Author's response to reviews

Title: Reporting of clinical trials: a review of research funders' guidelines

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Author's response to reviews: see over
I would like to thank the two Reviewers for their insightful and constructive comments. I have thoroughly revised the manuscript to take all these comments on board, as documented in detail below. This has resulted in a much more thorough manuscript that more clearly describes this review of guidelines from organisations and charities that fund randomised controlled trials.

I now respond to each of the comments in turn and detail any changes I have made to the original manuscript. The referee/editor comments are shown in bold italics, and the responses are in normal text. N.B. My comments refer to page numbers in the new revised version of the paper.

1)  Response to Referee 1 Comments

Reviewer's report:
This manuscript addresses a critical issue threatening to undermine the basis of evidence-based medicine. RCTs represent the culmination of research translation before adoption in routine clinical practice. As the authors note, publication bias remains an influential factor. They conduct a meticulous review of organizations to examine guidelines in reporting and disclose potential limitations that surround outcome reporting bias. In many subspecialty fields, there remains a dissociation between trial protocol content and adherence with ultimate publication. Selective attention may be devoted to certain outcomes in a publication, irrespective of the original, planned outcome measures. Space and cost are often cited as limiting factors by trialists, organizations, and even editors, yet the public is misled by such midstream changes. The authors are to be congratulated on tackling what remains only a first step in critically evaluating and reforming the process of reporting important clinical research information.

Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Many thanks for your positive report.
2)  **Response to Referee 2 Comments**

**Reviewer's report:**
Selective outcome reporting is a relatively recently described form of publication bias. The authors seek to determine if guidelines provided by funding organizations and charities incorporate recommendations regarding reporting of all outcomes described in the initial RCT protocol of studies for which they provide funding. In addition, the authors wish to describe recommendations provided in guidelines regarding publication bias (mainly reporting of negative or null results), and trial registration. The first question, which the authors implicitly ask, is whether funding agencies provide guidelines at all. This is an important question and to my knowledge has not been previously addressed. The second aspect of the question, then, is if guidelines are provided, what recommendations are included in the guidelines. Again, the research question is pertinent. The general approach seems reasonable and the study conduct appears appropriate. The main difficulty I had with the manuscript is in the presentation. The writing is not focused and definitions are generally not present, making it difficult to understand and interpret exactly what the authors have found. On the other hand, the discussion was a reasonable attempt to interpret the findings and bring other areas into the interpretation (e.g., possible revisions to the CONSORT statement).

Many thanks for your constructive suggestions, which we respond to below.

**Major Compulsory Revisions:**

1. The abstract conclusions do not follow from the results; there is no mention of outcome reporting bias in either the methods or results, yet the main conclusion is that "there is a need to provide more detailed guidance ...to help prevent the selective reporting of outcomes."

The background states that ‘National and international organisations and charities give recommendations for good research practice in relation to RCTs but to date no review of these guidelines has been undertaken with respect to reporting bias.’

We have amended the methods to include information on how guidelines were reviewed with respect to outcome reporting bias, so that the conclusions follow on from this. (pages 2 and 3)

The results state that ‘However, only thirteen of these organisations or charities mention the publication of negative as well as positive outcomes and just four of the organisations specifically state that the statistical analysis plan should be strictly adhered to and all changes should be reported.’ This in itself refers to the selective reporting of outcomes.

2. The introduction lacks focus. For example, it starts off describing RCTs, but then goes into a description of systematic reviews without describing any connection between funding organization recommendations for RCT reporting and systematic reviews.
The authors then describe reporting bias and outcome reporting bias, but fail to mention trial registration.

The description of generally recognized guidelines in the next section requires more focus. Why not start out with a definition of “guidelines” including a brief description of the types of domains that should be included, with a particular focus on those related to the research question. For example, while participant safety can certainly be considered an important aspect of any guideline developed for conduct of an RCT, the research question the authors ask is about publication biases and registration; there is no question related to participant safety in the questionnaire (Appendices 2 and 3). Similarly, “high quality” research and reporting as described by CONSORT, while laudable for guideline development, are not pertinent to the research questions posed by the authors, as currently written. There is more than a page of text describing these domains of guidelines, even though these are related to the research question in being a domain which should be included in a guideline. I would suggest that these areas need only a few sentences or a brief description, followed by a more detailed description of the domains of interest identified in the research question.

