PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Bias in dissemination of clinical research findings – structured OPEN framework of what, who, and why based on literature review and expert consensus
AUTHORS	Bassler, Dirk; Mueller, Katharina; Briel, Matthias; Kleijnen, Jos; Marusic, Ana; Wager, Elizabeth; Antes, Gerd; von Elm, Erik; Altman, Doug; Meerpohl, Joerg

VERSION 1 - REVIEW

REVIEWER	Matthew J Page Monash University, Australia University of Bristol, UK
REVIEW RETURNED	27-Oct-2015

GENERAL COMMENTS	The authors have presented a very interesting and useful framework on bias in dissemination of clinical research findings. They have addressed all reviewer comments on the previously submitted manuscript. I only have a few minor comments. The “Strengths and limitations of this study” box could be improved. It’s not really clear why the first two dot points are strengths. Also, you could be a bit more explicit about why the focus on highly cited and publicly available articles on publication bias is limited. In Figure 1, I was unsure what the first category, “Selective publication” refers to, and how it differs to the remaining categories. Is it more appropriate to label this category as “Selective publication (not specified)”? In Table 2 and 3, I am not sure what you mean by “Decision making bodies”. Can you please provide a footnote to explain this, and list some examples? On page 13, I suggest removing lines 31-32 (i.e. no need to refer to the limited nature of the scoping review as this is adequately discussed in the fourth paragraph of the discussion).

REVIEWER	Andreas Lundh The Nordic Cochrane Centre Rigshospitalet Denmark
REVIEW RETURNED	18-Nov-2015

GENERAL COMMENTS	General comments I have previously reviewed two version of the manuscript for BMJ (reviewer #1). The current version is a revision based on the comments for the first version, but not the second. At least based on

	the point-by-point response the authors do not address my comments for the second version of the manuscript, though these comments are submitted along with the manuscript. Generally I feel that the manuscript has improved considerably. However, I still feel that a major limitation is problems related to the literature search. For example, primarily using search term publication bias, a strategy of must cited papers will favour older papers, many papers identified are systematic reviews of primary research (not methodological papers) etc. The authors have argued their case and addressed some of my concerns in limitations. However, since this is not the main focus of the manuscript I find it acceptable as an alternative would be to redo the whole study which would by too drastic for this type of study. In addition to this comment I only have minor comments written below which are somewhat similar to my comments to the second version of the manuscript (which the authors have not responded to). Major compulsory revision None Minor compulsory revision p5 para 7 line 3 The terms selective dissemination and dissemination bias are used here and throughout the manuscript. However, non-dissemination of research findings may not necessarily be biased (i.e. leading to systematic error). For example, a journal publication may report on all pre-specified outcomes and timepoints, but raw data may still be important for other researchers and research questions. This dissemination is not biased or selective, but a result of the current publication system. It seems that the manuscript somehow deals with both biased dissemination and unbiased non-dissemination, though based on the title the focus of the paper seems to be restricted to dissemination bias. It should be clearer what focus the paper has. Table 2 and Table 3 While Table 1 deals with dissemination of data outside the conventional publication system, Table 2 seems restricted to journal publication of protocols and papers only. Other sources of dissemination in relation to the players should also be addressed, for example, publishing the protocol on an institution website, making raw data available in a public depository etc. The same seems to go for Table 3. For example, researchers may have various motives for not making raw data available to everyone (want to benefit from the data themselves, do not want data to be scrutinised by others, do not have time or resources do make data available etc). I think it is important that these issues in relation to dissemination are also addressed for it to be consistent. Discretionary revision p4 para 1 line 1 I suggest deleting “high quality”. First, systematic reviews of all trials, not only high quality trials, are necessary. Second, risk of bias is now preferred over methodological quality. Table 1 Column ‘type of data’ Complete summary (analysed) data is in my mind not synonymous with raw data. Raw data or primary data is unprocessed and unanalysed data.

