PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Characteristics of funding of clinical trials: cross-sectional survey and proposed guidance
AUTHORS	Hakoum, Maram; Jouni, Nahla; Abou-Jaoude, Eliane; Hasbani, Divina; Abou-Jaoude, Elias; Lopes, Luciane; Khaldieh, Mariam; Hammoud, Mira; Al-Gibbawi, Mounir; Anouti, Sirine; Guyatt, Gordon; Akl, Elie

VERSION 1 - REVIEW

REVIEWER	Decullier, Evelyne Hospices Civils de LYOn, FRANCE
REVIEW RETURNED	10-Feb-2017

GENERAL COMMENTS	Although the objectives were promizing, the paper turned out to be too ambitious with too many subjects explored. We do not really know if it's review (as could be thought with table 1), a study (as suggested by table 3, 4, 5 and the 2 tables from appendices) or a methodological study with recommandations (with table 2 and appendix 3). Finally, I finished the paper without keeping in mind a simple, clear message. My advice to authors would be to simplify the paper (7 tables is far too much) and maybe to focus on only one aspect. Comments Page 6: globally, the background section does not help to identify what is the purpose of the study Page 6, 2nd paragraph: I am not sure that this part should be kept, at least it should be in the discussion section Page 8: This kind of table is often used in review article (but in the results section), or it is not supposed to be present in the background section of a study article. Page 12 line 34: please precise what the authors mean by "stepwise approach" Page 12 line 39: Is the citation number 40 really necessary? Page 12 line 47 : mention of a table 2 is troubling, because it seems to be a result, but referred in the method section (again confusion between the different scopes of the article). Page 12 line 53: the people involved in the process should be more described (for example, which status/function?). If this article is supposed to be a recommendation article, the authors should have more focused on the composition of this group, with involvement of lawyers, journal editors for example. Page 14 table 2: the use of a table does not seem necessary for providing definitions. Moreover, the table does not stand alone since we have to search information in other part of the article to understand how the authors found "evidence" that there was support from private-for-profit. I am not sure to really understand this.. it hypothesizes that non-profit organization which receive money from

	for-profit organization (which is very often the case) should be considered as non-independent? Page 15 line 35 : the authors should precise which number was expected (from the flow chart we know that they extracted 350) and why this number was chosen (sample size consideration). Page 15 line 40: 3 reviewers and 2 teams, this mean that one of the reviewer was present in both teams? This might explain why the concordance rate was high. This should be better explained. Not sure that the expression “in duplicate” is adapted. Page 15 line 49: who was the third reviewer? Page 16 line 413: again the authors should explain how 9 authors (odd number) were dispatched in teams of 2 people. Did all the teams reviewed all the references? This should be added Page 16 line 27: how the authors defined “trialists”? is this supposed to be the number of authors on the publication? Page 16 line 32: maybe the authors should provide here the grading. Page 17 line 11-12: the reliability of the information seems to be low Page 17 line 44: did the authors study the agreement between reviewers or between teams of reviewers? Page 18 line 6: this is again a kind of new objective here Page 18 line 25 : maybe a simple concordance rate should be added to better understand the repartition Table 3: the titles for the 2 last items are misleading (should be “Reporting of conflicts of interest” instead of “paper with autors reporting..” since the first category is “not reported”). Depending of the final objective of the paper, the authors could cross funding and conflict of interest Page 21 line 10: please specify if the subjects are “articles” or “lines of funding” (more than one line of funding per article) Table 4: please explain how the variable “source of funding” was computed for article with more than one line fo funding. Table 5: the denominator is not clear.. how do they author defined that a role was not reported? For example how do they differentiate between an article telling that author A and B were involved in the preparation and an article not defining who was involved in the preparation? Page 27 line 5 I do not understand why this has to be in an appendix, this seem to be the consequence of an article with too many aspects presented. The models are difficult to understand, the causality is not straightforward. Page 28 line 29: the authors should explain why they chose the corresponding author and not the first author? Page 29 discussion: the discussion is a kind of repetition of results, the authors should present a synthesis. No table should be named in a discussion Page 29 line 25: the authors should be very cautious with this interpretation Folw chart: please add year and source at the beginning. Please better explain the difference between the 45 not identified as RCT and the 11 not comparing 2 interventions. Flow chart: the authors state that 3 articles were rejected because exceeding sample size, but there is no mention of any sample size target in the manuscript. How the 3 articles were selected? Randomly, chronically? Page 44: if they are kept, I suggest that the 2 tables are gathered in a single table, with a column for each analysis Appendix 3 to my mind, this document is much too long and much too complex. I am not sure that people will take time to correctly fulfill this document.

	Appendix 3 question 3: the dot is not at the right place Appendix 3 question 4: how authors are supposed to mention a supply of devices? Appendix 3 question 5: what are the authors supposed to write in the column “grant. Is the mention of the total amount mandatory? Not sure that the authors would at full information available. Provision of supplies, absence of answer would suggest “no provision of supplies”? maybe the authors should add a filter Appendix 3 quesstion 6: maybe the authors mean by involvement? Appendix 3: to my mind there is a lot of work before having a template which would be usefull, this would necessitate a full study maybe with analysis of concordance on answers between multiple investigators of a study. Some words and questions are subjects to interpretation and are therefore not reliable To conclude, this article is too long and complex to be easily read. The authors should focus on one direction instead trying to cover simultaneously a literature review, a study of articles and an elaboration of recommandations

REVIEWER	Hector Pardo-Hernandez. Iberoamerican Cochrane Centre, Spain.
REVIEW RETURNED	14-Feb-2017

