Paris, October 28, 2016

Dear Editor,

Please find enclosed our revised manuscript, entitled "Impact of searching clinical trial registries in systematic reviews of pharmaceutical treatments" by Marie Baudard, Amélie Yavchitz, Philippe Ravaud, Elodie Perrodeau and Isabelle Boutron, for publication consideration in the **British Medical Journal.**

Thank you very much for the opportunity to revise our manuscript. We thank the editors and peer reviewers for their thoughtful comments that helped us improve the quality of our manuscript.

We answered all the editors and reviewers' comments and modified the manuscript accordingly.

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Sincerely,

Amélie Yavchitz

Responses to editors and peer reviewers' comments

****Response to the BMJ's manuscript committee ****

1. In addition to showing the change of effect size, it may also be useful to see whether results including RCT trial databases would change the significance or even change the direction of the finding.

We agree that this information is important. We now report in the table 2 and in the text the change of effect size and change of significance and direction of the findings. The inclusion of the RCTs identified by a trial registry search changed the summary effects but did not change the statistical significance or the direction of the results.

We now clarify these results in the text (page 14 lines 19-24).

"The change in summary statistics ranged from 0% to 29% and was greater than 10% for 5 of 14 systematic reviews and greater than 20% for 2. For example, in the meta-analysis with a 29% change in summary effect, the mean difference changed from -0.35 [-0.51; -0.19] to -0.45 [-0.55; -0.36], for a larger effect. However, including the RCTs identified by a trial registry search did not change the statistical significance or the direction of the results."

Furthermore, we added one column in table 2 that described the significance of the change in the summary statistic.

2. Table 2. It is unclear how the specific summary statistic for each SR has been selected, and exactly what summary statistic has been used in each instance. More explanation should be given, and the summary statistics should be named.

Thank you for this comment. We clarified that for each systematic review, we used an algorithm to select one meta-analysis in which at least one RCT with results available could be included.

For this purpose we proceeded as follows:

1. For each systematic review, we recorded all the outcomes of the meta-analysis reported in the systematic review report.

2. For each eligible RCT with results available, we determined whether the RCT could be included in the meta-analyses previously recorded.

3. When RCT(s) could be included in several meta-analyses, we selected only one meta-analysis according to the following order of outcomes analyzed: 1) the primary efficacy outcome of the systematic review, 2) the primary safety outcome, 3) the patient-important outcome such as mortality, quality of life or morbidity outcome. If several of these outcomes could be used to include a new RCT, we selected the first meta-analysis reported. If none of these outcomes could be used to include a new RCT, we selected the first meta-analysis reported.

Overall, for the 14 systematic reviews with new RCTs included in the meta-analysis:

- 6 systematic reviews clearly defined primary and secondary outcome(s). We selected the meta-analysis of the primary efficacy outcome in 2 systematic reviews, the primary safety outcome in 3 and one patient-important outcome reported as a secondary safety outcome. All outcomes were patient important outcomes.

- 8 systematic reviews did not clearly define primary and secondary outcome(s). All the selected outcomes were patient-important outcomes, except one, which was a surrogate marker (HbA1c).

This is now clarified on page 9 line16 to page 10 line 14 and table 2.

Furthermore, we modified table 2 as follows:

- We added one column with a clear description of the selected outcome with clarification whether the outcome was reported as primary, secondary or not clearly reported as such in the systematic review report.
- We added one column that described whether the outcome was a safety or efficacy outcome and the direction of the change in the summary statistic (i.e., decrease or increase efficacy or less or more harm).

- We added one column that described whether the change in the summary statistic was significant or not. Of note, the addition of new RCTs did not change the significance of any systematic review.
- Lines were re-organized by type of outcome safety or efficacy, and we regrouped lines by type of summary statistics.
- We deleted from the table the 27 lines corresponding to systematic reviews for which no RCTs with available data were retrieved. These reviews are now described in appendix 3. Table 2 now focuses on the 14 recalculated meta-analyses.

3. Table 2. Why is systematic review number 15 included in the n=14 're-analysed' SRs ? Additional RCT data do not appear to have been found with results that contribute to a meta-analysis for this SR. Hence it has a weight of 0 and a change in summary statistic of zero. Surely, there are only n=13 systematic reviews which could be re-analysed, not 14?

We apologize; there was an error in Table 2 for systematic review 15. The trial registry search retrieved 1 RCT including 166 participants. The results of this RCT could contribute to the meta-analysis and the weight of the new RCT included was not 0% but 0.2%.

We now modified Table 2 accordingly.

Comments from Reviewers

Reviewer: 1

I have only one major comment. Having looked at the summary effect estimates in Table 2, it is clear that the direction and statistical significance of each summary effect does not appear to have changed for any meta-analysis once the new RCTs are included. This is an important finding, and one that should be emphasised at the end of this section of text in the Results, and also in the Abstract and Discussion. For example, you could state that none of the changes to summary effect estimates led to a qualitative change in the interpretation of the result once the new trials are added. Also, because I think that it might be difficult for some readers to appreciate how big a 29% change in summary effect is, you could report in this section the summary effect estimates before and after inclusion of the new RCTs for the meta-analysis with a 29% change in summary effect (that is, MD -0.35 to MD -0.45). It would even be worth pointing out that in this instance, inclusion of the new RCTs led to a larger (rather than smaller) treatment effect.

We agree that this is an important issue. We modified the abstract, discussion and conclusion as requested.

We added the following sentence: "None of the changes to summary effect estimates led to a qualitative change in the interpretation of the results once the new trials were added." (Abstract page 3, lines 3-5, results page 14 lines 23-25 and discussion: page 15 lines 9-11)

To clarify the understanding of the change in summary statistics, we added an explanation in the results section, page 14 lines 12-25.

