Author’s response to reviews

Title: WHAT'S THE UPTAKE? Pragmatic RCTs may be used to estimate uptake, and thereby population impact of interventions, but better reporting of trial recruitment processes is needed.

Authors:

Katy Bell (katy.bell@sydney.edu.au)

Amanda McCullough (amccullo@bond.edu.au)

Chris Del Mar (cdelmar@bond.edu.au)

Paul Glasziou (pglaszio@bond.edu.au)

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Author’s response to reviews:

Zachary Munn

Associate Editor

Diagnostic and Prognostic Research

31/05/2017

Dear A/Prof Zachary Munn

Re: Manuscript BMRM-D-17-00133R1

Thank you for the further opportunity to revise and resubmit our paper titled ‘WHAT'S THE UPTAKE? Pragmatic RCTs may be used to estimate uptake, and thereby population impact of interventions, but better reporting of trial recruitment processes is needed.”

We sincerely thank the editor and reviewers for their considered and constructive comments on our paper. Our responses to their comments, and our proposed changes to the manuscript, are presented on the following pages.

Yours sincerely

Katy Bell,

School of Public Health, University of Sydney
Reviewer 1

You replaced the ambiguities and imprecisions of the first manuscript version with new ambiguities and imprecisions.

No operational definition is provided for a "pragmatic" RCT. Based on the content of your manuscript I cannot determine if a trial should be classified as a "pragmatic" RCT or not. I consider that due to this absence of a clear operational definition for a "pragmatic" RCT, your method can not be applied.

Response: We now provide more detailed explanation on what may be considered a pragmatic trial

Change: [Page 3, first paragraph]

“The effectiveness of an intervention in real clinical practice may be estimated in pragmatic trials conducted on patients who represent the full spectrum of the population to which the treatment might be applied, and where the comparator group receives usual care.[1] Pragmatic trials are designed to determine the effects of an intervention under the usual conditions in which it will be applied,[2] and focus on the choice between options for care rather than biological understanding.[3] They may be contrasted to explanatory trials designed to determine the effects of an intervention under the ideal conditions, [2] in order to test causal research hypotheses, such as whether the intervention causes a particular biological effect.[3] Tools have been developed to help trialists with design decisions on how pragmatic or explanatory they wish their trial to be,[4][5] and an extension of the CONSORT statement guides the reporting of pragmatic trials.[6]”

It is not clear if the trials used in the "Example" are "pragmatic" RCTs.

Response: We have made it clearer that only pragmatic trials were used to demonstrate the method.

Change: [Page 6, first paragraph]
“The RCTs were all primarily of pragmatic type, with high applicability to the actual clinical settings the intervention was intended to be used, and a very good match between the trial usual care arm and the intended primary care population[5]. “

No operational definition is provided for "intention to treat analysis". Based on the content of your manuscript I cannot determine what do you mean by "intention to treat analysis". I consider that due to this absence of a clear operational definition for "intention to treat analysis", your method can not be applied.

Response: We now provide a definition for intention to treat analysis.

Change: [Page 3, second paragraph]

“Estimates of intervention effectiveness may then be made using an intention to treat analysis of outcomes in the intervention group compared to those in the usual care group (‘trial effectiveness’).[7] That is, patients are analysed in the group to which they were initially randomised, even if they drop out of the study or change groups[8].

I consider that no clear, robust justification for the validity of the method is provided.

Response: We are proposing a new method to estimate likely population impact of interventions and the theoretical underpinning for the method. We acknowledge that our proposed method needs to be validated by comparing trial uptake with uptake rates in practice before it can be considered reliably for making policy decisions. However, this paper forms a necessary first step and example in that process which Reviewer 3 describes as “ingenious and potentially useful”.

Change: Nil further

Reviewer 2

The definitions and the use of 'population impact' in place of 'population effectiveness' for the effect that is being estimated are very helpful in clarifying the methods. All comments were responded to adequately and the paper is much improved.

Response: Thank you.