We have amended the introduction, making the connections between RCTs, funding organisations for RCT reporting and removed information on systematic reviews. We have also included information on trial registration and how this can prevent reporting biases. We have also altered the layout of the introduction to improve clarity.

3. How were funding organizations and charities identified? Does the sample include all the organizations which fund UK research? Is it a representative sample? While you describe searching the AMRC site for charities, it is not clear how the other organizations were identified. Also, you mention 7 newly added charities when you last visited the AMRC site in September 2007 and that 2 charities had been excluded from the site. Could you clarify exactly how these were counted in the “140” contacted?

This is stated in paragraph 1 of the methods (page 8). We have edited it to make clearer that we used the same list as the DAMOCLES project. It is not a representative sample, it is supposed to be a complete list. “Collectively, the DAMOCLES group drew on its own experience to identify the most important funding organisations for trials within the UK, and supplemented this with information from key funders of trials in North America, South Africa and Australia. They also sought information from key organisations in industry and the regulatory agencies.”

There were 108 charities originally, plus another 7 newly added, which is 115 charities and 25 organisations which add up to the 140 contacted. Therefore, the 7 newly added charities and the 2 which were no longer on the website are all included. This is stated in the first paragraph of the results section.

4. It was not clear when the shortened version of the questionnaire (Appendix 2) was used and when the longer questionnaire was used (Appendix 3). Was the questionnaire in Appendix 3 always used with the questionnaire in Appendix 2 only used as a means of contacting the funding agency and requesting a copy of their guideline?
Yes this is correct, the questionnaire in appendix 3 was always used when reading through guidelines and the questionnaire in appendix 2 was only used as a means of contacting the funding agency and requesting a copy of their guidelines. This has been made clearer in the manuscript (page 10).

5. Including information from the guidelines from the four organizations that do not fund RCTs simply muddies the water. The inclusion criteria for this study was that only organizations that fund RCTs were to be included; this protocol should be adhered to (just as one would expect in a trial).

We have taken this information out of the main part of the study and included it in the background/discussion instead as this information is still important. We have also removed Table 5 which contains this information.

6. Given that you mention having difficulty in finding guidelines on the websites, indicate how many were identified and for how many you were required to request that information from the organization contact. In this context, it would be useful to know how the guidelines were issued to the researcher (question on Appendices 2 and 3) – if guidelines are difficult to find on the website, are they sent to the researcher or is s/he expected to find them?

We described this process in the results ‘Websites for all 73 eligible organisations and charities were accessed but the success in searching for guidelines was mixed. Some were relatively easy to find and well directed by the organisation (e.g. Medical Research Council), while others proved more difficult to find. The websites for Health Technology Assessment (HTA) and National Institute of Health (NIH), for example, provided a lot of information making it difficult to find the required guidelines.’ As the websites were searched several times and all organizations and charities were also contacted on several occasions, this information is not available. Even if information was found on the website, each charity and organization was contacted to enquire whether there was any other information available. Most of the information was obtained through contact with the organization/charity. Even if the questionnaire was returned the question on how the guidelines were issued to the researcher was often not answered with only 30 stating that the guidelines were sent by post/email, supplied with the grant application or that researchers were referred to their website.

We have added this information to the results section on page 12.

7. Table 1: Some definitions are needed here to understand the table. What is meant by “limited contact?” Does this mean that no guidelines were received? Please use full names, not acronyms for “other guidelines.” Also, what is meant by “Department of Health,” “Institution,” “Charity specific,” “National regulations and guidelines,” and “Legal?”

These have been added as footnotes to the table.
Limited contact meant that we did have contact with the organisation/charity to confirm that they did fund clinical trials and what the maximum grant available was, but then no further information was forthcoming. Acronyms have been changed to full names for other guidelines.
Department of Health refers to the Department of Health’s Research Governance framework (England).

Institution means the guidelines refer to the guidelines issued by the university or other institution were the trial was to be conducted from.

