PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Selective reporting of outcomes in randomised controlled trials in systematic reviews of Cystic Fibrosis
AUTHORS	Dwan, Kerry; Kirkham, Jamie; Williamson, Paula; Gamble, Carrol

VERSION 1 - REVIEW

REVIEWER	Alfonso Iorio Clinical Epidemiology and Biostatistics McMaster University
REVIEW RETURNED	27-Feb-2013

GENERAL COMMENTS	The paper describes the analysis of the occurence and typology of risk of bias from selective outcome reporting in the systematic reviews about Cystic Fibrosis produced by the Cystic Fybrosis and genetic disorders group of the Cochrane collaboration. The authors are the same who developed the ORB instrument and run the ORBIT project, identifying this specific source of bias and assessing its relevance in performing systematic review. The peculiarity of the present paper is the focus on secondary outcomes, the comprehensive assessment of the risk of selective reporting in the RCT included in the SR, the focus on a specific disease area. The study aim are clear and well described, the manuscript is well written, balanced and sequential. The message is clear and relevant to author and users of systematic review. In particular, the authors are objective in pointing out that full exploitation of the usage of the guideline they provide to assess the risk of selective reporting require clinical judgement. Similarly, they showed that including / excluding studies falling in category G may be excluded without important variation of the proportion of SR judged to be at risk or not for ORB. This is important information for implementation purposes. A few suggestions to consider for potential improvement of the manuscript Page 6, line 25. The authors state that they selected a field with low reporting standards. Implications for their study's results are left implicit, but could be shortly considered in the discussion. Page 6, line 52. The Cochrane guidance for assessing ORB was issued in 2011. Why the authors decided to focus only on reviews published on 2010 or before. This might be a consequence of the time needed to perform the study (which is easily imagined to be huge!), or a choice related to assessing a sort of baseline against which in the future audit of usage of the ORB logic and tool could be made. Abstract, page 2, line 12. Please consider adding "Cochrane's" systematic reviews. Abstract, page 3, line 27. The author define the observed outcome reporting bias as "greater". This implies a comparison term which is not provided. The same concept applies to the section "key concepts"

	P 13, line 19: “were” should likely be “where” One final question to the authors (for response to the referee, and inclusion on the paper only if that makes sense): did the authors provided feedback about specific reviews falling in the different categories of ORB, and for which of the included studies this applied? I mean, is there a plan to let the authors of the SR considered in this study to update (if they agree of course) their RoB assessment and table when needed by receiving the information specific to their specific review? I guess this would be possible in the framework of the Cochrane library, and would likely be worthy pursuing if possible.

REVIEWER	Ian Hambleton, PhD Professor of Biostatistics, Chronic Disease Research Centre, Tropical Medicine Research Institute, The University of the West Indies, Barbados, West Indies. Ian Hambleton is haematological and statistical editor with the Cochrane Collaboration Cystic Fibrosis and Genetic Disorders Group (CFGD) - the same group as that of the contact author.
REVIEW RETURNED	11-Mar-2013

THE STUDY	I have only ticked "No" to the question above in order to point the authors to my full list of comments, which are attached as PDF comments to their submitted manuscript. Generally, the article is very well written, and is quite clear. My comments are stratified into MINOR and MAJOR. The majority are minor comments, and thew authors should find these easy to enact, should they choose to do so. Several comments are slightly more important, and are linked to an intermittent lack of clarity on "systematic-review-level" reporting bias versus "trial-level" reporting bias.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Alfonso Iorio
Clinical Epidemiology and Biostatistics
McMaster University

The paper describes the analysis of the occurrence and typology of risk of bias from selective outcome reporting in the systematic reviews about Cystic Fibrosis produced by the Cystic Fibrosis and genetic disorders group of the Cochrane collaboration. The authors are the same who developed the ORB instrument and run the ORBIT project, identifying this specific source of bias and assessing its relevance in performing systematic review. The peculiarity of the present paper is the focus on secondary outcomes, the comprehensive assessment of the risk of selective reporting in the RCT included in the SR, the focus on a specific disease area.
The study aim are clear and well described, the manuscript is well written, balanced and sequential. The message is clear and relevant to author and users of systematic review. In particular, the authors are objective in pointing out that full exploitation of the usage of the guideline they provide to assess the risk of selective reporting require clinical judgement. Similarly, they showed that including / excluding studies falling in category G may be excluded without important variation of the proportion of SR judged to be at risk or not for ORB. This is important information for implementation purposes.