"Inclusion of the RCT results in meta-analyses

[…]

The weight of the eligible RCTs included ranged from 0% to 58% and was greater than 10% for 5 of 14 systematic reviews, 20% for 3, and 50% for 1. The change in summary statistics ranged from 0% to 29% and was greater than 10% for 5 of 14 systematic reviews and greater than 20% for 2. For example, in the meta-analysis with a 29% change in summary effect, the mean difference changed from -0.35 [-0.51; -0.19] to -0.45 [-0.55; -0.36], for a larger effect after inclusion of the new RCTs. However, including the RCTs identified by a trial registry search did not change the statistical significance or direction of the results."

The discussion section was modified (page 15 lines 9-11)

"The addition of data from a register mainly adds to the precision of summary estimates, but none of the changes led to a qualitative change in the interpretation of the results once data for the new trials were added."

Other minor comments are as follows:

Abstract

It might help to indicate what you mean by "terminated RCTs" (both in the abstract and main text). From the conclusion it suggests you are advocating that both completed and terminated RCTs identified in trials registries be included in reviews. However, is it possible that some terminated RCTs provide problematic results (e.g. some trials terminated early may yield exaggerated effect estimates)?

We now clarify in the methods section that terminated RCTs were RCTs classified as such in the registry (i.e., clinical studies that stopped recruiting or enrolling participants early and would not start again).

We agree that terminated RCTs that end early for benefit can raise some issues when included in the meta-analysis, although this is the case for both published and unpublished RCTs. We think it is also important to include terminated RCTs identified in trial registries in systematic reviews but to be careful when assessing the risk of bias of these studies when they are stopped early for benefit.

In our sample of 122 RCTs retrieved from trial registries, only 18 were terminated:

- 3 had results available and were included in meta-analyses. None were stopped for benefit, 2 were stopped early because of adverse events and 1 was stopped early because of futility.
- 15 RCTs had no results available and no information on the reason for stopping early.

To avoid any misinterpretation, we also modified the abstract conclusion.

We modified the manuscript as follow:

1) In the abstract: "To evaluate the impact of searching clinical trial registries on including the results of additional randomized controlled trials (RCTs) in systematic reviews (i.e., eligible RCTs not originally included in the systematic review classified as completed or terminated in the registry)." Page 2 lines 2-5.

2) Abstract conclusion: "Trial registries are an important source for identifying additional RCTs." Page 3 lines 6-7.

3) In the methods section: "We screened the retrieved records and identified all eligible RCTs classified as completed (i.e., RCTs that ended normally) or terminated (i.e., RCTs that stopped recruiting or enrolling participants early and would not start again) that were not initially included in the systematic reviews." (page 7 lines 16-19).

4) In the results section: "Among the 122 RCTS, 104 (85%) were classified as completed and 18 (15%) terminated. Among the 18 RCTs classified as terminated, 3 had results available and were included in meta-analyses, 2 were stopped early because of adverse events and 1

was stopped early because of futility. The remaining 15 RCTs had no results available and no information on the reason for stopping early." Page 13 lines 8-13.

Page 7, line 35-40. I think it would be helpful to readers if you define what you mean by "determined whether RCTs with results could be included in at least one meta-analysis". I assume this means that, for continuous outcomes, the mean, standard deviation (or standard error or confidence interval) and sample size was reported? And that you did not attempt to impute missing standard deviations (i.e. when trialists have only entered the mean and sample size in the ClinicalTrials.gov record)?

We agree that this information needs to be clarified. Actually, we proceeded as follows:

For each systematic review, we determined whether the additional RCTs with results available could be included in at least one meta-analysis; that is, the RCT reports included the following:

- For continuous outcomes: sample size, mean and one measure of dispersion (standard deviation, standard error or confidence interval) by group. Standard errors and confidence intervals were converted in standard deviations to perform the meta-analyses. When results were given for separate subgroups, we pooled the results, the pooled sample size being the sum of the subgroup sample sizes, the pooled mean being the weighted mean of the subgroups and the pooled standard deviation combined by using the formulae given in the Cochrane Handbook (part 7.7.3.8, table 7.7.a).
- For binary outcomes: sample size and number of events by group
- For time-to-event outcomes: hazard ratio and 95% confidence interval or median survival times and confidence intervals by group (Cortès, JCE, 2014)

This is now clarified in the manuscript (page 9 lines 22 to page 10 line 7).

Page 10, line 16-23: To increase clarity, it might help to revise this to "We reanalysed the published meta-analysis using the same statistical method (Peto, Mantel-Haenszel, inverse variance), strategies for assessing heterogeneity, analysis model (fixed v random effects), and measure of effect (risk ratio, odds ratio, weighted mean difference) used by the original authors". Also, can you please provide an example of "strategies for assessing heterogeneity"? Do you mean that you used the same estimate of the heterogeneity variance (e.g. DerSimonian-Laird versus Sidik-Jonkman)? Or that you calculated I-squared statistics if the original authors did?

We apologize for this confusion. We now clarify that we reanalysed the published meta-analyses by using the same statistical method (Peto, Mantel-Haenszel, inverse variance), analysis model (fixed vs random effects), and measure of effect (risk ratio, odds ratio, weighted mean difference) used by the original authors. However, for all meta-analyses, we assessed heterogeneity by calculating the I^2 statistic and τ^2 (DerSimonian-Laird estimate).

We modified the methods section to clarify this point. Pages 11, lines 14-18.

"We reanalyzed the published meta-analyses by using the same statistical method (Peto, Mantel-Haenszel, inverse variance), analysis model (fixed v random effects), and measure of effect (risk ratio, odds ratio, weighted mean difference) used by the original authors. For all meta-analyses, we assessed heterogeneity by calculating the I^2 statistic and τ^2 (DerSimonian-Laird estimate).

Table 2: It would be useful to specify in the last column ("Change in summary statistic (%)") whether the percent change was positive or negative (I know readers can determine this be eyeballing the two effect estimates, but it would make it easier to interpret if such information was provided in the final column). Also, perhaps indicate whether each outcome was a benefit or harm outcome.