GENERAL COMMENTS	This is a very well designed and executed project that addresses and important research gap, namely the lack of standardized guidance for reporting funding information of clinical trials. The methodology of the study is sound and the main conclusions are supported by the obtained results. Below I present some comments, questions, and suggestions that should be incorporated to further improve the study. 1. Regarding the categories used to classify the agencies that provide funding, there is a discrepancy between the ones used in the study (Table 2) and the ones included in the proposed Instrument for reporting funding information (Appendix 3) (henceforth “Instrument”). Specifically, why was it decided to include inter-government agencies in the Instrument but not in the study? Additionally, the use of the term “Private” is different in the study and in the proposed Instrument. I believe the way it is reported in the Instrument is more intelligible, but authors should report how this change was decided when the Instrument was developed. 2. Related to the previous comment, how could international agencies not related to governments, such as the specialized agencies of the United Nations, be classified in the proposed Instrument? 3. Under Methods/Design overview and definitions, did authors look for disclosure of provisions of supplies only in the funding statements or did they also look at the methods sections of eligible studies, where these are sometimes declared? 4. How was the review of relevant literature conducted? Was this review limited to the three references provided (5, 36, 38), was it based on the authors’ expertise, or was it conducted using search terms? 5. There are no illustrative examples of the main types of sources of

	funding in Table 2, as mentioned under Methods/Data extracted. This discrepancy should be corrected. In this same section, authors report extracting data on whether the funding statement differentiated source of funding from sponsor. However, there is no matching data in the Results section. 6. Authors should discuss the sample size in the Methods section, even if just to explain that it was a convenience sample. 7. While the authors explain in detail how the proposed Instrument was developed, there is no mention of whether it was pilot-tested or assessed for face validity. If such is the case, this should be noted in the limitations of the study. Additionally, obtaining feedback of larger audience about the advantages and disadvantages of implementing this Instrument could be the object of future research projects. 8. The paper is very well written. To improve readability, I suggest: In the abstract, under objectives, remove "The objectives of this study were". • Also in the abstract, under results add "a" to the sentence "Of 54 funding statements in which the source was (a) not-for-profit…". • In the background, add "that" to the sentence "One study found (that) 86% of trial protocols…". • In Table 1, for Bero 2007, remove "(Table 1)" from the Main findings table (there is no corresponding Table 1 in the manuscript). • Under "Methods/Data abstracted", change the semi-colons with commas. • I would drop the "a" from "a proposed guidance" in the tile of the article.

REVIEWER	Susan Ellenberg Perelman School of Medicine, University of Pennsylvania USA
REVIEW RETURNED	10-Mar-2017

GENERAL COMMENTS	BMJ OPEN – MS 2017-015997 – REVIEW This is an interesting paper that presents important information on how clinical trial funding is reported in journal publications. <u>Specific Comments</u> 1. Background, lines 6-18: I believe that the authors are speculating about the degree to which funders influence reporting. The fact that one study found that 86% of trial protocols reviewed reflected a sponsor's right to disapprove or review manuscripts is not adequate to support the statement that sponsors "often" influence reporting. Allowing a sponsor to review a manuscript is not the same thing as giving it approval rights; a sponsor's review might simply correct factual errors or suggest clarifying wording for the authors' consideration. So, while the statement as written might be true, I would suggest substituting "may" for "often" in the first sentence.

	I note that in my experience with both industry-sponsored and federally-sponsored studies, the industry sponsors have been completely hands off the manuscript preparation process, and have not seen manuscripts prior to submission. In NIH-sponsored studies, on the other hand, program staff are very much involved in reporting of results and often retain approval rights for submission. So I think some statement about the possibility of sponsor influence in government funded trials is warranted, even though that was not the focus of the paper. 2. Methods, line 20: I think there should be a reference for "systematic review methodology." I would expect many readers interested in potential financial influences on data interpretation might not be knowledgeable about the methods of systematic reviews. Also, I'm not sure of the difference between a "survey" and a "methodological survey" in this context. 3. P. 15, Eligibility criteria, line 8: Is there a citation that would list the Core Clinical Journals? I myself do not know what they are. 4. P. 16, Data Abstracted, line 42: how was the risk of bias associated with allocation concealment addressed? Why was this source of bias particularly highlighted—there are many other possible sources of bias. 5. P. 18, lines 13-18: journal policies do change—how old was the information used on journal policies relative to the dates of the publications reviewed? 6. P. 19, Table 3: Industry trials often involve hundreds of sites, so I'm a little surprised to see the median and IQR for the number of trialists. It might be good to include the range in addition to the statistics shown. 7. P. 30, lines 20-27: the finding that industry studies had more explicit reporting on the funder's role is potentially attributed to the higher quality of industry trials; that may be the cause, but it might also be that industry studies tend to appear in higher rank journals (as you note below), and these journals might be more likely to have policies requiring this more explicit reporting. 8. P. 33, Implications for Practice, line 17: I don't understand this sentence—why are authors cautioned to not report funding information?

VERSION 1 – AUTHOR RESPONSE

Reviewer #1
Reviewer Name
Deculleir

Institution and Country
Hospices Civils de LYOn, FRANCE

Please state any competing interests or state ‘None declared’:
none declared

Please leave your comments for the authors below
Although the objectives were promizing, the paper turned out to be too ambitious with too many subjects explored. We do not really know if it’s review (as could be thought with table 1), a study (as suggested by table 3, 4, 5 and the 2 tables from appendices) or a methodological study with recommandations (with table 2 and appendix 3). Finally, I finished the paper without keeping in mind a simple, clear message. My advice to authors would be to simplify the paper (7 tables is far too much) and maybe to focus on only one aspect.

Response: Thank you for the helpful feedback and careful reading of the manuscript. We extensively revised the manuscript and used the Reviewer’s suggestions to improve the quality of the manuscript.

The paper reports a methodological study (now referred to as cross-sectional survey) with proposed guidance and instrument. The literature review is intended to support our background section and identify the gaps in the literature. We chose to present its results in a tabular format. We would like to suggest two ways to address the Reviewer’s concern:
• Move Table 1 summarizing the review to the appendix (we have already done so with this revision)
• Alternatively, and if the Editor prefers, we are willing to split this paper into two: one reporting the cross-sectional survey and another reporting the literature review along with the proposed guidance and instrument.

