Author's response to reviews

Title: Making trials matter: pragmatic and explanatory trials and the problem of applicability

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Author's response to reviews: see over
The Editor
Trials

26th April 2009

Dear Editor,

Re. MS 9773422132471958. Making trials matter: pragmatic and explanatory trials and the problem of applicability

I am pleased to submit a version of the above article revised in light of the two reviewers’ comments. A point-by-point explanation of the changes we have made in response to these comments is given in this letter.

We hope that these changes will enable Trials to consider our paper further.

Regards,

Dr Shaun Treweek
University of Dundee

On behalf of Dr Merrick Zwarensteint
Point-by-point response to reviewers’ comments

Reviewer 1: David Kent

1. More examples where pragmatic trials would have likely been more informative than explanatory trials
We have now added three additional examples of trials that we think would have been more informative had they been more pragmatic: the HOPE trial (page 4), VIGOR (page 5), NINDS (page 6) along with two studies that looked at applicability issues for two guidelines (GINA and GOLD) (page 6). The VIGOR example also addresses the reviewer’s comment about an example of an explanatory trial where we believe harm was done because of the trialists’ decision to not adopt a pragmatic attitude when making design decisions.

2. Aspirational trials provide useful information
There may, perhaps, be a difference in what we mean when we talk about a trial providing information and what the reviewer means by this. Trials of all stripes clearly provide information that is interesting to someone. But when we write, for example, ‘trials aimed at informing a clinical, health service or policy decision:’ (page 4) we mean exactly that: information that can be used directly by someone making a healthcare decision, today, in the real world. If the information is interesting to, say, a researcher, because it describes what would be possible if the healthcare delivery system were somewhat (or completely) different, then the trial is not, in our opinion, going to help a clinician make a decision in the real world because the trial describes an aspirational world, not the one in which he or she is actually working.

We have, however, added two sentences to mention the aspirational class of trial in the context of the Normalization Process Model (NPM). Our belief is that this type of trial is rarely justified unless there is a realistic chance of the aspirational requirements for real world implementation being put in place should the intervention prove effective. The NPM may alert trialists to problems at the design stage and allow them to make more informed judgements as to whether the trial is justified. Our new text is:

Some interventions can only be implemented with major structural or organisational changes to healthcare delivery; trials evaluating these interventions might be called ‘aspirational’. The Normalisation Process Model could help to identify such interventions and allow trialists and others to better judge whether the required changes are feasible on a wide scale and whether the likely benefit of the intervention justifies making them.

We are not saying ‘aspirational trials - just say no’, we are saying ‘think about it carefully’. With regard to the reviewer’s point about what to do if a pragmatic trial does not find the intervention to be beneficial (‘So, your pragmatic trial is null, now what?’) our response is simple: don’t implement the intervention. However, on page 7 we do state when a good case can be made for an explanatory trial, what one learns when such a trial demonstrates little evidence of benefit, and then mention where subgroup analysis may suggest that an additional trial is warranted for a group of individuals where there was, nevertheless, a suggestion of benefit.

With regard to the NINDS example mentioned by the reviewer, we provide an alternative view on this trial on page 6, along with a new description (at the bottom of the page) of when we think narrow inclusion criteria are justified. While being sympathetic to the reviewer’s point about inertia, we believe that a) more trials should deal with the real world, rather than the one we wished we had b) we often do not know the criteria with which to be selective and c) resources for trials are limited so we’d like to get results from the few trials we can do that are as widely applicable as we can make them. If there are good grounds to be selective and there is significant policymaker commitment to make structural changes should an aspirational trial show
an intervention benefit, then a case can be made for such a trial. Otherwise we think trialists should take a more pragmatic approach and generate results that apply to the many, now.

