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.

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Author’s response to reviews:

Thank you for inviting us to 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,

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Editor Comments

There is a discrepancy between the two reviewers in terms of their decision to accept this paper. After reading the reviewer's comments and the paper once again, it is my opinion that this approach is inventive and could be a very useful indicator, and that it is important that this approach is published and made available. However, there are concerns that need to be addressed, particularly regarding the provision of clear definitions. The reviewers have also raised some other important points that need to be addressed prior to publication.
Response: Thank you for your comments and the opportunity to address the reviewers’ concerns.

Change: See specific changes below.

Reviewer 1

The most important terms/concepts used in the article (‘effectiveness of interventions’, 'efficacy of interventions in trials', 'trial effect', 'trial efficacy estimates', 'population level effectiveness' etc.) are not defined. No conceptual definitions and operational definitions are provided. The article is characterized by ambiguity and imprecision.

Response: Thank you for highlighting the potential confusion stemming from our use of terms which are poorly defined. To increase the clarity of our method, we have now restricted our method to pragmatic trials which estimate effectiveness, and use the new term population impact to denote the effect of trial effectiveness multiplied by uptake. We provide definitions of these terms at the start of the paper.

Change: New text has been added to the Introduction:

- page 3: “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. 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’).[1] But within trial effectiveness does not translate directly into population level impact.[2].”

“In this paper, we propose a method for calculating population impact of clinical interventions that accounts for the intervention uptake. We suggest that population impact may be estimated by multiplying the two key components: (1) the effectiveness of the intervention in pragmatic trials (trial effect); and, (2) its uptake in clinical practice. That is, population impact = trial effectiveness x rate of uptake.”

My main concern is that you talk about ‘the efficacy of the intervention in trials (trial effect)’, however, it is not explained what exactly this ‘trial effect’ is. It is not clear what kind of statistical estimate is used for this ‘trial effect’. My understanding is that there are different statistical estimates of effects in trials (treatment effect on those treated, intention to treat, etc.). You don't cite the statistical literature on different statistical estimates of effects in trials and you don't provide an operational definition in statistical terms for what you labeled as 'trial effect' and 'trial efficacy estimates'. There is a large body of statistical literature about diverse statistical estimates
of effects in trials (such as the effect of the treatment on the treated, intention to treat, etc.) and the issues related to the effects in trials and in populations (for example, scholarly works by Joshua Angrist, Guido Imbens, Donald Rubin, Howard Bloom, Alexander Balke, Judea Pearl, Constantine Frangakis, Stephen Cole, Elizabeth Stuart, Jay Kaufman, Charles Poole, Herbert Weisberg, Alfred Sommer, Scott Zeger etc.).

Response: We use the term ‘trial effectiveness’ to indicate the commonly used definition of intervention effect estimated from a randomised controlled trial. That is, the estimate of the intervention from an intention to treat analysis of effects in the intervention group compared to effects in the placebo group.

Change: See additional text provided above

No explicit, clear, reasonable justification is provided for your estimation method.

Response: The key assumption in our method to estimate population impact is that the clinician participation rate in trials may predict the uptake of the intervention in clinical practice. We then multiply this proxy uptake rate by the actual trial effectiveness observed. We discuss challenges to this method, including the validity of this assumption.

Change: We have expanded the text on the section ‘Challenges to the Method’, including discussion on how our method might be validated.

Reviewer 2

This is an ingenious approach to estimating the effectiveness of interventions, and an interesting read. However, some limitations and further explanations might be considered.

Response: Thank you for this comment, and we address your specific concerns below

Change: Nil

In general, there could be additional attention given to the ways in which trials are different from practice, and in which they may affect practice. For example, isn't it possible that the willingness to participate in trials which are designed to estimate the efficacy of an intervention, might be different from uptake of interventions when their efficacy has been established? I would expect that rates of participation in a trial of an intervention for which there is uncertainty about efficacy may not be similar to rates of participation in an intervention where the intervention has been shown to be efficacious. Furthermore, interventions that have been shown to be efficacious or
effective may be promoted or even mandated in ways which would affect participation in practice. You have shown that the uptake in previous practice of delayed prescribing is similar to the uptake rate you estimated. However, estimates of participation from trials may only be starting points, and not so relevant to the actual population impact later on, as the results of trials are (one hopes) used to influence practice.

Response: Thank you for raising this interesting point, which we address in the Discussion of our paper. We agree that how use of the intervention is promoted or mandated will influence uptake in clinical practice, but suggest that this may be less important if the method is used to inform funding decisions pre-implementation.

Change:

- page 7-8 “A further issue is that the willingness of clinicians to participate in pragmatic trials where the effectiveness of an intervention is unknown, may be different to the uptake in clinical practice when effectiveness has been established. For instance, interventions that have been shown to be effective may be promoted or even mandated in ways which would affect participation in practice. However, in the early pre-implementation stage where we are suggesting the method may be used to inform funding decisions (i.e. after the completion of the trials, but before a decision to publically fund and/or promote the intervention have been made), these considerations may not be as important.”

Related to this, there is a lack of clarity in the paper about efficacy trials versus effectiveness trials. For example, were the interventions to reduce antibiotics compared to usual care in the SRs? Are these efficacy trials or effectiveness trials? This wasn't clear to me and would be helpful in understanding the context of recruitment. Might the nature of the trials influence rates of participation? Perhaps include a discussion of how estimating uptake from trials does or does not depend on the trials being oriented towards either efficacy or effectiveness.

Response: Thank you for this very helpful comment. To increase the clarity of our method, we have now restricted our method to pragmatic trials which estimate effectiveness, and use the new term population impact to denote the effect of trial effectiveness multiplied by uptake. We provide definitions of these terms at the start of the paper.

Change:

- page 3: “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. 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’).[1] But within trial effectiveness does not translate directly into population level impact.[2].”

“In this paper, we propose a method for calculating population impact of clinical interventions that accounts for the intervention uptake. We suggest that population impact may be estimated by multiplying the two key components: (1) the effectiveness of the intervention in pragmatic trials (trial effect); and, (2) its uptake in clinical practice. That is, population impact = trial effectiveness x rate of uptake.”

Note that effectiveness is highly context-dependent, and may not be easily translated across different settings. Could the same be said of uptake? How would you address this?

Response: We agree and have added some text to the Discussion ahead of our comments on the need for exploration of heterogeneity of trial estimates of uptake.

Change:
- Page 7 “Just as estimates of trial effectiveness may be context-dependent, so too may be the trial estimates of uptake, and results may not be easily translated across different settings.”

Finally, note that rates of participation in the trial on the part of clinicians and/or patients do not necessarily extend to rates of compliance with the intervention when in practice, and thus may not reflect the actual effects of the intervention. I guess this is obvious, but it may be worth addressing in the discussion.

Response: We agree with the reviewer and have added some text on this to the Discussion.

Change:
- Page 7 “The actual population impact may be lower than in these scenarios, as even when the clinician and patient decide to uptake the intervention, they are generally less adherent to this in real life than in the trial setting (and so the trial effectiveness overestimates the real life effectiveness).”