	Column ‘Format / Product’ I am unsure what is meant by ‘Scientific abstract published in a journal’. Is this the abstract for an original article in a journal or a conference abstract? For the former I would regard this as part of the journal publication and covered by ‘Full article published in a journal’. For the latter I do not see a great difference between a conference abstract published in a supplement issue of a journal or a conference abstract available from a conference book on a website. ‘Grey literature’ should therefore cover it. Column ‘Format / Product’ Under ‘Grey literature’ the ‘submission to regulatory authorities’ should be covered by ‘Clinical study report, study protocol and statistical analysis plan’ which is what is usually submitted. However, summary of this information (e.g. FDA’s medical and statistical reviews and EMA’s public assessment reports) are also important sources of grey literature. Could be called ‘regulatory drug trial reports’ (see Schroll J et al. J Clin Epidemiol 2015). Column ‘Format / Product’ Under ‘Grey literature’ database/statistical’ file is mentioned with the note ‘analysed outcome data’. But a database/statistical file is usually similar to raw data (i.e. unprocessed) and may contain other information than outcome data (e.g. baseline data) (please see previous comment). Table 2 Regulatory agencies (i.e. drug agencies) might also influence protocol design and analysis. For example, FDA or EMA may require specific efficacy and safety outcomes are included for granting approval. Similarly agencies might require specific analyses to be undertaken, e.g. in HIV drug trials FDA require a FDA snapshot analysis of viral load at week 48. I am unsure what role ‘research ethics committees’ have in ‘submitting the study protocol for journal publication’. Why do peer reviewers not have a role in publication of protocols and scientific papers? While it is ultimately the editors decision then peer reviewers have a considerable indirect influence (at least we like to think so). ‘Publication’ could be called ‘Publishing journal research paper’ similar to ‘publishing the study protocol’. Table 3 For ‘Publish or perish’ the text does not describe why this would lead to bias. According to reference 15 “Papers are less likely to be published and to be cited if they report “negative” results”. Also under ‘Journal editors’ it seems, that journals are favouring positive results. This is highly debated and research seems to indicate that the dissemination bias happens before submission to journals (Song F BMC Med Res Methodol 2009). ‘Winner takes it all’ line 5, I suggest using ‘authors’ instead of ‘investigators’ for consistency. Similar to ‘Intellectual interest’ the authors should consider addressing ‘professional interest’. For example, a study showing that no surgery is better than surgery or that a particular class of drugs used for many years within a medical specialty is in fact harmful may be particularly damaging to the reputation and financial interests of a profession. In my mind this is something different than intellectual interest. Under ‘research ethics committees’ I am unsure how this will lead to dissemination bias. The authors should please describe in the manuscript what is meant by decision making bodies. According to the authors’ previous response these are “Decision-making bodies’ are institutions with

	coverage of decision-making authority in health care systems". This should preferably be explained in the manuscript, for example via a footnote. Language: Acceptable. Stat review: Does not need to be reviewed by a statistician. Conflicts of interest: I have no conflicts of interest.

VERSION 1 – AUTHOR RESPONSE

Reviewer I

1) The authors have presented a very interesting and useful framework on bias in dissemination of clinical research findings. They have addressed all reviewer comments on the previously submitted manuscript. I only have a few minor comments.

We thank the reviewer for considering our manuscript interesting and useful.

2) The "Strengths and limitations of this study" box could be improved. It's not really clear why the first two dot points are strengths. Also, you could be a bit more explicit about why the focus on highly cited and publicly available articles on publication bias is limited.

We improved the 'strenghts and limitations of this study' box, which now reads as follows:

• We present a new comprehensive framework based on results from literature review and international expert consensus on (non-) dissemination of research results.
• Our three step approach considers for the first time issues that need to be taken into account when disseminating research findings (What?), different players who should assume responsibility (Who?), and motivations that might lead to selective dissemination of research findings (Why?).
• We only searched Web of Science with the simple search term 'publication bias'. This way, our literature search might have favoured older publications and systematic reviews of primary research.

3) In Figure 1, I was unsure what the first category, "Selective publication" refers to, and how it differs to the remaining categories. Is it more appropriate to label this category as "Selective publication (not specified)"?

We thank the reviewer for this specification and changed this label as suggested.

4) In Table 2 and 3, I am not sure what you mean by "Decision making bodies". Can you please provide a footnote to explain this, and list some examples?

