Author’s response to reviews

Title: A Systematic Review of Techniques and Inteventions for Improving Adherence to Inclusion and Exclusion Criteria During Enrolment into Randomised Controlled Trials

Authors:

Fiona Simpson (fsimpson@nsccahs.health.nsw.gov.au)
Elizabeth A Sweetman (easweetm@nsccahs.health.nsw.gov.au)
Gordon S Doig (gdoig@med.usyd.edu.au)

Version: 2 Date: 21 January 2010

Author's response to reviews: see over
Re: Manuscript entitled “A Systematic Review of Techniques and Interventions for Improving Adherence to Inclusion and Exclusion Criteria During Enrollment into Randomised Controlled Trials.”

Dear Iain,

We wish to submit the revised Commissioned Editor Review, for publication in the Journal Trials. We have addressed each of the reviewers’ comments, and believe our manuscript to be much improved as a result of the review process. Thank you.

Questions received from the Editor are addressed herewith:

I’d like the authors to pay particular attention to a couple of key points made by Reviewer 1:

1. The discussion uses examples from large trials. Most trials are small (Chan and Altman, Lancet 2005) and thus examples using smaller trials might be more useful for readers. It might also be that smaller trials are more prone to enrollment error.

Authors’ Response:

There is insufficient evidence for us to comment regarding whether smaller trials are more prone to enrollment errors or not. Other methodological reporting artefacts have been documented to be related to trial size, however we are unaware of any objective evidence relating trial characteristics to enrolment error rates. In response to Reviewer 1, and comments from the Editor, we have now explicitly discussed the need for more research in this area at the end of our manuscript.

In removing the ‘interventions recommended to reduce enrolment errors, but not evaluated’ section we have also removed many of the references to large trials in the revised manuscript.

2. and it is not clear why and how the discussion list was generated. This section needs more elaboration and organization? some readers will likely find it confusing to read.

Authors’ Response:

Thankyou for these comments relating to the discussion section on ‘interventions recommended to reduce enrolment errors, but not evaluated’. In response to the comments
received from Reviewer 1, and the Editor, and noting a request to shorten the paper from Reviewer 1, we felt this section of the paper could be deleted from the revised manuscript.

3. The authors should also pay specific attention to point 5 and point 6 raised by Reviewer 2.

Discretionary Question 5, Reviewer 2: Page 8, para 3- “has been shown to result in most harm”. Is this assertion warranted based on reference #2? Did the study compare harms resulting from various types of protocol violations and find a significant difference?

Authors’ Response: We apologise for the non-specific wording of this sentence. Although reference #2 does show harm (mortality) was higher in patients with enrolment errors, this finding was not statistically significant. We have modified the sentence to more accurately reflect the findings of reference #2.

4. Discretionary Question 5b, Reviewer 2: It would be helpful to elaborate on how harms may arise due to enrolment errors.

Authors’ Response: In response to Reviewer 2, and the Editors comments, we have now described how harms could arise as a result of enrolment errors in both the Background and Discussion sections of the revised manuscript.

5. Discretionary Question 6, Reviewer 2: Page 11, para 4 – There are many uses of the term ‘ITT’. Should ‘ITT' be defined in the text?

Authors’ Response: We have removed the entire section on ‘interventions recommended to reduce enrolment errors, but not evaluated’ where ITT is defined. This is in response to Reviewer 1, and the Editors comments. We no longer refer to the concept of an intention to treat analysis, and therefore do not require a definition.

Our detailed responses to each of the three reviewers can be found on the following pages below.