We agree. To clarify Table 2, we modified it as follows:

- We added one column with a clear description of the selected outcome with clarification as to whether the outcome was reported as primary, secondary or not clearly reported as such in the review's report.
- We added one column that described whether the outcome was a safety or efficacy outcome and the direction of the change in the summary statistic (i.e., decrease or increase efficacy or less or more harm).
- We added one column that described whether the change in the summary statistic was significant or not. Of note, the addition of new RCTs did not change the significance of any systematic review.
- Lines were re-organized by type of outcome safety or efficacy, and we regrouped lines by type of summary statistics.
- We deleted from the table the 27 lines corresponding to systematic reviews for which no RCTs with available data were retrieved. These systematic reviews are now described in appendix 3. Table 2 now focuses on the 14 recalculated meta-analyses.

Reference 24 can be updated to: Page MJ, Shamseer L, Altman DG, et al. Epidemiology and reporting characteristics of systematic reviews of biomedical research: a cross-sectional study. PLoS Medicine 2016;13(5):e1002028. DOI: 10.1371/journal.pmed.1002028.

We updated the reference as requested.

Appendix 3: The formatting in this file is a little odd, making it unclear to read many sections. Can this be edited, please?

We apologize for the unstable format of the appendix, now appendix 4, and we will provide a pdf to have a stable format.

Reviewer: 2

Specific comments:

- **The authors do not comment on the process of searching through trial registries. It would be useful feedback to know whether this is an easy process (which would be encouraging) or if they found it difficult and why (this would be useful in improving and facilitating searching).**

Thank you for this comment; we agree that this is an important issue.

Actually, the clinical trial searches were overall easy and quick to perform. The median [Q1-Q3] number of records to screen by systematic review was 23 [6-150].

Moreover, among the 63 RCTs with results available that were retrieved from the trial registry search, 41 (65%) had their results posted and therefore immediately available.

We modified the discussion to highlight this point, page 17 Lines 20-23: "Finally, searching trial registries in general represented a low burden. The median [Q1-Q3] number of records to screen by systematic review was low (23 [6-150]). The results for 41 of 63 trials were posted at ClinicalTrials.gov and therefore immediately available.

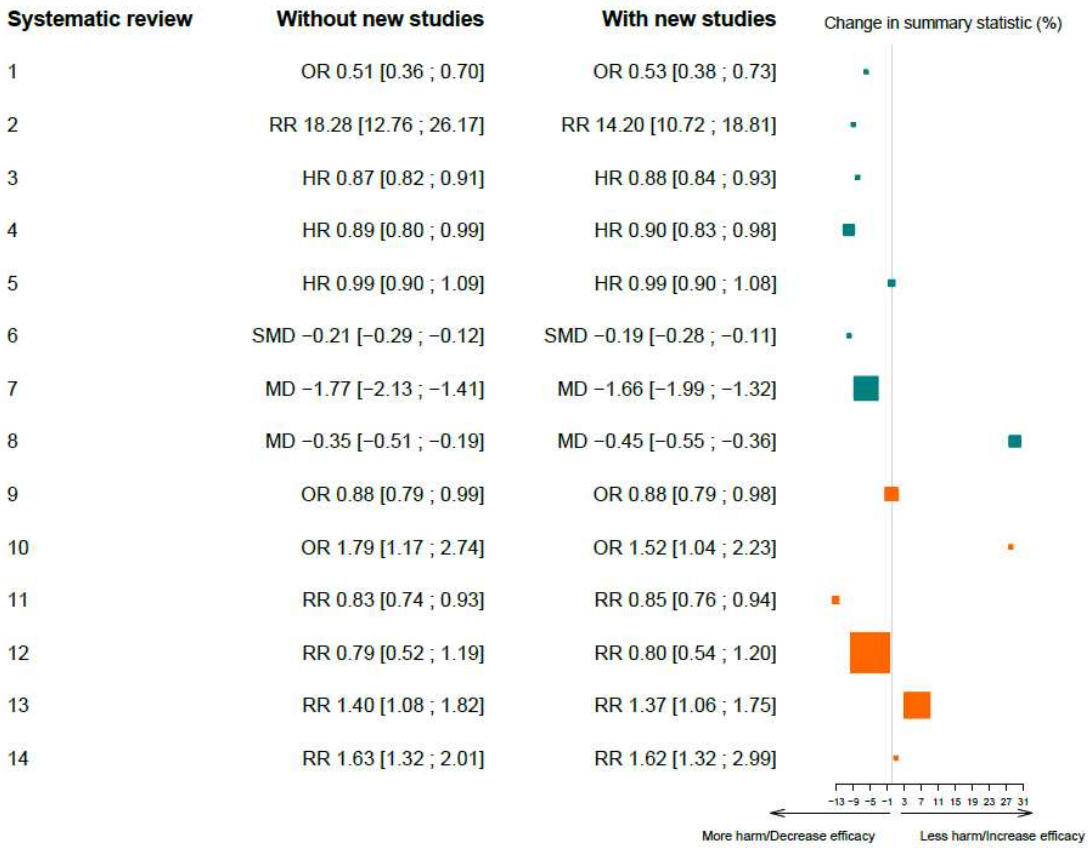
- **Since the authors calculated the effect of including registry data in the meta-analysis results for 14 systematic reviews, it would have been useful to see this change in a forest plot figure along the side the percentage change, since this is one of the best way to visualise results of meta analyses.**

Currently these data are reported in Table 2 and all forest plots are provided in appendix 4 (which was not readable when submitted; please accept our apologies for this)

Such a figure is difficult to create because of the variability in summary statistics (RR, OR, HR, SMD and MD).

We propose the figure below. In the figure, the size of squares is proportional to the weight of the additional data retrieved from the trial registry search. The safety outcomes are in orange and the efficacy outcomes are in green.