Charity specific means that the charity has specific guidelines for the particular disease/illness but not necessarily good research practice guidelines.

National regulations and guidelines are guidelines issued nationally e.g. for the UK, America e.tc.

Legal guidelines means the guidelines refer to specific legal guidelines for clinical trials or the specific disease/illness being studied.

Please address the following:

1. How was it decided if a guideline domain was mentioned "explicitly" versus "implicitly?"

By explicit we mean that the charities/organisations guidelines referred to one of the guideline domains (trial registration, protocol adherence, publication, or monitoring) within their guidelines. By implicit we mean that the charities/organisations guidelines referred to other guidelines such as CONSORT, ICH E6 guidelines etc which referred to the guideline domains.

We have included this information within the manuscript (page 11 final paragraph).

2. What do you mean by “Protocol adherence/amendment” (one assumes you mean by this that there are guidelines related to what the researcher should do if there is a protocol change – but please be explicit)

By protocol adherence/amendment we mean any reference in the guidelines to these issues, i.e. do the guidelines state that the protocol should be adhered to? Do the guidelines give any information on what to do if there are changes to the protocol? We have included this information in the manuscript (page 10). Detailed information on what the guidelines state about protocol adherence/amendment is given in table 3.

3. Trial publication – do you mean any statement about publication or a statement about publishing negative results, or the timing of publication?

By trial publication we mean any statement referring to publication i.e. if it should be published, where it should be published, when it should be published, what should be included in the publication etc. We have included this information in the manuscript (page 10). Detailed information on what the guidelines state about publication is given in table 3.

4. By “monitoring against guidelines,” do you mean monitoring for adherence to the published guidelines?

By monitoring against guidelines we do mean monitoring for adherence to the published guidelines but we found that most guidelines did not discuss this and only discussed the monitoring of trials. We have added this information to the manuscript (page 10). Detailed information on what the guidelines state about monitoring is given in table 3.
8. Please add the additional domains investigated (related to outcomes, outcome reporting bias, and publication bias (i.e., the information in Table 2) to Table 1. While Table 2 is useful in seeing exactly how the guidelines are stated, it is important to see which of these areas are covered by how many guidelines.

We have added numbers on publication of negative outcomes (ORB) and studies (publication bias) to Table 1.

9. There looked to be some differences in guidelines (yes/no or content) between “organizations” and “charities.” Please comment of these differences. How do you interpret these findings?

The organisations’ guidelines contained more information than the charities’ guidelines. We have commented on the differences in the discussion.

‘The main difference between the organisations and the charities was that it was the organisations that tend to have their own guidelines whereas the charities mostly had terms and conditions and referred to some of the organisations guidelines for thoroughness. This may be due to some of the charities being small and some had only recently advanced into funding RCTs or contributing to funding along with an organisation.’

Discretionary Revisions
1. The original studies examining publication bias were conducted by Dickersin and Easterbrook and should be cited rather than an “in press” publication. In addition, there is a published Cochrane protocol on this topic, as well as one on time to publication, both with Hopewell as lead author that should be acknowledged.

The cited article has now been published in PLoS ONE and is a review of the empirical evidence of publication bias and outcome reporting bias. The studies and Cochrane protocols and reviews referred to by the referee are referenced in this recently published review.

2. Exactly what are the differences and similarities between “terms and conditions of a grant” and guidelines. My perception was that the terms and conditions would include areas dealing with the legalities of passing monies between the funding organization and the researcher rather than research guidelines describing safety, research quality, publication, etc., yet you use them interchangeably. Confidentiality issues might prevent an agency from sending you a copy of terms and conditions, but I find it difficult to understand why confidentiality was a issue for research guidelines.

We requested guidelines as per Appendix 2. Sometimes all we were sent were the terms and conditions of the grant and when we followed this up to request research guidelines we were told that was all that was available. The terms and conditions were mostly as you have perceived. However sometimes extra information was included on publication etc, but often the terms and conditions did not include any information we needed and other information was obtained through contact with the charity/ organisation. There were two charities that would not send any information due to confidentiality and we did try to contact them again but with no success.
We have included this information in the results section (page 12).

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

All these changes have now been made.