Change: Nil
Reviewer 3

I have read the comments of previous reviewers and the authors responses to these comments. I agree with the reviewers that the problem the authors address is important, and the proposed solution ingenious and potentially useful. The authors' responses deal successfully with all of the comments raised by the reviewers, and so in this sense I think the paper should go forward for publication.

Response: Thank you for your supportive comments.

Change: Nil

However, and this is pretty much inevitable, new eyes see new problems. I appreciate that the narrowing of the scope of this paper to encompass only pragmatic trials has successfully dealt with the previous reviewers objections; but in so doing I see that inverse problems have arisen. These relate to the lack of clarity around what is meant by "pragmatic trials".

Response: We agree that more clarity is needed in what we mean by pragmatic trials, and have provided additional text and references as you suggest below.

Change: Text and references have been added to the first paragraph – see details below.

The authors' definition of pragmatic trials is simplistic (including the full range of patients), and doesn't have references. The concept of pragmatism in RCT design is not new, and has been under discussion over the last decade or so, with hundreds of citations to the following potential sources (each with their own approach), any or all of which could be cited. These include the original paper and book by two French statisticians, Schwartz and Lellouch from 1967, Dave Sacketts text book on Evidence Based medicine, from about 2005, the Consort Statement extension for pragmatic trials from the BMJ (Zwarenstein et al), the first PRECIS paper from the Jnl of Clin Epi (Thorpe et al), and the fairly recent PRECIS2 paper from the BMJ (Loudon et al).

All of these include far more specific and extensive definitions, explanations and descriptions of the characteristics that contribute to pragmatism in the design of randomized trials. I think any of these would be a suitable source for a better description and definition of pragmatic trials, which the paper needs, since it rests so heavily on this category of randomized trials.

Response: Thank you for these very helpful references, all of which we now include in the paper, along with a more detailed explanation on what we mean by pragmatic trials.

Change: [Page 1, first paragraph]
“The effectiveness of an intervention in real clinical practice may be estimated in pragmatic trials conducted on patients who represent the full spectrum of the population to which the treatment might be applied, and where the comparator group receives usual care[1]. Pragmatic trials are designed to determine the effects of an intervention under the usual conditions in which it will be applied,[2] and focus on the choice between options for care rather than biological understanding.[3] They may be contrasted to explanatory trials designed to determine the effects of an intervention under the ideal conditions,[2] in order to test causal research hypotheses, such as whether the intervention causes a particular biological effect.[3] Tools have been developed to help trialists with design decisions on how pragmatic or explanatory they wish their trial to be,[4][5] and an extension of the CONSORT statement guides the reporting of pragmatic trials.[6]”

It is therefore important to select only pragmatic trials: if the trials are not pragmatic in character it is quite likely that the overall effect size estimate will not translate directly to real world circumstance, and so it will be insufficient simply to multiply the trial effect size by uptake to produce an estimate of population impact. If some of the trials are more explanatory, a much more complex formula will be needed, one which adjusts the efficacy estimate to bring it closer to a true effectiveness estimate, prior to multiplying it by the uptake. Its hard to see what scientific basis this could use.

Response: We have made it clearer that only pragmatic trials were used to demonstrate the method

Change: [Page 6, first paragraph]

“The RCTs were all primarily of pragmatic type, with high applicability to the actual clinical settings the intervention was intended to be used, and a very good match between the trial usual care arm and the intended primary care population[5]. “

With a more detailed set of criteria for these trials, perhaps with a table of individual trial characteristics, it will be easier to explain how the selected trials are pragmatic, how these selections were made, and how reliable they are. This is glossed over in the paper at present. So, for this reason I think a more formal selection of pragmatic trials is required.

Response: While we appreciate that this suggestion would make it clearer that the trials included in our example were in fact pragmatic ones, this is not the main purpose of our paper and we feel that doing so will distract the reader from the main message about the importance of estimating uptake of the intervention, as well as the effectiveness.

Change: Nil further.