We did not add this figure to the manuscript because it is not easy to interpret and we are not sure the figure will be helpful for readers. If it is required, we could add the figure in the article.



- **Page 11, line 9. I would use the word "included" or similar, instead of "selected".**

We modified the manuscript as requested. Page12 line 9;

- **Figure 1. This figure is slightly confusing, since the 95 systematic reviews for which the authors search in the trial registries seem to be excluded, at least visually. While they constitute the reviews on which the analysis is done.**

We agree that the figure is confusing, and we modified it. We now clearly report the two types of systematic reviews, with and without a search of a clinical trial registry reported, and we reported their characteristics below each group.

- **For the trials who did search in the registry, did they include the results in the meta-analyses? I don't think this is clearly stated. The authors only state "The results of the clinical trial registry search was clearly reported (ie, with a description of the number and the identification of RCTs identified from the search) in only 47 (21%) reports (fig 1, table 1)." It should be reported if they searched and found results amenable for inclusion in the meta-analysis and did/did not include them and why.**

We agree that this is an important issue. Actually 47 systematic reviews reported the results of the search of a trial registry: 16 did not retrieve any eligible RCTs, 11 retrieved only on-going

studies, 13 retrieved RCTs but results were not available, and 7 retrieved RCTs with available results (among these 7, 3 included RCTs in at least one meta-analysis).

We now clarify in the results section:

"Among the 223 systematic review reports included, 107 (48%) reported searching at least one clinical trial registry: 48 of these (45%) reported searching only individual registries, 11 (10%) only portals and 44 (41%) a combination of individual registries and portals. The portal and individual register most frequently searched were the WHO ICTRP Search Portal (n=53/107, 50%) and ClinicalTrials.gov (n=89/107, 83%), and for 40 studies (37%), both were searched. In only 47 of the 107 (21%) reports were the results of the clinical trial registry search clearly described (ie, with a description of the number and identification of RCTs found from the search) (fig 1, table 1): 16 of these 47 reviews (34%) did not retrieve any eligible RCTs, 11 (23%) retrieved only ongoing studies, 13 (28%) retrieved at least one completed or terminated RCT without results available and 7 (15%) retrieved at least one completed or terminated RCT with results identified. Of these last 7, 3 included RCTs in at least one meta-analysis."(page 12 lines 9-20)

- **In the results section, I suggest using the denominator for each of the numbers given as otherwise it is hard to follow to what number it is referred.**

As requested we added in the results section the denominator for each number to detail what number is referred.

- **Page 12, line 12. I could not find figure 3 in the supplemental material.**

We apologize for this error and deleted the reference to the figure 3 that does not exist.

- **Page 13, line 5. Did the author try to recalculate the effect estimates for the primary outcome where possible? Or how did they "select" which meta-analysis to recalculate?**

We clarified that for each systematic review, we used an algorithm to select one meta-analysis in which at least one RCT with results available could be included.

For this purpose, we proceeded as follows:

1. For each systematic review, we recorded all the outcomes of the meta-analysis reported in the systematic review report.
2. For each eligible RCT with results available, we determined whether the RCT could be included in the meta-analyses previously recorded.
3. When RCT(s) could be included in several meta-analyses, we selected only one meta-analysis according to the following order of outcomes analyzed: 1) the primary efficacy outcome of the systematic review, 2) the primary safety outcome, 3) the patient-important outcome such as mortality, quality of life or morbidity outcome. If several of these outcomes could be used to include a new RCT, we selected the first

meta-analysis reported. If none of these outcomes could be used to include a new RCT, we selected the first meta-analysis reported.

Overall, for the 14 systematic reviews with new RCTs included in the meta-analysis:

- 6 systematic reviews clearly defined primary and secondary outcome(s). We selected the meta-analysis of the primary efficacy outcome in 2 systematic reviews, the primary safety outcome in 3 and one patient-important outcome reported as a secondary safety outcome. All outcomes were patient important outcomes.

- 8 systematic reviews did not clearly define primary and secondary outcome(s). All the selected outcomes were patient-important outcomes, except one, which was a surrogate marker (HbA1c).

This is now clarified in the text, page 9 line 16 to page 10 line 14 and table 2.

We changed the results section by adding “recalculated the effect estimates for the selected meta-analyses from the 14 systematic reviews". Page 14 lines 13-14.

- **Appendix 3 is very hard to read.**

We apologize for the unstable format of the appendix now numbered appendix 4 and we will provide a pdf to have a stable format.

- **Part of the limitations of including trial registry data is that it is hard to assess the quality.**

We agree. In registries, the information about the methods are succinctly described and a clear description of methodological points are often lacking.

However, the study protocols should be more available in the near future because registration policies have changed. In the final rule for trial registration in ClinicalTrials.gov, the 2007 FDAAA, made publicly available on September 16, 2016, requires submission of the full protocol and statistical analysis plan at the same time as submission of results. (Zarin NEJM 2016).

We added this important point in the discussion, page 17 lines 12-20: “Of course, one important limitation of this search is the lack of availability of the results for completed trials and the low level of details on the methodological quality recorded in the registries. Some initiatives to facilitate access to clinical trial results, such as the 2007 FDAAA, which requires the posting of clinical trial results[19] or pharmaceutical company policies [36], have been implemented. Some researchers have developed an intervention to improve posting, such as emailing a reminder of the FDAAA 801 requirement to responsible parties[37]; other interventions are necessary. Recently, the new rules of trial registration at ClinicalTrials.gov requires submission of a full protocol and statistical analysis plan at the same time as submission of results.”

Reviewer: 3

1. I failed to find any discussion of what is the critical question – does it make a difference if trials registers are searched on the results of meta-analyses. First is the scope of the problem – of 95 reviews where the review authors did not perform a search, the authors found RCTs that were usable in a meta-analysis for only 21, or about 1/4th. I would consider this an important proportion. However, the difference in the meta-analytic result was quite unimpressive. Of course, this is balanced by an increased precision with the increased sample size. With the evidence taken together, does this mean that it is not worth spending the time to search for trials in a trials register or should searching trials registers continue to be the recommendation? While there may not be a 'right' answer, the authors should at least address this question in the discussion.

