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.

We are grateful to the editors and peer reviewers for their thoughtful comments that helped us improve the quality of our manuscript.
We answered all the reviewers' comments and modified the manuscript accordingly.
We also updated the affiliation of the authors; because Marie Baudard and Amélie Yavchitz have contributed equally they are considered as co-first authors.

The corresponding author for negotiations concerning the manuscript is
Amélie Yavchitz (MD, PhD)
Centre d'Epidémiologie Clinique, Hôpital Hôtel Dieu
1, Place du Parvis Notre-Dame, 75181 PARIS Cedex 4
Tel 33(0)1 42 34 78 33
amelie.yavchitz@aphp.fr
ayavchitz@gmail.com

Sincerely,

Amélie Yavchitz

Responses to peer reviewers' comments

Reviewer: 1
The authors have done an excellent job addressing all reviewer comments, and I have no further suggestions. I believe the paper is acceptable for publication in the BMJ.
Matthew J Page

Reviewer: 2
This is a re-submission following a first review.
The authors have addressed all the comments and suggestions I made in the first review. The quality of the article has significantly improved.

Reviewer: 3
The comments relates to the document version with track changes.

Major compulsory revision
None.

Minor compulsory revision

p7 line 16-19 + p8 line 19-23 These two paragraphs seems to describe the same.
We agree and removed from the manuscript the paragraph p7 line 16-19

p9 line 9-13 It is not clear how the authors handled discrepancies in results between sources. For example, if number of events differs between results on clinicaltrials.gov and in trial publication.
Actually, we did not compare the results between sources. Indeed we considered and extracted the results from a single source according a pre specified order. In case of several sources, we considered and extracted first the data reported in the registry. If no data were registered, we considered and extracted the data reported in the published report. When the unique source of data was the sponsor web site, we considered and extracted this source.
This is now clarified in the manuscript p 10 line 17-18
"When the outcome data were available from several sources, we extracted a single source according a pre specified order; we considered the data reported 1) in the registry, 2) in a published report and 3) on the sponsor website."
p15 line 5-7 (+results in abstract) The authors should consider reporting this in intervals instead (e.g. 0-10% etc). Here it is unclear whether the 10 trials with 20% increase in patients are part of the 19 trials with 10% increase in patients.
To clarify, we modified the manuscript as requested p 14 line 17-21:
"Among these 41 systematic reviews with additional RCTs identified, the number of patients included increased by 10% to 20% in 9, 20% to 30% in 3, 30% to 40% in 2; 40% to 50% in 1 and more than 50% in 4."
p12 line 12 It is not clear how the percentage change in effect size was calculated. Did the authors use similar methodology as the Hart paper (reference 31)?
We used a similar methodology as the Hart paper that is now referenced.
We clarify that we reported the magnitude of the change in the result of the meta-analysis as a percentage change in the summary statistic after including data from the RCTs retrieved after trial registry search. For risk ratios and odds ratios, we calculated the percentage change of the log transformation as $(\log(E)-\log(I))\times 100/\log(E)$, where E is the effect estimate excluding newly retrieved data and I the effect estimate including newly retrieved data. We calculated the log transformation for relative risks and odds ratios so that the point of "no effect" was equal to 0 instead of 1, thus allowing for a calculation of

percentage change. For weighted mean differences, we calculated the percentage change by using the formula (E−I)×100/E.
This is now clarified in the manuscript p11 line 11-19.
Discretionary revision

p5 line 1 The authors should describe what searching trials registries impacts upon. For example, on the results.
We modified the manuscript as requested, p 4 line 25 p 5 line 1.
"Previous studies showed that clinical trial registry search is not systematically reported by authors of systematic reviews [24–26], but to our knowledge, none had systematically performed a trial registry search to quantify the impact of searching trial registries (i.e., to quantify the number of missing trials identified by trial registry search and the change in summary statistics when these missing trials are considered)"

p10 line 1 Meta-analyses.
We corrected this misspelling.
p13 line 9-11 48+11+44 = 103, but it is reported that 107 systematic reviews searched registries. The authors should explain this discrepancy.
We apologize for this discrepancy. Actually, there were 4 systematic reviews in which the type of registry or portal search was unclear. This is now clarified.
We revised the manuscript p13 line 11-12 : "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. Four did not report the type of registry or portal searched."
p18 line 3-15 This paragraph seems too detailed. The authors should consider shortening it.
We shortened this paragraph as follows:
"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. We re-analyzed 14 meta-analyses to include data from RCTs retrieved by the trial registry search. 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 trials were added."
p20 line 18-23 The authors should consider shortening this section as this seems just to be a repetition of the results.
We shortened this section by removing the repetition of the results as follow:
"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."
Table 2 and elsewhere in manuscript. I would suggest using harms instead of safety. Similar to CONSORT and PRISMA guidelines.
We modified the manuscript as requested.

p14 line 20-21 It is not completely clear whether the 3 RCTS with results available are the same trials as the 2+1 stopped early.
To clarify, we modified the manuscript p14 line 10 .
"Among the 122 RCTS, 104 (85%) were classified as completed and 18 (15%) as 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."

Reviewer: 4
The paper has been revised to take account of many of the issues raised by the committee and the reviewers.

• A more detailed description of the process used to select the meta-analyses, the RCTs and the outcomes is now provided

• Table 2 has been greatly improved by omitting those SRs with no new RCTs and by incorporating a description of the selected outcome and summarising the impact of the new included RCTs. Also, the previous incorrect zero weighting for one of the SRs has been amended.

• The Discussion now includes an acknowledgement that changes in the summary statistics have led to no qualitative change in the interpretation of the results.

There are still a couple of (relatively minor) changes which would be advisable:

1. A footnote should be added to Table 2 explaining the derivation of the % change statistic (ie. for RR and OR the percentage change relates to the log values )
We added a footnote to the Table 2 as requested.

2. In the text, descriptions of the range in the weight of the eligible RCTs should be changed from '0% to 58%' to '0.2% to 58%.

We modified the manuscript as requested, p15 line 20