Author's response to reviews

Title: Screening: the information individuals need to support their decision. Per protocol analysis is better than intention-to-treat analysis at quantifying potential benefits and harms of screening.

Authors:

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Author's response to reviews: see over
Reviewer’s report
Title: Screening: the information individuals need to support their decision. Per protocol analysis is better than intention-to-treat analysis at quantifying potential benefits and harms of screening.
Version: 1
Date: 24 January 2014
Reviewer: Stephen Duffy
Reviewer’s report:
1. This paper makes a case for use of per protocol estimates of benefit and harm in information provided to those offered screening. This makes some sense, in that ITT estimates will depend on the adherence rate in the population from which they are derived, which may be different from that in the population relevant to the information resource. Further, the subjects have already been offered the screening, and they need to know the benefits and risks of taking up the offer. Invitation of itself does not confer any benefit. However, this does beg the question, however: why only for screening, and why not for other interventions?

RE: I completely agree. I added a sentence stating that this kind of analysis may be applied also to other preventive interventions for which trials are designed to measure the impact on population, while the impact on individuals depends on participation.

2. In the Background section, it is worth noting that some of the reviews quote ITT estimates of the mortality benefit but per protocol estimates of the harm. This gives an estimate of benefit-harm balance which is misleading and biased against the intervention.

Re: This is exactly what I suggested.

3. I could not find the Box 1 referred to in the text.

RE: Sorry; it is in fact Table 1.

4. I was not aware of a ‘fact sheet’ produced by the UK review. The information resources sent to invitees in the UK breast screening programme were produced by a research group independent of both the programme itself and of the UK review.

RE: The figures are taken from the final narrative synthesis presented in the conclusions of the paper published in The Lancet. I have changed the table.

5. Table 1 reports the UK independent review estimating the same incidence and therefore the same additional cancers for invited and screened. If the author reads the UK review paper more carefully, he will see that this is not the case. This should be corrected.

RE: I thank the reviewer. I have emended this point in the number: in the PP analysis the overdiagnosed cancers should be increased by the non-participation rate and are 168.

6. The Hardin centre estimates seem to be simply lifted mainly from the Nordic Cochrane review— it may be more appropriate to quote this directly or to drop the
Hardin Centre estimates from Table 1.

RE: I have specified that the numbers are based on the Nordic Cochrane estimates, but I still want to highlight the way of presenting data, and the numbers here reported are those chosen by the Hardin Centre.

7. Page 5, line 2- should ‘incidence reduction’ read ‘mortality reduction’?

RE: Thank you, this was a mistake.

8. The paper relies a lot on secondary sources. In terms of per protocol estimates of the effect on mortality, the author would be well advised to study another review- Duffy et al, Breast Cancer Management 2013).

RE: Thank you for the citation. I had the opportunity to see this study just after the submission of the paper as a presentation at the San Antonio Symposium and I found it really relevant to this paper.
Reviewer's report
Title: Screening: the information individuals need to support their decision. Per protocol analysis is better than intention-to-treat analysis at quantifying potential benefits and harms of screening.
Version: 1
Date: 24 January 2014
Reviewer: David Cameron
Reviewer's report:
I am not sure that this paper has fully grasped the issue here. Whilst it is ethical and appropriate to provide patients with the information on which to make their decision, the uncertainty in the data must also be addressed, and switching from an ITT to a per-protocol approach will introduce additional uncertainty. For a person deciding about screening or not, the advantage of the ITT approach is that the data apply equally to all people when they were eligible for the trial, which since most of the RCTs were population-based is the case: for a per protocol analysis, the data ONLY apply if a person like them accepted the intervention, and we don’t necessarily have the ability to determine that. There are data that those people who did not accept the screening invitation are NOT the same as those who did. An example comes from the two Canadian randomised trials of mammographic breast screening which were NOT targeted at the whole female Canadian population in the appropriate age-range….and where there is some evidence that the women accepting may have had a higher incidence of cancer (or even symptoms) at trial entry. Interestingly, they don’t show anything like the same benefit as the other randomised trials….which makes interpretation of screening benefit more challenging.
Thus in my view, BOTH the ITT and per protocol analyses matter, since the former influenced policy makers, and the latter helps individuals. If the information to patients is to include both, then it needs to be made clear that the per protocol analysis relates to those who did attend screening in the trials…and is therefore only an estimate of the benefit for people considering going for screening since there are differences between those who did, and those who did not, accept the invitation in the trials. If people in the trials knew the benefits/downsides (which of course were not known at the time), then some of those accepting might not have accepted and vice versa: therefore one cannot be sure that the population that accepted in the trial would be the same as the population accepting in routine care, so that extrapolating the per protocol analysis to the population who accept public health screening may also not be perfect. The same issue applies to all clinical trials, and in clinical practice one tends to quote ITT data until there is good population-based data to confirm or deny the validity of ITT data to routine care. The authors point out the challenges of getting information leaflets into language that is easily understandable to the public, and it might be better to report the ITT data as the population benefits, and say that since not all patients accept, the actual benefits for those who do get screened are likely to be a bit higher (mathematically because the denominator is smaller so the effect is amplified when correcting for a fixed number of patients), but it is even more difficult to be precise about the benefits. The paper is also written in a very unstructured manner, and it might be better to lay it out more clearly with a baseline search strategy on how the trials were reported, and how leaflets/ information to the public is presented. They have used a few examples to illustrate their view – but for a scientific paper it might be better to analyse the available data first.
RE: What I suggest in this “opinion” is exactly what the reviewer summarised very well in the sentence: “BOTH the ITT and per protocol analyses matter, since the former influenced policy makers, and the latter helps individuals”
I am not convinced that the possible biases caused by self-selection of the participants could be so relevant and could be not adjusted for once we have the opportunity to compare non responders and controls (not invited). On the other hand, the dilution of the effect is certainly an important issue and may differ greatly in different contexts.
Most of this paper is dedicated to showing that the only reasonable bias, when we compare participants and non-participants in preventive trials like these, is a self-selection bias and that a correct adjustment for self-selection bias is possible if we know the outcomes in all the three groups: participating, non-participating, and controls.
Of course this paper proposes a point of view, which is, at least in principle, falsifiable. To conduct an extensive reanalysis of all the reviews assessing the self-selection bias is beyond the scope of this paper; that reanalysis would also require data that are not easily accessible.