We agree that our discussion section should be more focused on this critical question.

With the evidence taken together, our feeling is that it is worth spending time to search clinical trial registries and that such searches should continue to be a recommendation, with implementation strategies needed to improve adherence. The addition of new RCTs in meta-analyses did not change the statistical significance, but it increased precision.

Furher, the objective of systematic reviews is to collate all empirical evidence (Cochrane handbook, JPT Higgins, 2011). However, overall, results for only about half of clinical trials are published, and searching only electronic bibliographic databases gives access to only the "tip of the iceberg". In our study, searching clinical trials registries allowed for finding new evidence for almost half of the systematic reviews (41/95), and this new evidence was usable in at least one meta-analysis in one-third of these systematic reviews (14/41). Finally, searching trial registries in general represented a low burden. The median (Q1-Q3) number of records to screen by systematic review was low (23 [6-150]). The results for 41 of 63 trials were mainly posted on ClinicalTrials.gov and therefore immediately available. Registries could be an even more important source of results in the future. This point is now highlighted in the manuscript.

Nevertheless, this is now clarified in our discussion:

"Clinical trial registries have been developed and their use enforced by editors and policy makers to reduce waste in research and publication bias. They have been considered an important step toward more transparency and increasing research value.

Searching clinical trial registries is recommended when performing systematic reviews. In our study, the addition of new RCTs in meta-analyses affected treatment effect estimates but did

not change the statistical significance of the results or the direction of the treatment effect, although it increased precision.

Nevertheless, searching clinical trials registers remains an essential recommendation for the conduct of systematic reviews and should be enforced. In fact, the objective of systematic reviews is to collate all empirical evidence [3]. However, overall, results for only about half of clinical trials are published, and searching only electronic bibliographic databases gives access to only the "tip of the iceberg" [24–26]. In our study, searching clinical trials registries allowed for finding new evidence for almost half of the systematic reviews (41/95), and this new evidence was usable in at least one meta-analysis in one-third of these systematic reviews (14/41). Finally, searching trial registries in general represented a low burden. The median (Q1-Q3) number of records to screen by systematic review was low (23 [6-150]). The results for 41 of 63 trials were posted at ClinicalTrials.gov and therefore immediately available. Furthermore, a previous study showed that the reporting of results was more complete at ClinicalTrials.gov than in published reports[37]. Of course, one important limitation of this search is the lack of availability of the results for completed trials and the low level of details on the methodologic quality recorded in the registries. Some initiatives to facilitate the access to clinical trial results, such as the 2007 FDAAA, which requires the posting of clinical trial results[18] or pharmaceutical company policies[34], have been implemented. Some researchers have developed an intervention to improve posting, such as emailing a reminder of the FDAAA 801 requirement to responsible parties[35]; other interventions are necessary. Recently, the new rules of trial registration at ClinicalTrials.gov requires submission of a full protocol and statistical analysis plan at the same time as submission of results [36]. Registries could be an even more important source of results in the future."

This point is now highlighted in the manuscript. Page 16 line 21 to page 17 line 25.

2. Did you look to see if any characteristic of the review was associated with searching a trials register (e.g., Cochrane versus non-Cochrane or funding source)?

These analyses were not planned and not initially performed, but the data were collected. Following the reviewer's comment we performed these analyses and found that a search of a trial registry was more frequent in 1) 1) Cochrane than non-Cochrane reviews: [65/77 (84%) versus 42/146 (29%), $p<0.001$]; and 2) reviews with not-for-profit funding or no funding than other funding (for-profit funding, funding not reported or unclear) [79/139 (57%) versus 28/84 (33%), $p<0.001$].

We now reported in the manuscript:

- In the methods section: "In a post-hoc analysis, we used a chi-square test to compare the proportion of reviews reporting a trial registry search according to the type of systematic review (Cochrane vs non-Cochrane) and funding source (not-for-profit

funding or not funded vs for-profit funding, funding not reported or unclear)." Page 11 lines 4-8.

- In the results section: "A search of a trial registry was more frequent in Cochrane than non-Cochrane reviews [65/77 (84%) vs 42/146 (29%), p<0.001] and not-for-profit funding or no funding than for-profit funding, funding not reported or unclear [79/139 (57%) vs 28/84 (33%), p<0.001]." pages 12 lines 21-23.

3. The references used to support the statement about unpublished RCTs and publication bias are tangential at best. The authors should consider citing Schmucker et al PLoS ONE, 2014 as the appropriate reference instead of cites 15 and 16. Also, Antes (cite 9) seems a bit of a stretch also.

We replaced the citations 15 and 16 by the reference to the article from Schmucker, PLoS one 2014 and deleted the citation 9 (Antes).

Moreover, we added in the discussion section a recently published citation: Golder S Plos Med 2016. Page 15 line 20-23.

"Moreover, in a systematic review by Golder in 2016, aiming at quantifying the impact of the underreporting of adverse events in systematic reviews showed that the inclusion of unpublished data may reduce the imprecision of pooled effect estimates in meta-analysis of adverse events[32]. "

Reviewer: 4

Importance:
Publication and selective reporting biases play key roles in the quality of systematic reviews, so this topic is relevant to all areas of scientific research. The bridge between statistical and clinical relevance in this paper, however, require some further description/clarification. I feel that the "impact" of searching clinical trial registries should be appreciated in terms of how clinicians use the results of systematic reviews to choose how their patients are treated.

Thank you for your comments. We clarified the manuscript and answered all your questions below.

Some general thoughts:
- In the introduction it is stated that unpublished results may bias the results of a systematic review. A tangible example of this (or multiple) in pharmaceutical trials would be beneficial for readers to better gauge its importance and translation into clinical practice. An example that comes to mind is the update on the Cochrane systematic review on the efficacy of neuraminidase inhibitors for influenza after a plethora of unpublished data was identified.