Comments

Comment 1:
Page 6: globally, the background section does not help to identify what is the purpose of the study.

Response 1: Thank you for raising this issue. We have edited the introduction section, particularly the literature review and the objective to clarify how this study addresses the gaps in the literature, as follows:
Page 6 lines 21-23 and Page 7 lines 1-12
“We conducted a comprehensive review of the literature and found 22 studies that assessed reporting of funding in clinical trials (see Appendix 1). The main gap we identified in this literature is a detailed and current characterisation of funding of a representative sample of trials. Indeed, all of the identified studies focused on trials published in specific clinical areas or journals. Most (14, 64%) reported only on funded trials or did not differentiate between non-funded trials and those that do not report on funding. Seventeen studies (77%) did not always distinguish trials with no funding from those funded by the government or by not-for-profit sources. Moreover, these studies seldom assessed reporting on the role of funder (n=4), provision of supplies (n=2), and the amount of funding (n=0). None of the studies explored the relationship between not-for-profit organizations funding trials and for-profit organizations.

Therefore the main objective of this study was to provide a detailed and current characterisation of funding of a representative sample of clinical trials. We also aimed to develop guidance for standardised reporting of funding information.”

Comment 2:
Page 6, 2nd paragraph: I am not sure that this part should be kept, at least it should be in the

discussion section.

Response 2: Thank you for the suggestion. The aim of having this paragraph in the background section is to highlight the problem of relationship between not-for-profit organizations funding trials and for-profit organizations. This helps us justify why our data collection form addressed that none of the previous studies (according to our literature review) addressed it.

Comment 3:
Page 8: This kind of table is often used in review article (but in the results section), or it is not supposed to be present in the background section of a study article.

Response 3: Thank you. We have moved the table into the appendix (now Appendix 1). As mentioned above, we are willing to split the paper into two: one reporting the cross-sectional survey and another reporting the literature review along with the proposed guidance and instrument. We leave this decision to the Editor.

Comment 4:
Page 12 line 34: please precise what the authors mean by “stepwise approach”.

Response 4: Thank you for pointing this out. We now use ‘following approach’ instead of ‘stepwise approach’. We have also modified the subsequent statements (Page 11 line 22 and Page 12 lines 1, 4) to begin with terms such as ‘First’, ‘Second’, and ‘Finally’ to indicate the approach we had followed.

Comment 5:
Page 12 line 39: Is the citation number 40 really necessary?

Response 5: Thank you for the question. The article (http://www.bmj.com/content/344/bmj.e2809.full) was cited as it includes a simple classification of funding sources, as reported in Table 1 of that article. In any case, we have removed that citation given we already cite another paper.

Comment 6:
Page 12 line 47: mention of a table 2 is troubling, because it seems to be a result, but referred in the method section (again confusion between the different scopes of the article).

Response 6: Thank you. The table was intended to provide the classification of the types of funding sources that we used in our data extraction and did not report any results. We have now moved Table 2 to an Appendix (#2) and listed the types of funding sources under ‘Data extracted’ section as follows:
Page 10 lines 7-12
“•The type of source(s) of funding. These included internal funding (when it is an academic or hospital affiliation) and external funding, categorized into: government; private-for-profit; private not-for-profit with evidence of support by private-for-profit that is a health industry; private not-for-profit with evidence of support by private-for-profit that is not a health industry; and private not-for-profit with no evidence of support by private-for-profit.”

Comment 7:
Page 12 line 53: the people involved in the process should be more described (for example, which

status/function?). If this article is supposed to be a recommendation article, the authors should have more focused on the composition of this group, with involvement of lawyers, journal editors for example.

Response 7: Thank you for the helpful suggestion. We have added the following description:
Page 12 lines 7-14
"The process included both in-person and email discussions among the authors of this article and feedback from external experts. The individuals involved have the following profiles: author EAA is a clinical epidemiologist and was an associate journal editor for Health and Quality of Life Outcomes journal; author GG is a clinical epidemiologist and has been a member of editorial boards of 8 journals. The external experts we consulted include Dr. Elie Al-Chaer (health researcher with a law degree and editor-in-chief of International Journal of Women's Health and Dove Press), Dr. Joerg Meerpohl (associate editor of Health and Quality of Life Outcomes journal), and Dr. Peter Tugwell (co-editor of the Journal of Clinical Epidemiology)."

Comment 8:
Page 14 table 2: the use of a table does not seem necessary for providing definitions. Moreover, the table does not stand alone since we have to search information in other part of the article to understand how the authors found "evidence" that there was support from private-for-profit. I am not sure to really understand this.. it hypothesizes that non-profit organization which receive money from for-profit organization (which is very often the case) should be considered as non-independent?

Response 8: Following the reviewer's suggestions, we have moved Table 2 to an Appendix (# 2) (please see response to Comment 6). In the 'Data extracted' part of the methods section, we report on the process for identifying whether a not-for-profit organization receives support from a for-profit organization as follows:
Page 10 lines 12-15
"As needed, we performed an online search to accurately assign the type of the funding source. When a funding source was identified as a not-for-profit organisation, we searched the organisation's website for any information on partnership with or support from a for-profit entity (see appendix 4 for details)."

To our knowledge, no study has previously classified not-for-profit funding sources into three types:
1- Supported by private-for-profit that is a health industry
2- Supported by private-for-profit that is not a health industry
3- No evidence of support by private-for-profit

While we believe that the issue of a non-profit organization receiving money from a for-profit organization) should be explored, at no point we state that such organizations should be considered as non-independent.

Comment 9:
Page 15 line 35: the authors should precise which number was expected (from the flow chart we know that they extracted 350) and why this number was chosen (sample size consideration).

Response 9: Thank you for the question. Our target number of papers was 200 RCTs based on the sample size calculation that we had clarified in the 'Data analysis' part of the methods section as follows:
"Our sample size allows for a narrow 95% confidence interval (+/- 5%) around proportions of studies reporting sources of funding."