A few suggestions to consider for potential improvement of the manuscript

1. Page 6, line 25. The authors state that they selected a field with low reporting standards. Implications for their study's results are left implicit, but could be shortly considered in the discussion.
We have clarified this sentence to indicate that this was when comparing trial reports to the CONSORT statement. A sentence has also been added to the discussion to consider this "A study by von Mosch and Dwan (2011) that compared the reporting in trial reports of CF to the CONSORT statement found that from a maximum of 57 points available, the scores rose from a median of 17.5 (Inter quartile range (IQR) 15.5-24.5) in 1994 to a median of 32 (IQR 22.8-41.5) in 2008. Along with the current study, this also indicates that there is still room for an improvement in the reporting of outcomes. "

2. Page 6, line 52. The Cochrane guidance for assessing ORB was issued in 2011. Why the authors decided to focus only on reviews published on 2010 or before. This might be a consequence of the time needed to perform the study (which is easily imagined to be huge!), or a choice related to assessing a sort of baseline against which in the future audit of usage of the ORB logic and tool could be made.

The beginning of 2010 was chosen as this was when the work began so all reviews up to this date were taken. The Cochrane guidance was first released in 2008, therefore many of the reviews in this cohort had assessed selective reporting.

3. Abstract, page 2, line 12. Please consider adding "Cochrane's" systematic reviews.
Cochrane has been added.

4. Abstract, page 3, line 27. The author define the observed outcome reporting bias as "greater". This implies a comparison term which is not provided. The same concept applies to the section "key concepts"
Sentence has been edited to "Assessment of ORB within a systematic review, of a single primary outcome, underestimates the risk of ORB in comparison to the assessment of multiple primary and secondary outcomes."

5. P 13, line 19: “were” should likely be “where”
Were has been changed to where.

6. One final question to the authors (for response to the referee, and inclusion on the paper only if that makes sense): did the authors provided feedback about specific reviews falling in the different categories of ORB, and for which of the included studies this applied? I mean, is there a plan to let the authors of the SR considered in this study to update (if they agree of course) their RoB assessment and table when needed by receiving the information specific to their specific review? I guess this would be possible in the framework of the Cochrane library, and would likely be worthy pursuing if possible.
Yes, as the contact author works daily with the CFGD review group, as each review is updated the contact author will ensure the assessments are fed back to the lead review author through the groups managing editors (for all reviews, not just those where the lead reviewer was involved in the classification process anyway). This process will ensure the information is considered in the update when the lead reviewer has time to work on the review. We have added a sentence to the discussion to make this clear “However, these assessments will be provided to the review authors when their review is due to be updated.”

Reviewer: Ian Hambleton, PhD
Professor of Biostatistics,
Chronic Disease Research Centre,
Tropical Medicine Research Institute,
The University of the West Indies,
Barbados, West Indies.

Ian Hambleton is haematological and statistical editor with the Cochrane Collaboration Cystic Fibrosis and Genetic Disorders Group (CFGD) - the same group as that of the contact author.

1. Should the title make mention of Systematic Review level reporting bias?

The title has been updated “Selective reporting of outcomes in randomised controlled trials in systematic reviews of Cystic Fibrosis”. We haven’t mentioned systematic review level reporting bias as we only considered discrepancies in outcomes at the review level.

2. MINOR COMMENTS
First. The highlighted phrase may encourage a confounded interpretation. Is the conclusion of possibly increased ORB because (A) trials are small, or because (B) reviews have >1 endpoint.

This sentence has been deleted.