We thank the reviewer for this comment. In tables 2 and 3 we refer to 'decision-making bodies', when talking about decision-making authorities in health care systems, i.e. legal entities that define details of statutory regulations, such as the Federal Joint Committee (FJC) in Germany. We added a footnote for further explanation, which reads as follows:

1) decision-making authorities in health care systems (for example legal entities, such as the Federal Joint Committee in Germany)

5) On page 13, I suggest removing lines 31-32 (i.e. no need to refer to the limited nature of the scoping review as this is adequately discussed in the fourth paragraph of the discussion).

We agree with the reviewer that lines 31-32 on page 13 are redundant, since we address the limitation of our literature review later on. Therefore, we removed these lines as suggested.

Reviewer II

General comments

1) I have previously reviewed two version of the manuscript for BMJ (reviewer #1). The current version is a revision based on the comments for the first version, but not the second. At least based on the point-by-point response the authors do not address my comments for the second version of the manuscript, though these comments are submitted along with the manuscript.

Generally I feel that the manuscript has improved considerably. However, I still feel that a major limitation is problems related to the literature search. For example, primarily using search term publication bias, a strategy of must cited papers will favour older papers, many papers identified are systematic reviews of primary research (not methodological papers) etc. The authors have argued their case and addressed some of my concerns in limitations. However, since this is not the main focus of the manuscript I find it acceptable as an alternative would be to redo the whole study which would be too drastic for this type of study. In addition to this comment I only have minor comments written below which are somewhat similar to my comments to the second version of the manuscript (which the authors have not responded to).

We thank the reviewer for considering our manuscript considerably improved. We deliberately did not address the comments on the second version since it had a different focus and format than the first version of our manuscript. Nevertheless, we attached this review because we were asked for by the Editors of BMJOpen. We followed their reasonable suggestion to address the comments related to our initial submission to the BMJ, which has a focus and format comparable to the version submitted to BMJ OPEN.

We appreciate the reviewer's concerns about our literature search. As explained before the scope of our literature research was to create a review of the most popular definitions of 'publication bias' and we did not aim to create a comprehensive systematic review. However, we take the limitations of our literature search seriously and have stated them upfront in the revised 'strengths and limitations study box' (please see our reply to comment #2 from the first reviewer) and also specifically address them now in the Discussion section of the manuscript:

We conducted only a very limited literature search and included only 50 articles, since we were interested in the most prevalent definitions of 'publication bias' only. Since we only searched Web of Science with the simple search term 'publication bias', our literature search might have favoured older publications and systematic reviews of primary research and might have missed methodological publications. A more comprehensive literature search might have concluded in a wider range of definitions. Also, the representativeness of these articles might be limited since all of the included articles have been published in English, therefore also language bias might play a role.

We further agree with the reviewer that the focus of our manuscript is clearly on the development of the new framework and not on the scoping review.

Minor compulsory revision

1) p5 para 7 line 3 The terms selective dissemination and dissemination bias are used here and throughout the manuscript. However, non-dissemination of research findings may not necessarily be biased (i.e. leading to systematic error). For example, a journal publication may report on all pre-specified outcomes and timepoints, but raw data may still be important for other researchers and research questions. This dissemination is not biased or selective, but a result of the current publication system. It seems that the manuscript somehow deals with both biased dissemination and unbiased non-dissemination, though based on the title the focus of the paper seems to be restricted to dissemination bias. It should be clearer what focus the paper has.

We agree with the reviewer that non-dissemination of research findings may not necessarily be biased but want to add that it bears a high risk of introducing bias. In order to address the concern of the reviewer, we added a sentence clarifying this issue in the Introduction section of the manuscript

It has long been recognized that the identification of the entire relevant research evidence is essential to produce an unbiased and balanced summary, although non-dissemination of research findings may not necessarily lead to bias. For example, a journal publication may report on all pre-specified outcomes and time-points, but raw data may still be important for other researchers and research questions. This dissemination is not biased or selective, but a result of the current publication system. Nevertheless, ideally all research conducted should be published and easily identifiable.

Since we consider the risk of introducing bias by non-publication as dominant, we reflect this in the objective and in the primary outcome of our study (Objective: The aim of this study is to review highly cited articles that focus on non-publication of studies and to develop a consistent and comprehensive approach to defining (non-) dissemination of research findings. Primary outcome: We propose a new approach to the comprehensive conceptualization of (non-) dissemination of research) and believe that the focus of our paper is clear.)