To obtain a sample of 200 RCTs, we screened a sample of 450 RCTs randomly drawn from the total set of 3778 RCTs identified by our search until we reached a total of 200 eligible RCTs. We now place the sample size calculation statement in the 'Selection process' part of the methods section, and preceded the statement with the following:
Page 8 lines 14-15
"We followed the order of the randomization list to screen citations until we obtained 200 eligible RCTs."

Comment 10:
Page 15 line 40: 3 reviewers and 2 teams, this mean that one of the reviewer was present in both teams? This might explain why the concordance rate was high. This should be better explained. Not sure that the expression "in duplicate" is adapted.

Response 10: The reviewer is correct in that one author served as the reviewer on both teams. In fact, that person was the most experienced member of the team. Our aim was to ensure higher reliability (i.e., concordance). As a result, each citation was screened in duplicate, hence our use of the term. Additional reasons for high rate of reliability include the use of explicit eligibility criteria, the use of a standardized and pilot tested screening form, and all reviewers undergoing calibration exercises.

We now clarify this in the text as follows:
Page 8 lines 18-19
"Following calibration exercises, three reviewers (MBH, NJ, MK) worked in teams of two (MBH was the reviewer on both) to screen titles and abstracts in duplicate and independently."

Comment 11:
Page 15 line 49: who was the third reviewer?

Response 11: Thank you for the question. The third reviewer is the senior author on this paper (Elie Akl). We now clarify this in the text as follows:
Page 9 lines 1, 10-11
"…, or with the help of a third reviewer (EAA) as needed"

Comment 12:
Page 16 line 413: again the authors should explain how 9 authors (odd number) were dispatched in teams of 2 people. Did all the teams reviewed all the references? This should be added.

Response 12: One of the authors (the most experienced in this topic) served as the first reviewer on all 8 teams (i.e., the second reviewers consisted of 8 other reviewers). This ensured that each of the 200 RCTs were extracted by a team of two that includes the most experienced team members. The process was done in duplicate and independently by dividing the 200 RCTs across the 8 second reviewers. We now clarify this as follows:
Page 9 lines 8-9
"After completing calibration exercises, nine authors divided into teams of two extracted data in duplicate and independently (MBH was a reviewer on each of the eight teams)."

Comment 13:

Page 16 line 27: how the authors defined “trialists”? is this supposed to be the number of authors on the publication?

Response 13: Thank you for pointing this out. To avoid confusion, we replaced the term ‘trialists’ with ‘trial authors’ throughout the manuscript.

Comment 14:
Page 16 line 32: maybe the authors should provide here the grading.

Response 14: Thank you for the helpful suggestion. We now include the grading as follows:
Page 9 lines 17-19
“•Classification of the income level of the country in which the first author’s institution is located (as high, upper-middle, lower-middle, or low income country according to the July 2015 World Bank list of economies);”

Comment 15:
Page 17 line 11-12: the reliability of the information seems to be low.

Response 15: Thank you for the comment. We acknowledge that we have not examined the reliability of our approach to assessing whether a not-for-profit funder is supported by a for-profit one is as such. Unfortunately, we did not identify any other study that have made such assessment. Therefore, we did our best to ensure that our methods are objective and reproducible by following a step-by-step process, including. We have added Appendix 4 to describe the process followed to verify whether a private not-for-profit-organisation was supported by a private-for-profit entity. While one could conduct a formal study to assess the reliability of the approach, that would be out of the scope of this study.

Comment 16:
Page 17 line 44: did the authors study the agreement between reviewers or between teams of reviewers?

Response 16: Thank you for the question. We now clarify this in the ‘Methods’ and ‘Results’ sections as follows:
Page 11 lines 6-7
“We assessed agreement between reviewers of each team for inclusion of RCTs at the full-text screening stage using chance-corrected agreement (kappa statistic).”

Page 12 lines 17-18
“Agreement proved substantial (kappa= 0.78) and near perfect (kappa= 0.86) respectively for each of the two teams at the full-text screening stage.”

Comment 17:
Page 18 line 6: this is again a kind of new objective here.

Response 17: We believe the regression analysis addresses the main objective of providing a “detailed and current characterisation of funding of a representative sample of clinical trials”. We could add it as a separate objective if the Reviewer insists and the Editor prefers so.

Comment 18:
Page 18 line 25: maybe a simple concordance rate should be added to better understand the repartition.

Response 18: Thank you for pointing this out. We now present the results of the agreement coefficient as follows:
Page 12 lines 17-18
“Agreement proved substantial (kappa= 0.78) and near perfect (kappa= 0.86) respectively for each of the two teams at the full-text screening stage.”

Comment 19:
Table 3: the titles for the 2 last items are misleading (should be “Reporting of conflicts of interest” instead of “paper with autors reporting..” since the first category is “not reported”). Depending of the final objective of the paper, the authors could cross funding and conflict of interest.

Response 19: Thank you for bringing this to our attention. We have modified the titles of those last 2 items in Table 3 (now Table 1) as follows:
From “Paper with authors reporting conflicts of interest” to “Reporting of conflicts of interest”
From “Paper included a funding statement” to “Inclusion of a funding statement”

Comment 20:
Page 21 line 10: please specify if the subjects are “articles” or “lines of funding” (more than one line of funding per article).

Response 20: Thank you for helpful suggestion. We now clarify this as follows:
Page 16 lines 3-4
“The median number (IQR) of funding sources for each funded trial was 1 (1-3), with a range of 1 to 12 sources per trial.”

Comment 21:
Table 4: please explain how the variable “source of funding” was computed for article with more than one line fo funding.

Response 21: Thank you for pointing this out. We counted for each source of funding the number of trials that reported on that type. Since a trial may have reported more than one source of funding, the variables listed in Table 4 (now Table 2) are not mutually exclusive. We now clarify this in a footnote in Table 4 (now Table 2) as follows:
“ $ More than one type could apply for trials reporting more than one source of funding.”