Second. Aren't multiple endpoints a feature of most SRs in the Cochrane domain? Are there areas in which a single primary outcome is more common?

Yes, the Cochrane handbook recommends up to 3 primary outcomes and a limited number of secondary outcomes. Therefore few reviews will include one primary outcome. However due to the nature of outcomes included in CF reviews, they can be measured and reported in many ways. Hence, reviews of CF tend to include many ‘sub outcomes’ compared to reviews of cancer for example which may include overall survival and disease free survival.

However, the sentence actually referred to the fact that the ORBIT study only considered a single review primary outcome and this study considers multiple primary outcomes.

These two comments don't detract from what is a really good rationale for the study!

3. MAJOR COMMENT
For the uninitiated (including myself!)...

Because the authors are so familiar with their subject matter, I feel that they have not always done enough to discriminate between "systematic review-level" reporting bias and "trial-level" reporting bias.

I have highlighted the issue occasionally through the document, but the authors should work through methods and results, making sure that this important distinction is always made.

They might also want to make the two assessments clear on the flow diagram, which could then be an important reference point throughout the document.

This study does not look at reporting bias at the review level. It considers discrepancies in review outcomes between protocol and review and does not focus on effect estimates.
We have increased clarity between review, trial and outcome levels in the manuscript.

4. MINOR/MAJOR COMMENT
Related to previous comment. This text suggests that ORB was only performed at the trial-level. But in the Methods summary it says that the aim "was to assess ORB ... in systematic reviews"

Could the authors clear up terminology a little. Is the acronym "ORB" used for both "SR-level" and "trial-level" reporting bias. Or restricted to "trial-level"...?

This sentence has been reworded for greater clarification.

5. MINOR COMMENT
Should probably note here: greater than what?
Sentence has been edited to “Assessment of ORB within a systematic review, of a single primary outcome, underestimates the risk of ORB in comparison to the assessment of multiple primary and secondary outcomes.”

6. MAJOR COMMENT
I'm assuming that this is ORB at the trial-level. Am I right or wrong?
This is at the outcome level and we have included this in the sentence “Assessment of outcome reporting bias at the outcome level across all efficacy systematic review outcomes.”

7. MINOR COMMENT
This wasn't discussed in the abstract, I don't think. Do you mean to then look at the contribution of ORB to the overall risk of bias?
We did not look at the contribution of ORB to the overall risk of bias, but rather whether considering only primary review outcomes had a different assessment of risk of bias from selective reporting than when considering all review outcomes. We have deleted ‘overall’ from this sentence and edited it to “Assessment of the risk of bias of a trial from selective outcome reporting within a systematic review.”

8. MINOR COMMENT

Repetition on my part, --> don't most reviews have multiple primaries / secondaries?
There is no work that can be referenced to support the frequency of reviews with single versus multiple primary outcomes. In some areas there is greater consensus of the primary outcome however our experience in CF compared with other areas is that the reviews frequently have a multiple primary outcomes.

And greater then what?
This is in comparison to when one outcome was considered in ORBIT. This has been reworded, please see response to comment 5.

9. MINOR COMMENT
This sentence is long and hard to assimilate. Is it missing a comma perhaps? Between "trials" and "increasing"? Consider re-wording...
This has been reworded. “This study may have underestimated this problem as review primary outcomes are chosen due to their clinical importance and are more likely to have been measured and reported in trials. Therefore, there is concern regarding the prevalence and impact of outcome reporting bias in reviews where multiple primary outcomes are specified, or in secondary outcomes.”

10. MINOR/MAJOR COMMENT
These two aims are clear and are good.
Do the three points (in Article Focus) need to be aligned/reduced to match these two aims?
We’ve included a third aim which then matches to the article focus. This was included previously but not explicitly stated as an aim. “Assess the risk of bias of trials from selective outcome reporting when considering review primary outcomes only in comparison to all review outcomes.”

11. MINOR COMMENT
Sounds like a sensible approach. Might be useful to know how often this fudge was required?
This is stated in the second paragraph of the results section. There were nine that did not distinguish between primary and secondary outcomes.