Sincerely,

Fiona Simpson,
Senior Lecturer in Intensive Care,
Northern Clinical School,
University of Sydney and
Royal North Shore Hospital ICU
e-mail: f simpson@nsccahs.health.nsw.gov.au
Reviewer 1:
1. Was an identifiable question formulated? Unclear
   It's not surprising there is a lack of evidence in this field; however, I wonder if the question was the wrong one. Why not start with an indirect comparison of effects. For example, it might have been fruitful to examine a number of trials with specific enrollment error rates reported and determine what “interventions” were applied and compare all similar efforts. For example if 10 studies were identified that reported NO EFFORT to reduce errors and their rate of enrollment error was say a median of 5%, this could be compared to all studies that staggered their enrollment start-date (or some similar such intervention). Indirect comparisons are more complicated to analyze, but would have been more informative.

Authors' Response to Comment 1: Thank you for this suggestion, it is an excellent idea for a follow-up paper. We note that the systematic review reported in this current paper was conducted in response to an Invitation issued by the Journal Editorial Board. We would not wish to deviate from the question the Editorial Board invited us to address.

2. This manuscript will be evaluated using the Oxman and Guyatt OQAQ tool:
   Were the search methods used to find evidence (primary studies) on the primary question(s) stated? Yes. A complete list of these concept-related terms are presented in Table 1. Databases searched up to 2009, unpublished and non-English language articles were searched for.
   Was the search for evidence reasonably comprehensive? Yes. EMBASE, MEDLINE, Cochrane Database of Systematic Reviews and grey literature searched.
   Were the criteria used for deciding which studies to include in the review reported? Yes. Any intervention designed to reduce any form of protocol error or violation were retrieved in full text for detailed review. Very broad inclusion criteria: Any design, any error type and any form of evaluation of effectiveness were accepted.

Authors' Response to Comment 2: Thank you for your kind review.

3. Was bias in the selection of articles avoided?
   Two reviewers for screening and 3 for selection; differences resolved by consensus. No comment on independence and blinding?

Authors' Response to Comment 3: We have now been more explicit in the revised manuscript and have stated that screening and selection of articles was undertaken independently. We also report selection and screening was not done blind to publication source or authorship list. Thank-you for pointing out this omission.

4. Were the criteria used for assessing the validity of the studies that were reviewed reported?
   No mention of the quality assessment or scoring system.

Was the validity of all of the studies referred to in the text assessed using appropriate criteria (either in selecting studies for inclusion or in analyzing the studies that are cited)? No. No mention of the quality assessment or scoring system.

Authors' Response to Comment 4: Our a priori formed intent was to report sufficient detail concerning the major design features of each included study such that a reader could apply
any form of reasonable quality assessment instrument they personally preferred to use and
thus satisfy their own interpretation of 'rigour'. There is evidence to suggest that the use of
composite quality scales that sum 'scores' assigned to different design features may actually
mask important defects [1]. Likewise, we suggest that the use of a controlled lexicon, which is
common to most scales [2], may also result in information loss. For example in a report of a
randomised controlled trial, we believe much more information is communicated with a
description of exactly how authors reported that allocation concealment was maintained as
opposed to imposing our own, sometimes subjective, judgements inherent in the use of the
common lexicon of 'clear, unclear or not maintained'.


5. Were the methods used to combine the findings of the relevant studies (to reach a
conclusion) reported? – No. No methods for combining were discussed. This would be
especially important for indirect comparisons of trials that used a method to reduce
enrollment errors and reported error rates; however, no primary publications were found.
Were the findings of the relevant studies combined appropriately relative to the
primary question the review addresses – No. No primary publications were found.
Were the conclusions made by the author(s) supported by the data and/or
analysis reported in the review? - Partially.
Overall, how would you rate the scientific quality of this review?
Moderate.

Authors' Response to Comment 5: Thank you.

6. In the large section in the discussion entitled: “Interventions recommended to
reduce enrolment errors, but not evaluated.” How sure can the readers be that this list is
comprehensive? It’s not stated where this list came from. Off the top of my head, I would also
suggest mock scenarios, simulations scenarios, study check-lists, double (PI)- review, and
several other techniques may be useful. A focus group or survey could have helped to inform
the research question here.