2) Table 2 and Table 3 While Table 1 deals with dissemination of data outside the conventional publication system, Table 2 seems restricted to journal publication of protocols and papers only. Other sources of dissemination in relation to the players should also be addressed, for example, publishing the protocol on an institution website, making raw data available in a public depository etc. The same seems to go for Table 3. For example, researchers may have various motives for not making raw data available to everyone (want to benefit from the data themselves, do not want data to be scrutinised by others, do not have time or resources do make data available etc). I think it is important that these issues in relation to dissemination are also addressed for it to be consistent.

As we state in the our manuscript in the Results section under the heading ‘OPEN framework of (non-) dissemination of research findings’, table 2 has a more specific approach and lists the ‘stakeholders who could assume responsibility for the various stages of conducting a clinical trial and disseminating clinical trial documents’, while table 1 has a more general approach and lists ‘issues that need to be considered when exploring possible biases due to selective dissemination of research findings’. This might explain the different perceptions of the tables, because their respective focus is slightly different.
We appreciate the additional suggestions for table 3 on motivations of researchers that might lead to biased dissemination of research. We included these suggestions in table 3 under the heading ‘Miscellaneous’:

Miscellaneous
Researchers might decide not to share their data, as they want to benefit from the data themselves, or do not want data to be scrutinised by others, or do not have time or resources to make data available.

Discretionary revision

1) p4 para 1 line 1 I suggest deleting “high quality”. First, systematic reviews of all trials, not only high quality trials, are necessary. Second, risk of bias is now preferred over methodological quality.

We understand the reviewer’s concern and, therefore, deleted ‘high quality’ as suggested.

2) Table 1
Column ‘type of data’ Complete summary (analysed) data is in my mind not synonymous with raw data. Raw data or primary data is unprocessed and unanalysed data.

We agree with the reviewer that raw data is unprocessed and unanalysed data and refer to it as ‘individual data’ in table 1.

Column ‘Format / Product’ I am unsure what is meant by ‘Scientific abstract published in a journal’. Is this the abstract for an original article in a journal or a conference abstract? For the former I would regard this as part of the journal publication and covered by ‘Full article published in a journal’. For the latter I do not see a great difference between a conference abstract published in a supplement issue of a journal or a conference abstract available from a conference book on a website. ‘Grey literature’ should therefore cover it.

We thank the reviewer for this attentive comment. With the label ‘Scientific abstract published in a journal’ we referred to the abstract of an original article. We listed it separately as sometimes only the abstract but not the whole original article is freely accessible. However, this might be hairsplitting and we therefore decided to remove ‘scientific abstract published in a journal’ from table 1.

Column ‘Format / Product’ Under ‘Grey literature’ the ‘submission to regulatory authorities’ should be covered by ‘Clinical study report, study protocol and statistical analysis plan’ which is what is usually submitted. However, summary of this information (e.g. FDA’s medical and statistical reviews and EMA’s public assessment reports) are also important sources of grey literature. Could be called ‘regulatory drug trial reports’ (see Schroll J et al. J Clin Epidemiol 2015).

We thank the reviewer for this comment. We agree that summary information of evaluation agencies of medical products, such as FDA and EMA are important sources of grey literature. For this reason we initially listed them in the column ‘format/product’ as ‘regulatory documents’. However, we are happy to add them as ‘regulatory trial reports’ to the ‘grey literature’ list, as suggested by the reviewer.

Column ‘Format / Product’ Under ‘Grey literature’ database/statistical’ file is mentioned with the note ‘analysed outcome data’. But a database/statistical file is usually similar to raw data (i.e. unprocessed) and may contain other information than outcome data (e.g. baseline data) (please see previous comment).

We thank the reviewer for this thoughtful comment. We agree that a database/statistical file might contain raw data as well as analyzed outcome data. Therefore, we added the footnote 1) referring to ‘all raw data’.

3) Table 2 Regulatory agencies (i.e. drug agencies) might also influence protocol design and analysis. For example, FDA or EMA may require specific efficacy and safety outcomes are included for granting approval. Similarly agencies might require specific analyses to be undertaken, e.g. in HIV drug trials FDA require a FDA snapshot analysis of viral load at week 48.

We thank the reviewer for this comment and agree that regulatory agencies might play a role in the protocol design and analysis. Therefore, we now ticked the appropriate boxes of table 2 in the revised manuscript.