12. MINOR COMMENT
I would change this to "should". It should follow in a well organised trial. But it is not axiomatic, I don't think.
This has not been changed as it should be ‘must’ because you can not assign a reason for death without knowing how many there are. The sentence states that overall survival must have been measured – this does not mean that it must have been reported.

13. MINOR COMMENT
Minor I think. Are you saying here that many review authors contributed to the ORB assessment in this paper? If I've got this right, is it worth having a list of these article contributors somewhere (perhaps in acknowledgements)?

We have acknowledged the authors globally. If we were to name all authors we would need to ask their permission.

14. MINOR COMMENT
Tables 3 and 4 are linked to this section. For both Tables, I found myself wanting to know the following:
(A) the total number of reported primary and secondary outcomes.
(B) What proportion of these total outcomes were discrepant

Much consideration was given to the best way to convey this information. Given the impact was

considered on the review level we reported the number of reviews affected by discrepancy with the protocol. Given variable number of outcomes per review presentation of results would be skewed by problematic reviews. No amendment has been made to this table.

15. MINOR COMMENT
This is a long section.
It does include a mix of methodology and results, with some of the methodology (eg. The FEV1, FVC etc description on p11 was also on p8) being partly a repetition from the methods section.
Maybe this section can be reduced, just a little.

The seventh paragraph has been moved to the methods section and edited.

16. MINOR/MAJOR COMMENT
Could the authors comment (perhaps in the discussion) on whether they feel that this n=12 non-response (and possibly also the N=13 partly assessed reviews) constitutes an important bias in the paper?
Any systematic quality difference (I wonder) between reviews of responding and non-responding SR authors?
We have added the following “Many review authors did not respond to our request to provide classifications (68%), but for those with no response we did obtain clinical input for the primary outcome from within the CFGD group, Although we can not exclude the possibility of response bias it is likely the decision to respond was influenced by time commitments rather than review characteristics.”
17. MINOR COMMENT
Same as the comment for Tables 2/3 --> as I read Table 1, I find myself wanting to know
(1) How many primary endpoints
(2) How many secondary endpoints

Again, much consideration was given to the best way to convey this information. Due to the variable number of outcomes per review, it was decided to present the classifications as a percentage of the overall number of outcomes per review multiplied by the number of eligible trials within the reviews, separated by primary and secondary. This has been added to Table 1 with footnotes to describe the denominator used. Percentages have also been included in the text and the number of trials that fully reported review outcomes.

Following this (but possibly beyond the scope of this paper), are there endpoint types that are more prone to reporting bias than others, I wonder?
This could be a fairly important practical question, as it relates to the creation of CF endpoint reporting standards.

This has been addressed throughout the paper with the discussion of lung function as an example, due to the different ways it can be measured, analysed and reported there is a large scope for selective reporting. However, as the reviewer states this is beyond the scope of this study but would make for interesting further work.

typo?
where...
This has been amended.

18. MAJOR COMMENT
Its not completely clear to me why...

Is this to do with the 12+13 SRs for which authors did not provide endpoint categorization? Or another reason?
Would reference to an expanded flowchart help here?

We were unable to assess some outcomes, partly to do with the lack of reviewer input on some reviews or the lack of a standard definition. Where this was the case we followed the same approach as the ORBIT study which did not assess reviews if no standard definition of the primary out¬come existed. One example is relapse in schizophrenia trials, for which definitions include a change in symptom score and hospital readmission. We have also focussed on efficacy outcomes as stated in the manuscript and there is currently a study being undertaken which is investigating the selective reporting of harms (ORBIT 2).

We have edited the sentence “Due to limited reviewer input or the lack of a standard definition, we were unable to assess outcomes (including: adverse events, symptoms, complications, biochemical measures of glycaemic control, symptoms of sleep disordered breathing and measures of specific indices of strength, mass, effort and general fatigue) for 102 trials for review primary outcomes and 59 trials for review secondary outcomes.”