Comment 22:
Table 5: the denominator is not clear.. how do they author defined that a role was not reported? For example how do they differentiate between an article telling that author A and B were involved in the preparation and an article not defining who was involved in the preparation?

Response 22: Thank you for the question. The denominator used in the table (now Table 3) is 171 trials that reported being funded (in the title we present this number as an upper case ‘N’). For each role, only one option may apply per trial (‘Involved’, ‘Not involved’, or ‘Not reported’) so the numbers in three columns across a specific row will always add up to 171. To clarify this, we now present the

numbers in each column as a lower case ‘n’. This information is not specific to any author (A vs. B), but to the funder.

We did not define the ‘role of the funder’ for the purpose of this study. Instead, we collected data on ‘Role of the funder’ as reported in the Methods section or funding statement of the article.

Please see the following examples:
• If an article reported that ‘The funder was involved in the design of the study’ we considered that as “involved” in ‘Protocol/design of the study’.
• If an article reported that ‘The funder was not involved in the writing of the manuscript’, we considered that as “not involved” in ‘Preparation of the manuscript’.
• If an article did not mention or report on a specific ‘role of the funder’, we considered that as “not reported” for that respective role.

Comment 23:
Page 27 line 5 I do not understand why this has to be in an appendix, this seem to be the consequence of an article with too many aspects presented. The models are difficult to understand, the causality is not straightforward.

Response 23: Thank you for raising this issue. We now present the results of the regression in Table 4 instead of in the text, and the full details (including tables) of the regression analysis in Appendix 5. We modified the text as follows:
Page 22 lines 2-5
“Reporting being funded was positively associated with two variables (table 4), based on data from all included trials (N=200). Explicit reporting on the role of funder was positively associated with four variables (table 4), based on data from trials reporting being funded (N=171).”

Comment 24:
Page 28 line 29: the authors should explain why they chose the corresponding author and not the first author?

Response 24: We have chosen the corresponding author given his/her role as per the description provided by the British Medical Journal: “The corresponding author takes primary responsibility for communication with the journal during the manuscript submission, peer review, and publication process, and typically ensures that all the journal’s administrative requirements, such as providing details of authorship, ethics committee approval, clinical trial registration documentation, and gathering conflict of interest forms and statements, are properly completed, although these duties may be delegated to one or more coauthors.” (http://www.bmj.com/about-bmj/resources-authors/article-submission/authorship-contributorship).
In addition, the corresponding author is also responsible to address any comments or questions by the readers.

Accordingly, we have added the following to the results section:
Page 25 lines 2-4
“As for the process of reporting funding information, we suggest that the corresponding author plays the role of the guarantor of this information (given his/her primary responsibility of communicating with both the journal and the readers) and take responsibility for:…”

Comment 25:

Page 29 discussion: the discussion is a kind of repetition of results, the authors should present a synthesis. No table should be named in a discussion.

Response 25: The BMJ Open instructions for authors suggest to include the following in the discussion section: “a statement of the principal findings; strengths and weaknesses of the study; strengths and weaknesses in relation to other studies, discussing important differences in results; the meaning of the study: possible explanations and implications for clinicians and policymakers; and unanswered questions and future research” (http://bmjopen.bmj.com/pages/authors/). We dedicate a few paragraphs to synthesize the findings and discuss their implications. We have removed references to tables as suggested.

Comment 26:
Page 29 line 25: the authors should be very cautious with this interpretation.

Response 26: On Page 29 line 25 (now Page 25 line 22) we simply provide a description of the results. We provide our interpretation on Page27 lines 7-16. This is our best interpretation of these findings, and we would be interested to learn how the reviewers would interpret them differently.

Comment 27:
Folw chart: please add year and source at the beginning. Please better explain the difference between the 45 not identified as RCT and the 11 not comparing 2 interventions.

Response 27: Thank you for the helpful suggestion. We now include the year and source in the first cell of the diagram as follows:
“3778 records identified by the search strategy (run on 24/09/2015 in Ovid Medline)”

We apologize for the mistake in the study flow diagram as ‘did not compare at least two therapeutic intervention on humans’ should have been ‘non-clinical interventions’. We have made that correction.

Comment 28:
Flow chart: the authors state that 3 articles were rejected because exceeding sample size, but there is no mention of any sample size target in the manuscript. How the 3 articles were selected? Randomly, chronically?

Response 28: Thank you for the question. We had included a statement on sample size that we now moved from the ‘Data analysis’ to the ‘Selection process’ section and clarify the process as follows:
Page 8 lines 14-16
“We followed the order of the randomization list to screen citations until we obtained 200 eligible RCTs. Our sample size allows for a narrow 95% confidence interval (+/- 5%) around proportions of studies reporting sources of funding.”

We excluded the 3 eligible articles that were the last 3 citations in our randomization list.

Comment 29:
Page 44: if they are kept, I suggest that the 2 tables are gathered in a single table, with a column for each analysis.

Response 29: Thank you for the suggestion. We have merged the tables as suggested and kept them

in the appendix (#5).

Comment 30:
Appendix 3 to my mind, this document is much too long and much too complex. I am not sure that people will take time to correctly fulfill this document.

Response 30: Thank you for pointing this out. We merely propose the developed instrument as a tool for the standardized reporting of funding information (a comparable example is the developed form for reporting on conflicts of interest - http://www.icmje.org/conflicts-of-interest/).

Comment 31:
Appendix 3 question 3: the dot is not at the right place.

Response 31: Sorry, it not clear to us which dot the Reviewer is referring to.

Comment 32:
Appendix 3 question 4: how authors are supposed to mention a supply of devices?

Response 32: Thank you for the question. The appropriate answer would be ‘conduct’. We have now added a clarification to the guidance document as follows:
Box 1, lines 11-12
“When funding relates to provision of supplies, the appropriate answer is ‘conduct’.”