3. Generalizability
The reviewer suggests that we believe that ‘including all different sorts of patients, in all different sorts of settings, somehow means that the overall results generalize to all included patients, in all included settings’. We do not expect there to be an identical effect for all included participants; there will be a range of benefits, as well as harms. The point of a pragmatic trial designed to support a real healthcare decision is that a family doctor, say, hoping to use trial results to inform his or her decision generally will not know how an individual patient will respond to, or comply with, a treatment. Given this, any single patient to whom we wish to apply the results of a trial is far more likely to be found within the ranks of unselected patients included in a pragmatic trial, than in the highly selected patients of an explanatory trial. If the older patients, or patients with multiple comorbidities mentioned by the reviewer are candidates for the treatment in the real world then they should be included in a trial evaluating the effect of that treatment. There are sometimes good reasons for not having broad inclusion criteria but the results of trials are always averages and clinician-patient dyads will never have information specific to a single patient unless the trial is an N of one trial. We have added some new text explaining our thinking on this issue at the bottom of page 6 and on page 7.

4. JCE review articles on similar topic and what this review adds
The JCE articles have a different focus to the current review and four of the five 2009 JCE articles to which we refer are a debate between researchers who can be divided into two camps - ‘pragmatists’ (in which we sit) and ‘mechanists’ proposing that the explanatory-pragmatic framework needs to be replaced by an alternative framework called the mechanistic-practical framework. These articles are principally defending their standpoint rather than our current aim of attempting to support trialists in making their trials more widely useful and helping users of trial reports make more informed decisions about the wider use of existing trials. The fifth 2009 JCE article describes a tool for placing a trial on the explanatory-pragmatic continuum and is very different to the current paper.

What does our review add? We believe that we make clear at the beginning of our article (page 3) what our review hopes to achieve, primarily that ‘It is intended to help the former group make their trials more widely useful and to help the latter group make more informed decisions about the wider use of existing trials.’ It includes discussion of issues raised in recent publications not covered in existing reviews, such as those of Karanicolas (the importance of perspective and context), the new CONSORT extension for pragmatic trials, PRECIS (a new tool for aligning design with purpose), work that can identify contextual factors of importance to applicability and implementation (the NPM) and the possibilities of statistical modelling. None of these appear in earlier reviews. In particular, we believe that our review brings to the fore the important idea that trialists should think about applicability at the design stage of a trial, along with issues of internal validity, because both are equally important, which is not made in such a explicit way in previous reviews. In short, we believe that the current narrative review builds on, and extends, earlier reviews.

5. Difficult at times to know what our point is
We agree that the original draft did meander in places. We have deleted some of our original text, especially that related to the mechanistic-practical framework vs explanatory-pragmatic framework debate, which is the text the reviewer referred to as problematic on the original page 6/7. This discussion is addressed in references 37-40 and the reviewer was right to question its relevance. We have also deleted text from the original page 5 and the Discussion on drug licensing and the pharmaceutical industry, which was a distraction.
6. Confusing sentence, page 7 (sic): “of 26 trials, 13 of 18 were judged to be effectiveness trials…”

We agree. This section has been greatly expanded to make clearer both Gartlehner’s and colleagues’ work and the PRECIS work, more details on which the reviewer requested. We have added a figure showing two PRECIS diagrams so that readers have a greater understanding of how these diagrams help to highlight differences between design and purpose.

Reviewer 2: Peter Rothwell

1. An example of the PRECIS approach

We have added a figure showing how a highly pragmatic and a highly explanatory trial would look on the PRECIS diagram.

2. More actual examples

Reviewer 1 also requested more examples so we have repeated our response to Reviewer 1’s comment below. The GINA and GOLD examples are the work by Justin Travers, Richard Beasley and colleagues, which Reviewer 2 suggested would be useful to include. We agree and have done this.

‘We have now added three additional examples of trials that we think would have been more informative had they been more pragmatic: the HOPE trial (p4), VIGOR (p5), NINDS (p6) along with two studies that looked at applicability issues for two guidelines (GINA and GOLD) (p6). The VIGOR example also addresses the reviewer’s comment about an example of an explanatory trial where we believe harm was done because of the trialists’ decision to not adopt a pragmatic attitude when making design decisions.’