Authors' Response to Comment 6: Thank you for your comments concerning this section of
our Discussion. We have reflected upon your comments in the context of the primary focus of
the paper. In consideration of your recommendation to shorten the paper, and based on the
Editor's comments on this section, we feel the paper is better served by deleting this entire
section. It has therefore been deleted.

7. The discussion seems to focus on large trials, and I would think the effect of
enrollment error there may be less than smaller trials. Can you comment?

Authors' Response to Comment 7: We are unable to comment. Although there may be
evidence to suggest that the presence of other methodological reporting artifacts are related to
trial size, we are unaware of any objective evidence concerning any trial characteristics that
are associated with enrolment error rates. In response to your comment, we now explicitly state at the end of our paper that more research is needed in this area.

8. Strengths and Limitations:
Should discuss the exclusion of indirect comparisons and why.

Authors' Response to Comment 8: This issue is covered under our general statement recognising the need for further research in the field.

9. Overall, its well written but could be shortened.

Authors' Response to Comment 9: Thank you. We have shortened the revised manuscript in response to your comments.

Reviewer 2:
The authors present an excellent systematic review on an important topic. My comments are minor and mostly for clarification.

Minor Essential Revisions
1. Page 4, para 2 -- Capitalize MEDLINE

Authors' Response to Essential Revision 1: We apologise for this oversight. We have ensured that all references to ‘Medline’ have now been capitalised to ‘MEDLINE’ in the revised manuscript.

2. Page 12, para 1 – ‘associateD’

Authors' Response to Essential Revision 2: Thank you for picking this up. We have changed ‘associate’ to ‘associated’, as indicated.

Discretionary Revisions
1. Is the term ‘eligibility criteria’ preferred to ‘inclusion and exclusion criteria’, as an inclusion criterion can simply be the reverse of an exclusion criterion (eg. Include >17 yrs old vs exclude <18 yrs old)?

Authors' Response to Discretionary Revision 1: We agree that the term ‘eligibility criteria’ may be preferred in most situations. We have now consistently used this term throughout the manuscript.

2. Should the paper discuss that a contributing factor for lack of adherence to eligibility criteria could be poor definitions of criteria in the trial protocol?

Authors' Response to Discretionary Revision 2: Thank you, this is a good point. We have addressed the issue of clarity of definitions of the criteria in our Discussion section, paragraph 3 of the Background sub-section (page 9).
3. Page 3, paragraph 1 – Brief examples or elaboration on what harms may occur due to enrolment errors would be useful.

Authors' Response to Discretionary Revision 3: As suggested, we have added brief examples of the types of harms that can be attributed to enrolment errors in the requested section.


Authors' Response to Discretionary Revision 4: We have moved the definition of ‘recognized experts’ the suggested location where it is first used. Thank-you for highlighting this oversight.

5. Page 8, para 3 – “…has been shown to result in most harm”
Is this assertion warranted based on reference #2? Did the study compare harms resulting from various types of protocol violations and find a significant difference?

Authors' Response to Discretionary Revision 5: We apologise for the non-specific wording of this sentence. Although reference 2 does show that harm (mortality) was higher in patients with enrollment errors, this finding was not statistically significant. We have adjusted the sentence to more accurately reflect the findings of reference #2.

5b. It would be helpful to elaborate on how harms may arise due to enrolment errors.

Authors' Response to Discretionary Revision 5b: We now describe how harms could arise due to enrolment errors in the Background and Discussion sections of the revised manuscript.

6. Page 11, para 4 – There are many uses of the term ‘ITT’. Should ‘ITT’ be defined in the text?

Authors' Response to Discretionary Revision 6: In response to comments from other Reviewers, we have removed the entire section on ‘interventions recommended to reduce enrolment errors, but not evaluated’ where ITT is defined. We no longer refer to the concept of an intention to treat analysis. Therefore the definition is not required.

Reviewer 3:
1. On page 4, Primary literature search – did the authors have an information specialist helping them?