Comment 33:
Appendix 3 question 5: what are the authors supposed to write in the column “grant. Is the mention of the total amount mandatory? Not sure that the authors would at full information available. Provision of supplies, absence of answer would suggest “no provision of supplies”? maybe the authors should add a filter

Response 33: Thank you for the questions. In relation to the column ‘Grant’, we imply the grant identification number when applicable. We have clarified that.

In relation to the value of monetary support (i.e., amount), we are proposing that authors do report this information if available.

The Reviewer is right in relation to the column ‘Provision of supplies’. Authors would be expected to fill these 2 columns only ‘if applicable’; an absence of an answer would indicate no supplies were provided.

Comment 34:
Appendix 3 quesstion 6: maybe the authors mean by involvement?

Response 34: Unfortunately, this question is not clear to us. In case the question is about what is meant by involvement, we kindly refer to the links below on the involvement of funding sources in research studies:
• http://www.spirit-statement.org/sponsor-and-funder/
• http://www.consort-statement.org/checklists/view/32--consort-2010/128-funding

Comment 35:
Appendix 3: to my mind there is a lot of work before having a template which would be usefull, this would necessitate a full study maybe with analysis of concordance on answers between multiple investigators of a study. Some words and questions are subjects to interpretation and are therefore not reliable.

Response 35: Thank you for raising this issue. We agree that such types of tools need to be reliable. We believe that we have ensured content validity of the tool by basing it on a thorough review of the related literature and on the cross-sectional survey we report in this paper. We have also ensured face validity by having journal editors and a lawyer review the tool and make suggestions on it.

Comment 36:
To conclude, this article is too long and complex to be easily read. The authors should focus on one direction instead trying to cover simultaneously a literature review, a study of articles and an elaboration of recommandations.

Response 36: As mentioned above, we are willing to split the paper into two: one reporting the cross-sectional survey and another reporting the literature review along with the proposed guidance and instrument. We leave this decision to the Editor.

Reviewer #2
Reviewer Name
Hector Pardo-Hernandez.

Institution and Country
Iberoamerican Cochrane Centre, Spain.

Please state any competing interests or state ‘None declared’:
None to declare.

Please leave your comments for the authors below
This is a very well designed and executed project that addresses and important research gap, namely the lack of standardized guidance for reporting funding information of clinical trials. The methodology of the study is sound and the main conclusions are supported by the obtained results. Below I present some comments, questions, and suggestions that should be incorporated to further improve the study.

Response: Thank you for the very positive evaluation! We have used the Reviewer’s feedback to improve the quality of our manuscript.

Comments

Comment 1:
1. Regarding the categories used to classify the agencies that provide funding, there is a discrepancy between the ones used in the study (Table 2) and the ones included in the proposed Instrument for reporting funding information (Appendix 3) (henceforth “Instrument”). Specifically, why was it decided

to include inter-government agencies in the Instrument but not in the study? Additionally, the use of the term “Private” is different in the study and in the proposed Instrument. I believe the way it is reported in the Instrument is more intelligible, but authors should report how this change was decided when the Instrument was developed.

Response 1: Thank you for raising this point. Our initial classification was based on previous studies in the literature. We refined the classification through an iterative process of discussion and revisions based on funding statements reported in this sample of RCTs, as well as in a sample of systematic reviews. In one of our ongoing studies, we came across statements that reported funding from inter-governmental agencies. As a result, we refined our classification and added it a as type of funding source.

As for our use of the term “private”, we had omitted it from the instrument for formatting issues. We realize this might be confusing so we have now put it back in the instrument.

Comment 2:
2. Related to the previous comment, how could international agencies not related to governments, such as the specialized agencies of the United Nations, be classified in the proposed Instrument?

Response 2: Thank you for the question. UN-related agencies would be classified under the “inter-governmental” type (taking for example, the UNHCR that is governed by the UN General Assembly).

Comment 3:
3. Under Methods/Design overview and definitions, did authors look for disclosure of provisions of supplies only in the funding statements or did they also look at the methods sections of eligible studies, where these are sometimes declared?

Response 3: Thank you for raising this important issue. We looked at the funding statements, acknowledgement statements, and the methods section. We now clarify this in our methods under ‘Data extracted’ as follows:
Page 10 lines 4-5
“We then focused on trials that included funding information. We extracted the following funding characteristics reported in the paper:”

Page 10 lines 19-22
“•Whether information was reported (across the paper) on supplies in trials on pharmacological or surgical interventions (i.e., drugs, devices, equipment, samples, or placebos) and whether the supplier is a funding source. We looked for that information in the funding statements, acknowledgement statements, and the methods section.”

Comment 4:
4. How was the review of relevant literature conducted? Was this review limited to the three references provided (5, 36, 38), was it based on the authors’ expertise, or was it conducted using search terms?

Response 4: Thank you for the question. We extensively reviewed the literature for studies that assessed reporting of funding in trials. We did not develop a systematic search strategy but used a list of relevant search terms. We identified 22 studies that we summarized (now Appendix 1) and used to support our background section. Of the 22 studies, we refer to three (5, 36, 38) that helped us

develop our classification of types of funding sources.

Comment 5:
5. There are no illustrative examples of the main types of sources of funding in Table 2, as mentioned under Methods/Data extracted. This discrepancy should be corrected. In this same section, authors report extracting data on whether the funding statement differentiated source of funding from sponsor. However, there is no matching data in the Results section.

Response 5: Thank you for the excellent points. We placed the types of funding sources in-text on Page 10 lines 7-12, instead of Table 2 (now Appendix 2), and removed the phrase “along with illustrative examples”.

In relation to results of whether the funding statement differentiated source of funding from sponsor, we report on that in Table 4 row 12 “Paper reported to be sponsored by a source different than the source of funding/support”. To clarify this, we now match this statement to that in the Methods section under ‘Data extracted’ as follows:
Page 10 lines 17-18
“• Whether the paper reported to be sponsored by a source different than the source of funding/support;”

Comment 6:
6. Authors should discuss the sample size in the Methods section, even if just to explain that it was a convenience sample.