I am unsure what role 'research ethics committees' have in 'submitting the study protocol for journal publication'.

Part of the OPEN project (To Overcome failure to Publish nEgative fiNdings) focused on the role of research ethics committees in the dissemination process. The results suggested that ethics committees sometimes require a publication of the study protocol in order to make the process more transparent when granting their approval for the study. Therefore, we ticked 'research ethics committees' in the row 'submitting the study protocol for jounal publication' in table 2.

Why do peer reviewers not have a role in publication of protocols and scientific papers? While it is ultimately the editors decision then peer reviewers have a considerable indirect influence (at least we like to think so).

We thank the reviewer for this comment and agree that peer reviewers play an important role in the publication process even if the final decision is made by the editors. Therefore, we decided to tick the appropriate boxes in table 2 in the revised manuscript.

'Publication' could be called 'Publishing journal research paper' similar to 'publishing the study protocol'.

We changed the label in the table since we agree with the reviewer that the suggested terminology is more consistent.

4) Table 3 For 'Publish or perish' the text does not describe why this would lead to bias. According to reference 15 "Papers are less likely to be published and to be cited if they report "negative" results". Also under 'Journal editors' it seems, that journals are favouring positive results. This is highly debated and research seems to indicate that the dissemination bias happens before submission to journals (Song F BMC Med Res Methodol 2009).

We thank the reviewer for this attentive comment and agree that more clarification is needed. Dissemination bias does not exclusively happen before submission to journals. According to published literature, it also happens after the submission based on the research results. To clarify, why in this context, the 'publish or perish' attitude might lead to bias, we added the following explanation.

Therefore, researchers might be pushed to preferably submit manuscripts with positive results, as they are more likely to be published.

5) 'Winner takes it all' line 5, I suggest using 'authors' instead of 'investigators' for consistency.

We thank the reviewer for this attentive comment and exchanged the term 'investigators' by 'authors'. The text now reads as follows:

On the other hand, authors have no interest in 'wasting their time' in preparing manuscripts with results they consider not sufficiently interesting to achieve publication.

6) Similar to 'Intellectual interest' the authors should consider addressing 'professional interest'. For example, a study showing that no surgery is better than surgery or that a particular class of drugs

used for many years within a medical specialty is in fact harmful may be particularly damaging to the reputation and financial interests of a profession. In my mind this is something different than intellectual interest.

We thank the reviewer for this suggestion and are very happy to include it in table 3. It now reads as follows:

Researchers might be pushed to preferably publish results which support current practice in their respective medical specialty as conflicting results might be damaging to the reputation and financial interest of their profession.

Under ‘research ethics committees’ I am unsure how this will lead to dissemination bias.

For research ethics committees we listed two possible motivations which might lead to dissemination bias. Both of them refer to the limited possibilities of ethics committees to fight dissemination bias.
A possible idea to limit dissemination bias for ethics committees would be to grant approval only if previous studies by the submitting authors have been published. In order to check this they would need sufficient financial and personal resources which they often lack.
Alternatively, they could ask for a trial to be registered in a trial registry before granting approval. However, the legal basis for such an approach is insufficient.
According to the results of the OPEN-project, research ethics committees could be a valuable tool to limit dissemination bias but currently they often lack the financial resources or the legal requirements to do so.

7) The authors should please describe in the manuscript what is meant by decision making bodies. According to the authors’ previous response these are “Decision-making bodies’ are institutions with coverage of decision-making authority in health care systems”. This should preferably be explained in the manuscript, for example via a footnote.

We agree with the reviewer that the term ‘decision making bodies‘ needs further explication. Please see our reply answer to comment #4 by reviewer I.

VERSION 2 – REVIEW

REVIEWER	Matthew J Page Monash University, Australia, and University of Bristol, United Kingdom
REVIEW RETURNED	08-Dec-2015

GENERAL COMMENTS	Thank you for addressing all comments. The manuscript is now acceptable for publication

REVIEWER	Andreas Lundh The Nordic Cochrane Centre
REVIEW RETURNED	27-Dec-2015

GENERAL COMMENTS	The authors have dealt with my previous comments in their response. I have no additional comments. I therefore recommend the paper for publication.