19. MINOR COMMENT
Could improve wording a little here...
Give date the guidance was introduced.
This has been edited “Eighteen reviews (49%) had not yet assessed the risk of bias for selective outcome reporting as although the Cochrane guidance on the risk of bias was introduced in 2008 and the cut off for this study was the beginning of 2010, these reviews were still to be updated.”
20. MINOR COMMENT
Reword --> something like:
"However, this is confounded by the different publication date ranges of reviews in each article"
Perhaps give the date ranges...
This has been reworded to what was suggested. “However, this is confounded by the different publication date ranges of the reviews (assessed as up to date between 2006 and 2009)”.

Typo?
Where
This has been amended.

21. MINOR COMMENT
This seems like a pretty useful observation. It wasn't in the results section...
This is shown in table 4, but a sentence has now been added to the results section when table 4 is discussed.
22. MINOR COMMENT
Also a really important observation.
Is a figure quoted for the number erroneously excluded.
Could be another study, I suspect...
Yes, this is included in the PRISMA diagram and also on page 10 of the results section, paragraph 3.

23. MINOR COMMENT
Yet another useful observation. Would you envisage this being a simple descriptive summary of the number of participants in the eligible trials?
Yes, we have edited the sentence to reflect this “They should consider the amount of missing data from their meta-analysis (i.e. the percentage of the sample sizes of the studies that were included compared to those that would have been eligible to be included in the meta-analysis but no outcome data reported) and this information should be included along with the pooled effect estimate.”

Useful comment, but a nod to "how" might be useful?
This sentence has been edited and a reference added “If appropriate, a sensitivity analysis should be applied to assess the robustness of the conclusions of the review, such as the Copas bound for maximum bias (Copas et al, 2004; William and Gamble 2007, Dwan et al 2010) or a model based correction (Copas et al, 2013).”
24. MINOR COMMENT
One can imagine that a formalised contact process within the Cochrane paradigm would be very useful.

Yes we agree, but it really is dependent on resources and although recommended by Cochrane would be difficult to enforce. No addition has been made here.

25. MINOR COMMENT
This is very sensible advice, but I'm not sure it stems directly from evidence in this article. What part of the analysis indicated that endpoints were not well-defined?
At the end of this paragraph the authors state that this improved definition will aid the assessment of selective reporting - perhaps this should be nearer the start of the paragraph to give immediate context to the recommendation?

The reviewers comment has been taken into account and the suggestion of moving text to the beginning of the paragraph has been followed. It now does not read as though it involves evidence from this article.

26. MINOR COMMENT
Repetition...
See page 8, lines 36-41
This has been edited slightly, as it is an important point to make and the different ways in measuring lung function were not fully described in the methods as this was only an example. The discussion is trying to enforce the scope for selective reporting due to the numerous ways that some outcomes can be measured and analysed and reported.
27. MINOR COMMENT
I agree entirely, but should think about adding some specifics on how this will improve ORB...

The sentence has been extended “A core set of outcomes should be agreed upon for cystic fibrosis which in turn will have a positive impact on systematic reviews as future trials are conducted they should specifically set out to measure and report these outcomes therefore reducing the prevalence of selective reporting.”

VERSION 2 – REVIEW

REVIEWER	Ian Hambleton Professor of Biostatistics, Chronic Disease Research Centre, The University of the West Indies, Jemmott’s Lane, Bridgetown, BARBADOS
REVIEW RETURNED	20-Apr-2013

THE STUDY	One (very small) suggestion. The title is now:

	"Selective reporting of outcomes in randomised controlled trials in systematic reviews of Cystic Fibrosis" I wonder if it sounds better to say: "Selective reporting of randomised controlled trial outcomes in systematic reviews of Cystic Fibrosis"
GENERAL COMMENTS	The authors have gone to great effort to accommodate the (many!) comments of both reviewers. Most of my comments have been addressed, and where changes were not made the authors have been diligent in responding with a considered rebuttal. I'm grateful that on occasion the authors were also able to point out my errors of interpretation - making this a good learning experience for me! This article is ready for publication, I would say.