Response 6: Thank you for the comment. We provide a sample size justification in the Methods section under ‘Selection process’ as follows:
Page 8 lines 15-16
“Our sample size allows for a narrow 95% confidence interval (+/- 5%) around proportions of studies reporting sources of funding.”

Comment 7:
7. While the authors explain in detail how the proposed Instrument was developed, there is no mention of whether it was pilot-tested or assessed for face validity. If such is the case, this should be noted in the limitations of the study. Additionally, obtaining feedback of larger audience about the advantages and disadvantages of implementing this Instrument could be the object of future research projects.

Response 7: The Reviewer makes an excellent point. As explained above, we believe that we have ensured content validity of the tool by basing it on a thorough review of the related literature and on the cross-sectional survey we report in this paper. We have also ensured face validity by having journal editors and a lawyer review the tool and make suggestions on it. We have added a statement to the limitation section as follows:
Page 28 lines 5-8
“While we did not conduct a formal and extensive validation of the guidance (and instrument), we believe that it has both face and content validity given that we based it on a thorough review of the related literature, on the cross-sectional survey of trials, and we revised it based on feedback from journal editors and a lawyer.”

Also, we have added the following statement to the implication section:

Page 30 lines 20-22
“Finally, our proposed guidance and instrument for the standardised reporting of funding information would benefit from formal and extensive validation.”

Comment 8:
8. The paper is very well written. To improve readability, I suggest:

• In the abstract, under objectives, remove “The objectives of this study were”.
• Also in the abstract, under results add “a” to the sentence “Of 54 funding statements in which the source was (a) not-for-profit…”.
• In the background, add “that” to the sentence “One study found (that) 86% of trial protocols…”.
• In Table 1, for Bero 2007, remove “(Table 1)” from the Main findings table (there is no corresponding Table 1 in the manuscript).
• Under “Methods/Data abstracted”, change the semi-colons with commas.
• I would drop the “a” from “a proposed guidance” in the tile of the article.

Response 8: Thank you for the helpful suggestions. We have applied most changes as suggested by the Reviewer.

In relation to our use of semi-colons, that is because one or more items in our lists contain internal commas (http://writing.wisc.edu/Handbook/Semicolons.html).

Reviewer #3
Reviewer Name
Susan Ellenberg

Institution and Country
Perelman School of Medicine, University of Pennsylvania
USA

Please state any competing interests or state ‘None declared’:
None declared

Please leave your comments for the authors below
Comments are in attached file.

Comments
This is an interesting paper that presents important information on how clinical trial funding is reported in journal publications.

Response: Thank you for the positive evaluation. We appreciate the reviewer’s careful reading of the manuscript. We have used the Reviewer’s suggestions to improve the quality of our manuscript.

Comment 1:
1. Background, lines 6-18: I believe that the authors are speculating about the degree to which funders influence reporting. The fact that one study found that 86% of trial protocols reviewed reflected a sponsor’s right to disapprove or review manuscripts is not adequate to support the statement that sponsors “often” influence reporting. Allowing a sponsor to review a manuscript is not

the same thing as giving it approval rights; a sponsor's review might simply correct factual errors or suggest clarifying wording for the authors' consideration. So, while the statement as written might be true, I would suggest substituting "may" for "often" in the first sentence. I note that in my experience with both industry-sponsored and federally-sponsored studies, the industry sponsors have been completely hands off the manuscript preparation process, and have not seen manuscripts prior to submission. In NIH-sponsored studies, on the other hand, program staff are very much involved in reporting of results and often retain approval rights for submission. So I think some statement about the possibility of sponsor influence in government funded trials is warranted, even though that was not the focus of the paper.

Response 1: Thank you for raising this excellent point. We have now replaced the term "often" with "may" as suggested on Page 6 line 2. We also added the following statement to the Background section:
Page 6 lines 4-5
"This might also apply to other types of funders, for example, government."

Comment 2:
2. Methods, line 20: I think there should be a reference for "systematic review methodology." I would expect many readers interested in potential financial influences on data interpretation might not be knowledgeable about the methods of systematic reviews. Also, I'm not sure of the difference between a "survey" and a "methodological survey" in this context.

Response 2: Thank you for this helpful suggestion. To avoid any confusion, we have omitted the use of 'systematic review methodology' and replaced the term 'methodological survey' by the term 'cross-sectional survey'.

Comment 3:
3. P. 15, Eligibility criteria, line 8: Is there a citation that would list the Core Clinical Journals? I myself do not know what they are.

Response 3: Thank you for raising this issue. We now include the citation as a reference: https://www.nlm.nih.gov/bsd/aim.html on Page 8 line 8.

Comment 4:
4. P. 16, Data Abstracted, line 42: how was the risk of bias associated with allocation concealment addressed? Why was this source of bias particularly highlighted—there are many other possible sources of bias.

Response 4: Thank you for raising this point. We assessed allocation concealment as an indicator of risk of bias; it would have been very burdensome to assess all methodological features that contribute to bias. We used the Cochrane risk of bias tool to assess allocation concealment. We now include this information in the text and provide the appropriate citation to the Cochrane Handbook risk of bias tool.
Page 9 lines 22-23
"• Level of risk of bias associated with allocation concealment (based on the Cochrane Collaboration's tool for assessing risk of bias [43]);"

We realize this might not be the best approach, and we would be happy to take it out if the Editor and/or the Reviewer prefer so.

Comment 5:
5. P. 18, lines 13-18: journal policies do change—how old was the information used on journal policies relative to the dates of the publications reviewed?