We modified the introduction by adding an example as requested.

"Indeed, results for half of RCTs are never published and the publication status is affected by the nature and direction of results, which may bias the results of the systematic review[14]. In some cases, the importance of unpublished trials can be considerable; for example, the addition of unpublished data in the updated Cochrane review assessing the efficacy of neuraminidase inhibitor for influenza modified the conclusion [15,16]." Page 4 lines 5-10.

- Results: It is identified that a considerable portion of meta-analyses in this cohort have changes in their summary statistics once trial registry data are identified and included. The clinical implications of these changes are difficult to conclude as a reader, however, as careful dissection of Appendix 3 is required to even identify the outcome assessed in each case. I would prefer to have descriptions within the results/discussion about notable differences identified and the potential changes in the conclusions of the reviews and clinical practice.

We agree that the clinical implication of the changes in summary statistics should be clarified. Actually the addition of new RCTs changed the summary statistics but not the statistical significance of any systematic review. Similarly, the addition of new RCTs did not change the direction of the treatment effect. This is now highlighted in the manuscript, page 14 lines 23-25.

Also, we modified Table 2 to clarify the understanding of our results. Particularly, we added one column that described whether the outcome is a safety or efficacy outcome and the

direction of the change in the summary statistic (i.e., decrease or increase efficacy or less or more harm). We also added one column reporting whether the change in the summary statistic was significant or not.

Scientific reliability:
- The research question is broken down into two components, 1) identifying if and how clinical trial registries were searched in this cohort of systematic reviews; and 2) identifying the impact of additional RCTs found by repeating searches using trial registry data (if not initially/adequately performed). Part 1 is simplistic and clear, but part 2 could be made more specific - i.e., is the "impact" referring to the amount of additional patient data identified? The statistical impact on the main meta-analysis (and can this analysis be called the most clinically important, as only one analysis was performed per review)? The change in treatment effect estimate? Each of these were carried out in the project itself.

Thank you for this comment.

We agree that we did not clearly define to what the "impact" is referring and this is confusing. We believe that the impact of clinical trial registry search is at 3 levels.

Clinical trial registries search allows for the following:

1. To identify of all evidence (i.e., all completed and terminated RCTs whether they are published or not). Lack of searching trial registries implies that we could have missed evidence, but the objective of a systematic review is to collate all empirical evidence (Cochrane handbook, JPT Higgins, 2011). In our study, in absence of a trial registry search, we could have missed completed and terminated RCTs for 41 of 95 systematic reviews.

2. To determine the amount of missing data in the meta-analyses (unpublished trials without results available). This step is important to grade the quality of evidence for each outcome of the systematic review. In our study, among the 122 RCTs identified, 63 (52%) had results available.

3. To include in the meta-analysis the results obtained for unpublished RCTs. In our study, we could add new data and recalculated meta-analyses for 14 systematic reviews.

This is now clarified. We particularly changed the headings in the results section which are now reported as follow:

1) Identification and characteristics of reports

2) Reporting of clinical trial registry search in systematic reviews

3) Impact of searching clinical trial registries

a. Identification of completed or terminated RCTs

b. Availability of RCT results

c. Inclusion of RCT results in meta-analyses

- Study design - I appreciate the decision/justification to search only the WHO ICTRP portal. Data collection was duplicated and thorough. Baseline data regarding systematic reviews included was relevant. The decision to re-do the meta-analysis of one outcome per review where possible makes sense to make the workload manageable, but the clinical importance of the various outcomes assessed with additional RCTs would of course vary considerably.

We clarified that for each systematic review, we used an algorithm to select one meta-analysis in which at least one RCT with results available could be included.

For this purpose, we proceeded as follows:

1. For each systematic review, we recorded all the outcomes of the meta-analysis reported in the systematic review report.
2. For each eligible RCT with results available, we determined whether the RCT could be included in the meta-analyses previously recorded.
3. When RCT(s) could be included in several meta-analyses, we selected only one meta-analysis according to the following order of outcomes: 1) the primary efficacy outcome of the systematic review, 2) the primary safety outcome, 3) the patient-important outcome such as mortality, quality of life or morbidity outcome. If several of these outcomes could be used to include a new RCT, we selected the first meta-analysis reported. If none of these outcomes could be used to include a new RCT, we selected the first meta-analysis reported.

Overall, for the 14 systematic reviews with new RCTs included in the meta-analysis:

- 6 systematic reviews clearly defined primary and secondary outcome. We selected the meta-analysis of the primary efficacy outcome in 2 systematic reviews, the primary safety outcome in 3 and one patient-important outcome reported as secondary safety outcome. All outcomes were patient important outcomes.
- 8 systematic reviews did not clearly define primary and secondary outcome(s). All selected outcomes were patient-important outcomes, except one, which was a surrogate marker (HbA1c).
- This is now clarified in the text, page 9 line 16 to page 10 line 14 and table 2.

- Results - The layout of Table 2 is easy to read, but it leaves me wondering what the changes in summary statistics are actually referring to (i.e., which outcome is now changed and is that clinically relevant?). This information can be gleaned from Appendix 3 but I feel it could be presented in a more user-friendly manner, like a table. Perhaps additional columns could be added to Table 2 to define the outcome re-analysed (primary efficacy, harm, etc) and what the outcome is.

We fully agree this information are important and are lacking in table 2 to be clearly understandable.

We now modified table 2 as follows:

- We added one column with a clear description of the selected outcome with clarification whether the outcome was reported as primary, secondary or not clearly reported as such in the review report.
- We added one column that described whether the outcome is a safety or efficacy outcome and the direction of the change in the summary statistic (i.e., decrease or increase efficacy or less or more harm).
- We added one column that described whether the change in the summary statistic was significant or not. Of note, the addition of new RCTs did not change the significance of any systematic review.
- Lines were re-organized by type of outcome safety or efficacy, and we regrouped lines by type of summary statistics.
- We deleted the 27 lines corresponding to systematic reviews for which no RCTs with available data were retrieved. These systematic reviews are now described in appendix 3. Table 2 now focuses on the 14 recalculated meta-analyses.

