossover as the alternating continues until the required sample size is filled. In the features of the on off section the following statement describes this:

Recruitment to clusters is on an alternating defined time frame (e.g., one month), until the required sample size is obtained or the time for identification expiries.

Comment 3) Third, there is no reference to the uncertainty principle. Clinicians can exclude patients from studies if they are reasonably sure that the experimental intervention would benefit them.

Response: The following statement exists in current text (page 5) referring to the principle of uncertainty in the description of the features of the on-off design:

“As with any controlled trial, for the on-off design to minimize threats to internal validity, a prior belief of equipoise must exist; that is, it is assumed there is genuine uncertainty about the benefits of the intervention over usual care.”

Minor comments

1) It is generally nonsense to do baseline testing between groups in a randomized trial, but in this particular case, it makes sense, because the authors are testing whether the lack of allocation concealment inevitable in their chosen design leads to bias. This should be much more clearly stated in the paper, i.e. that this sort of hypothesis should not normally be tested, but there is a very specific reason to do so here.

Response: Thank you. To emphasize this point, we have added the following statement to the description of the quantitative analysis:
……characteristics were compared. Ordinarily it is unnecessary to test for differences in participant characteristics of a controlled trial, however in this case it is advisable to test if the lack of allocation concealment may have led to bias. We used the students $t$-test.

**Comment** 2) In table 1 and 2, please provide differences between groups with 95% C.I. part of the question is whether we can exclude the possibility of important bias). Also, report p values to only a single significant figure unless close to 0.05.

**Response:** Please see edited tables, confidence intervals have been added for all continuous variables