Response 5: Thank you for raising this point. Data on journal policies were obtained in mid 2014 whereas our search for clinical trials was done in September 2015. We have clarified this in the text as follows:
Page 11 lines 16-18
"For variables related to journal policy for reporting funding information, we used unpublished data we had collected in mid 2014 for another cross-sectional survey.[44]"

Comment 6:
6. P. 19, Table 3: Industry trials often involve hundreds of sites, so I'm a little surprised to see the median and IQR for the number of trialists. It might be good to include the range in addition to the statistics shown.

Response 6: Thank you for the helpful suggestion. We now include the range related to that variable as a footnote in the table (now Table 1) as follows:
"* The number of trial authors per trial ranged between 1 and 91."

Comment 7:
7. P. 30, lines 20-27: the finding that industry studies had more explicit reporting on the funder's role is potentially attributed to the higher quality of industry trials; that may be the cause, but it might also be that industry studies tend to appear in higher rank journals (as you note below), and these journals might be more likely to have policies requiring this more explicit reporting.

Response 7: The Reviewer makes a very reasonable point. However, we have attempted to identify evidence that journals with higher impact factor are more likely to have policies requiring explicit reporting of funding but were not successful. Our discussion section reads as follows:
Page 28 lines 16-23 and Page 29 lines 2-5
"Explicit reporting on the role of funder was positively associated with trial funding from private-for-profit sources. This may be due to the adherence of the industry to higher standards of reporting. Indeed, several studies found that industry-funded trials had higher quality scores as compared to trials funded by other sources.[24, 50-53]

Both reporting being funded and explicit reporting on the role of funder were associated with higher journal impact factor. This is consistent with our previous findings that better reporting of authors' conflicts of interest is associated with higher journal impact factor for both systematic reviews and trials published in Core Clinical Journals.[46,54]"

Comment 8:
8. P. 33, Implications for Practice, line 17: I don't understand this sentence—why are authors cautioned to not report funding information?

Response 8: Thank you for the question. In our two previous studies assessing reporting of conflicts of interest in clinical systematic reviews and trials (https://www.ncbi.nlm.nih.gov/pubmed/27515760 and https://www.ncbi.nlm.nih.gov/pubmed/28412465), we noticed a trend where authors report on a funding source only to repeat it in the COI statement as a grant received for the conduct of that same

study. In order to avoid “double-counting”, we advise authors to report on funding once in the assigned funding section.
Page 30 lines 8-10
“We suggest that authors do not report funding information (i.e., grants received for the conduct of the study) in both the funding section and the conflict of interest section of the manuscript, but only in the former one.”

VERSION 2 – REVIEW

REVIEWER	Hector Pardo-Hernandez Iberoamerican Cochrane Centre
REVIEW RETURNED	01-Jun-2017

GENERAL COMMENTS	The authors have improved the manuscript based on my initial assessment and that of the other reviewers. My only and final suggestion is to remove the semi-colons from the lists presented under Methods/data extracted.

REVIEWER	Susan Ellenberg Perelman School of Medicine University of Pennsylvania USA
REVIEW RETURNED	22-May-2017

GENERAL COMMENTS	The authors have responded adequately to most of my concerns. I have a couple of remaining issues, which are relatively minor but which I think should be addressed. 1. With respect to the assessment of allocation concealment; I recommend that the authors' explanation of why they limited attention to this specific source of bias be included in the manuscript. They have explained this in their response to my comment, but the addition of a reference to the Cochrane manual does not explain why they looked only at this bias source. 2. With regard to the data in Table 1, the authors now report on number of authors, rather than the number of study sites. I think the number of study sites is more informative about the trial; the number of authors is often substantially less than the number of sites. In particular, some trials have only a single "corporate" author, with the participating sites listed separately, often in supplementary on-line-only material. So I think reporting on the number of authors is not very helpful in understanding how the trial was structured.

VERSION 2 – AUTHOR RESPONSE

Reviewer #1
Reviewer Name
Hector Pardo-Hernandez

Institution and Country
Iberoamerican Cochrane Centre

Please state any competing interests or state ‘None declared’:

None declared

Please leave your comments for the authors below
The authors have improved the manuscript based on my initial assessment and that of the other reviewers. My only and final suggestion is to remove the semi-colons from the lists presented under Methods/data extracted.

Response: Thank you for the suggestion. We have removed the semi-colons as suggested.

Reviewer #2
Reviewer Name
Susan Ellenberg

Institution and Country
Perelman School of Medicine, University of Pennsylvania, USA

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
The authors have responded adequately to most of my concerns. I have a couple of remaining issues, which are relatively minor but which I think should be addressed.

Comments

Comment 1:
1. With respect to the assessment of allocation concealment; I recommend that the authors' explanation of why they limited attention to this specific source of bias be included in the manuscript. They have explained this in their response to my comment, but the addition of a reference to the Cochrane manual does not explain why they looked only at this bias source.

Response 1: Thank you for the suggestion. We now include an explanation in the text as follows:
Page 10 lines 1-3
"•Level of risk of bias associated with allocation concealment, a methodological feature as an indicator of risk of bias (based on the Cochrane Collaboration's tool for assessing risk of bias) [43]);"

Comment 2:
2. With regard to the data in Table 1, the authors now report on number of authors, rather than the number of study sites. I think the number of study sites is more informative about the trial; the number of authors is often substantially less than the number of sites. In particular, some trials have only a single "corporate" author, with the participating sites listed separately, often in supplementary on-line-only material. So I think reporting on the number of authors is not very helpful in understanding how the trial was structured.

Response 2: Thank you for raising this issue. We collected the data related to number of trial sites and included the findings in Table 1. We added the following statement in-text:
Page 13 lines 3-4
"About half the trials (54%) were multi-center, and had two as the median number of sites."

We have also added it to the multivariable regression analyses as an independent variable, and updated our findings accordingly.

VERSION 3 – REVIEW

REVIEWER	Susan Ellenberg University of Pennsylvania USA
REVIEW RETURNED	10-Jul-2017

The reviewer completed the checklist but made no further comments.