Discussion/Conclusions - As mentioned above, I believe the component that needs more explanation is the clinical relevance of the quantitative differences noted once the additional RCT data is included. There is a comment that the lack of registry searching is considered unethical by some authors and I think the reasons why should be stated in the text. Interestingly, there was a lack of outcome data available in 18 of the additional RCTs identified which precluded their inclusion in their respective analyses. This is also worth commenting on as an example of evidence of outcome reporting bias.

We agree. We now highlight that in our study; the addition of new RCTs in meta-analyses affected treatment effect estimates but did not change the statistical significance of the results or the direction of the treatment effect, although it increased precision.

The lack of registry searching is considered unethical by some authors because such search strategy will miss unpublished trials**.**

However, we deleted this sentence with the reference as another reviewer suggested.

As well, we now comment on the lack of outcome data available in 18 of the additional RCTs identified, which could be related to differences in definition or metrics used between the outcomes reported in the RCT and the outcomes of the systematic review, or to outcome reporting bias.

We now highlight this point in the results: 13 lines 22-25.

“The 18 remaining RCTs with results could not contribute to the quantitative analysis because of differences in definition or metrics used between the outcome reported in the RCT and the outcome of the systematic review or outcome reporting bias.”

References - no glaring omissions from my perspective

Abstract - The conclusion in the abstract does not mention changes in effect estimates at all, which I feel is the most important component of the "impact" of including the additionally identified RCTs. The clinical relevance of omitting/including these trials should also be mentioned.

Actually the addition of new RCTs did change effect estimates but did not change the statistical significance of the meta-analyses. Similarly, the addition of new RCTs did not change the direction of the treatment effect. This is now highlighted in the abstract.

“The change in summary statistics ranged from 0% to 29% and was greater than 10% for 5 of 14 systematic reviews and greater than 20% for 2. However, none of the changes to summary effect estimates led to a qualitative change in the interpretation of the results once the new trials were added.” Page 3 lines 2-5.

Reviewer: 5

Major compulsory revision
None.

Minor compulsory revision

p4 para 3 line 2-3 The authors write that the impact of searching trial registries has never been evaluated. While this is true in the sense that no previous papers have assessed the impact of adding the data on effect estimates, previous studies have tried to quantify the amount of additional trials and data retrieved from registries. For example, the Keil paper (ref 25) in Emergency Medicine, Sinnett (PLoS ONE 2015) in neurology, Bibens (ObstetGynecol 2016) in obstetrics and gynecology, Enst (ref 29) in Cochrane reviews, Jones (ref 27) in major journals and Potthast (ref 28) for industry trials. While the authors cite many of these studies in their discussion I suggest that they mention some of them in the introduction and describe why their study adds important information to the literature.

We agree that these papers are important. However, none had systematically performed the trial registry search to quantify the amount of trials missing. We now highlight this in the introduction.

"Previous studies showed that clinical trial registry search is not systematically reported by authors of systematic reviews [22–24], but to our knowledge, none had systematically performed a trial registry search to quantify the impact of searching trial registries." Page 4 lines 22-25.

p8para 4 and p9 para 1 The authors searched for additional trial data using trial registries, publications and sponsor websites. In their discussion (p15 para 1 line 8-10) they argue why they did not contact investigators, which seem reasonable. However, the authors could have searched for additional data presented in conference abstracts and searched FDA and EMA websites (see Schroll J ClinEpidemiol 2015). This would likely have lead to additional data being included. The authors should address this in their discussion.

We agree and added a sentence to highlight this in the limitations section of the manuscript.

"We did not search for additional data presented in conference abstracts or search US FDA and EMA websites. Therefore, the number of systematic reviews with trials identified by a search of clinical trial registries and the results of RCTs retrieved from clinical trial registries may be underestimated." Page 16 lines 12-15.

p11para 2 The authors focus on systematic reviews that did not perform a search of trial registries. Since the authors also found 107 systematic reviews with a search I wonder why the authors did not report the results for this group.

We agree that these results should be reported.

Overall, among the 223 systematic review reports included, 107 (48%) reported searching at least one clinical trial registry: 48 of these (45%) reported searching only individual registries, 11 (10%) only portals and 44 (41%) a combination of individual registries and portals. The portal and individual register most frequently searched were the WHO ICTRP Search Portal (n=53/107, 50%) and ClinicalTrials.gov (n=89/107, 83%), and for 40 studies (37%), both were searched. In only 47 of the 107 (21%) reports were the results of the clinical trial registry search clearly described (ie, with a description of the number and identification of RCTs found from the search) (fig 1, table 1): 16 of these 47 reviews (34%) did not retrieve any eligible RCTs, 11 (23%) retrieved only ongoing studies, 13 (28%) retrieved at least one completed or terminated RCT without results available and 7 (15%) retrieved at least one completed or terminated RCT with results identified. Of these last 7, 3 included RCTs in at least one meta-analysis.

This now described in the results section. Page 12 lines 9-20

p12para 1 line 4 A figure 3 is mentioned, but I was unable to find it in the manuscript. The heading 'Figure 3' is mentioned on p69 in the appendix, but there is no figure.

We apologize for this error and deleted the reference to the figure 3 that does not exist.

p12para 3 line 2 The authors identified 45 trials with relevant data related to 14 unique systematic reviews. These systematic reviews had a total of 73 meta-analyses (on average 5.2 per review) of which data from the 45 trials were related to 59 of these 73 meta-analyses. The authors then report that 31 meta-analyses were considered complete, but I do not understand what they mean by this. The authors should please clarify this..