Authors' Response to Comment 1: We are unaware of the specific and objective criteria required to qualify as an 'information specialist'. We note that our team has extensive experience in this field.

One of the Authors (GSD) is an Ex-IBM Systems Engineer and has a professional interest in Natural Language Parsing and search algorithm optimisation. Two of the Authors (FS and GSD) have published a primary paper on optimised processes for medical information retrieval [1], which has been referenced in a positive light by leading experts in the field [2] and has resulted in many invitations to conduct workshops and deliver plenary talks on
information retrieval. All three authors (FS, EAS and GSD) have been primarily responsible for numerous systematic literature searches that have supported National-level evidence-based guidelines and systematic reviews, a few examples of which are included below [3-8].

Whilst we are not certain that these experiences, accumulated over a period of 20 plus years, qualify us as 'information specialists', we do believe they demonstrate our team is reasonably well experienced in this field. Personal experience notwithstanding, we always welcome new opportunities for collaborative relationships.


2. The authors should include as an appendix a search strategy from one of the main searches they completed (e.g., Medline).

**Authors’ Response to Comment 2:** Thank you for this suggestion. We have included an example of a search strategy from one of the main searches in the appropriate MEDLINE syntax (Appendix 1 of revised manuscript).

3. Did the authors have their search strategy peer reviewed (Sampson M, McGowan J, Cogo E, Grimshaw J, Moher D, Lefebvre C. An Evidence-Based Practice Guideline for the Peer Review of Electronic Search Strategies (PRESS) was developed. *Journal of Clinical Epidemiology.* 2009;62:944-52)?
Authors' Response to Comment 3: Thank you for providing this fascinating reference. This may indeed be the way of the future however we were unable to find any Journal Editorial Boards that have currently accepted these recommendations as a requirement for publication. We believe the search we conducted adheres to the key criteria outlined in the guideline and have presented the details of our search such that this Journal's Peer Reviewers have sufficient confidence in the processes that we used.

4. Page 5. How many content experts did the authors contact?

Authors' Response to Comment 4: We used an informal process to consult and contact experts. We discussed methods to reduce protocol violations with investigators who had extensive experience in clinical trials methodology or were known to have published on the topic. Contact with these experts occurred over a number of years. We have provided more detail regarding the informality of the process in the methods section of the revised manuscript. Unfortunately we did not keep track of the number of experts who were consulted.

5. Page 5. The authors are silent on whether, a priori, they were going to perform any assessment of the rigor of the primary studies and if so how this was to be conducted?

Authors' Response to Comment 5: Our a priori formed intent was to report sufficient detail concerning the major design features of each included study such that a reader could apply any form of reasonable quality assessment instrument they personally preferred to use and thus satisfy their own interpretation of 'rigour'. There is evidence to suggest that the use of composite quality scales that sum 'scores' assigned to different design features may actually mask important defects [1]. Likewise, we suggest that the use of a controlled lexicon, which is common to most scales [2], may also result in information loss. For example in a report of a randomised controlled trial, we believe much more information is communicated with a description of exactly how authors reported that allocation concealment was maintained as opposed to imposing our own, sometimes subjective, judgements inherent in the use of the common lexicon of 'clear, unclear or not maintained'.


6. Page 5. The authors should provide some description of the data items they were planning on extracting.

Authors' Response to Comment 6: Thank you for alerting us to this omission. We have added descriptions of data items extracted to the Methods section of our revised manuscript.

7. In the figure of the paper the authors report not including any studies. In the text they report including one. This needs to be resolved – one should appear in the figure.
Authors’ Response to Comment 7: We have adjusted Figure 1 as recommended.

8. Reference 24 is out of date.

Authors’ Response to Comment 8: Thank you. In response to other Reviewers requests to shorten the manuscript, and a suggestion from the Editor that this section was a bit confusing, we have deleted the section that contains Reference 24. However, before it was deleted, we did update it.