Thank you for this comment. We considered a meta-analysis as complete if all new RCTs identified by the trial registry search had available results and could be included in the meta-analysis. This was the case for 31 meta-analyses. For the remaining meta-analyses included in the 14 systematic reviews, some RCTs identified had results available, but we could not obtain the results for some; therefore, the meta-analysis did not include all existing evidence and was incomplete.

In addition, they include one meta-analysis per systematic review according to criteria based on types of outcome (primary efficacy, primary safety etc)(p9 para 3). The types of outcomes related to the 14 meta-analyses should be reported.

This is now reported in table 2. We added one column with a clear description of the selected outcome with clarification as to whether the outcome was reported as primary, secondary or not clearly reported as such in the review report.

Lastly, the authors choose only to include one meta-analysis per systematic review. While this strategy ensures that the results are equally weighted it also seems that relevant data is wasted. The authors should please address this in their discussion

This is now highlighted in the limitation section of the discussion: "Fourth, we chose to include only one meta-analysis per systematic review to make the workload manageable." page 16 lines 16-17.

p14para 1 The authors emphasise that only one-fifth of systematic reviews reported the search of trial registries in sufficient detail. However, this is mainly a problem related to poor reporting since almost half of trials actually searched registries. Also the authors should consider shortening this section as it is somehow too detailed, for example a lot of the data has just been reported in the previous paragraph.

We modified the manuscript as requested. Page 15 lines 3-8.

"Despite recommendations [23], about half of the published systematic reviews performed a trial registry search and only one-fifth reported the results of the search. When we performed the search, we identified additional studies for 43% of the systematic reviews. However, because of the lack of data availability, data for half of the eligible RCTs retrieved could not be included in systematic reviews. We re-analyzed 14 meta-analyses to include data from RCTs retrieved by the trial registry search."

Discussion It seems that despite the identification of 122 trials related to 41 systematic reviews only data for 45 trials related to 14 systematic reviews could be included. Also it seem that addition of data from registries mainly adds to the precision of summary estimates and not the direction or significance (clinical and statistical) of results. This should be emphasised in the discussion.

We agree. This is now highlighted in the discussion.

"The addition of data from registries mainly adds to the precision of summary estimates, but none of the changes led to a qualitative change in the interpretation of the results once the new trial data were added." Page 15 lines 9-11.

However, I am unsure what the last 27 lines represent. Are they different meta-analysis each from a different trial? Again in relation to my queries concerning p12+13 then the different numbers are confusing (73, 59 and 31 meta-analyses).

We agree that these 27 lines are not necessary for table 2. Actually they did not describe meta-analyses but rather the results of trial registry searches in systematic reviews featuring no RCT with data retrieved.

We modified table 2: we deleted the 27 lines to focus on the description of the 14 systematic reviews with new data, which allowed for recalculating the meta-analyses.

These 27 lines are included in appendix 3.

Discretionary revision

Abstract-results line 8-9 + p13 para 1 line 3-5 The authors state that the weight was increased. I am unsure about what the authors mean and cannot seem to find these numbers in Table 2. Do they mean that the number of patients increased?

We clarify that this represents the weight of the new RCTs in the recalculated meta-analysis.

We modified the description on page 2 line 25 to page 3 line 1 and page 14 lines 18-19.

"The weight of the additional RCTs in the re-calculated meta-analyses ranged from 0% to 58% and was greater than 10% in 5 of 14 systematic reviews, 20% in 3, and 50% in 1.

p6para 1 +2 The authors should consider having a subheading for the 'search' and one for 'inclusion/exclusion criteria'.

We modified the manuscript as requested (page 6 lines 3 and 10)

p8para 1 line 2 The term 'portal' used here and later in the manuscript (e.g. p11 para 2 line 4) may not be clear to all readers. A short explanation may help.

We added the following explanation: "We searched the World Health Organization International Trials Registry Platform (WHO ICTRP Search Portal). We chose this portal (i.e., a portal provides access to a central database containing the trial registration data sets provided by several registries) because it includes 16 national and international primary registries including ClinicalTrials.gov." Page 8 lines 3-9.

p11para 1 line 1 I suggest 'included' instead of 'selected'.

We modified the manuscript as requested. Page 12 line3

p15para 2 line 7 107 of 223 is 48% not 47%.

We apologize for this error and corrected the manuscript.

Figure 1 The main focus of the paper is systematic reviews without a search of registries. It therefore seems counterintuitive that the flowchart focuses on systematic reviews with a proper reporting of registry search.

We agree and modified figure 1. We now clearly report the two types of systematic reviews, with and without a clinical trial registry search reported, and we report their characteristics below each group.

Figure 1 + 2 + Table 1 The authors should consider avoiding the abbreviation SR since it does not seem to provide additional space in the figures.

We replaced “SR” by “systematic review” in figures 1 and 2 and in table 1.

Table 1 The term private funding is unclear. Is this similar to commercial/industry/for-profit funding? Private could also mean a private foundation.

We agree. We clarified that in our study we considered private funding as for-profit sources of funding and public funding as not-for-profit sources of funding. We now modified the manuscript accordingly. Page 7 lines 1-4; page 11 lines 6-8; pages 13 lines 21-23.

Table 2 This table contains 41 lines of which 14 seems to represent the systematic reviews with meta-analyses with changes in summary statistics reported on page 13. And the rest the 27 systematic reviews where data could not be added to the meta-analysis. This is not completely clear from the heading of the table. Maybe the heading should contain ‘systematic review’ instead of meta-analysis?

We deleted the 27 lines to focus on the description of the 14 systematic reviews with new data that allowed us to recalculate the meta-analyses. These 27 systematic reviews with no data retrieved from trial registries search are now described in a table in appendix 3.

Appendix 3 The layout of this appendix is unreadable.

We apologize for the problem of the unstable format of the appendix now numbered appendix 4 and we will provide a pdf to have a stable format.