MJ - Decision on
Manuscript ID
BMJ.2016.034967

Body: 26-Sep-2016

Dear Dr. Yavchitz

Manuscript ID BMJ.2016.034967 entitled "Impact of searching clinical trial registries in systematic reviews of pharmaceutical treatments"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Jose Merino
jmerino@bmj.com

https://mc.manuscriptcentral.com/bmj?URL_MASK=080e6168ee734a4c95344cb1f4ffbd72

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Elizabeth Loder (chair), Julie Morris (statistician), John Fletcher, Tiago Villanueva, Amy Price. Written comments from José Merino, Rubin Minhas, Georg Roggla, Tobias Kurth

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the 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.

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.

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?

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Comments:
General
This is an incredibly important study that addresses an as yet unexplored question: what impact does searching trial registries have on the effects of meta-analyses? The authors have performed a very carefully conducted study and have clearly and concisely presented the findings. The implications drawn by the authors are reasonable, and I hope that this research will improve that rates at which systematic reviewers use trial registries.

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.

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)?

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)?

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?

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.

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.

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

Additional Questions:
Please enter your name: Matthew J Page

Job Title: Research Fellow

Institution: Monash University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

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Reviewer: 2

Comments:
The authors of this manuscript conducted a systematic search of clinical trial registries for randomised controlled trials (RCT) not included in systematic reviews of pharmaceutical interventions, but meeting the inclusion criteria specified in the systematic reviews. The aim was to evaluate the impact of including results from these RCTs in the relevant systematic reviews and therefore quantify the extent of the use of data available in trial registries as a resource for systematic reviews.
They found that of the systematic reviews of pharmaceutical interventions matching the pre-specified criteria more than half did not report having searched through trial registries. In half of the systematic reviews for which they could perform a search in trial registries, they found additional RCTs that could have been included.

They conclude that it is essential when conducting a systematic review to search trial registries and include results from relevant RCTs. At the same time, posting RCT results in trial registry should be promoted.
This article is important since it highlights two aspects of trial registries and their use in evidence base research.
1. Trial registries are still underutilised in systematic reviews, while their importance is known for not just adding to the body of evidence found in published material but also for identifying possible publication bias.

2. Regardless of the efforts made to promote registration of trials in publicly available trial registries and inclusion of results in such registries, this process is still sporadic and not systematic.
This should bring to the attention of clinicians, researchers and policymakers the fact that the quality of decision making and policy which is often based on systematic reviewing of the literature can be improved with the use of trial registries, where additional data which is not found in the published domain is available and can be added to the body of evidence. This should also encourage those who conduct trials to systematically register the trial and upload the results once the trial is completed. While the article focuses on pharmaceutical trials, it can easily apply to non-pharmaceutical trials since it has now become mandatory for any trial to be registered (http://www.wma.net/en/30publications/10policies/b3/).
While the usefulness of data included in trial registries has already been emphasised, this article is original since it gives a quantitative example of underutilization of registries for including trial data and underutilization of these data in systematic reviews.
The article reads fairly well (see comments below) and has a clear message.
The research question is clearly defined and the methods and results are quite well described for the purpose of the study. The methods and results first focus on giving an estimate of how many systematic review have not included a search of trial registries, and then on giving an estimate of the impact on the results from including such data. At the same time presenting also the important point that many trials in the registries do not include summary results. The interpretation of the results and the discussion are in line with what is presented.

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).
• 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.
• Page 11, line 9. I would use the word "included" or similar, instead of "selected".
• 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.
• 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.
• 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.
• Page 12, line 12. I could not find figure 3 in the supplemental material.
• 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?
• Appendix 3 is very hard to read.
• Part of the limitations of including trial registry data is that it is hard to assess the quality.

Additional Questions:
Please enter your name: Francesca Fiorentino

Job Title: Senior Statistician and Epidemiologist

Institution: Imperial College London

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 3

Comments:
Review for "Impact of searching clinical trials registries in systematic reviews of pharmaceutical treatments" by Gauthier et al.
The authors of this manuscript have examined the proportion of a sample of systematic reviews that report searching clinical trials registries for reports for randomized clinical trials. For those that did not search any registry, they searched ICTRP for RCTs that could have been used in the systematic review using the same keywords and search terms as the systematic review authors. For reviews where there was at least one additional RCT that could have been used, they re-calculated at least one meta-analysis and compared the results with the original meta-analyses. Overall the methods are clearly presented and well-conceived. Whether to search a clinical trial registry is an important topic addressing the rigor with which a systematic review is conducted. Their findings are important from this perspective and worthy of publication.
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.
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)?
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.

Additional Questions:
Please enter your name: Roberta Scherer

Job Title: Senior Scientist

Institution: Johns Hopkins Bloomberg School of Public Health

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 4

Comments:
Originality:
It is known already that trial registries are to date not consistently being used in conducting the searches for systematic reviews, and that search strategies are not always sufficiently described. This work adds to our knowledge on the effect of incomplete registry searching on the statistical results of recently published systematic reviews.

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. 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.
- 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.

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.
- 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.
- 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.
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.
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.

Additional Questions:
Please enter your name: Emma K Reid

Job Title: Clinical Pharmacist

Institution: Vancouver General Hospital

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 5

Comments:
General comments
The authors took a sample of systematic reviews of drug trials containing at least one meta-analysis. They included 223 systematic reviews of which 107 (48%) reported searching at least one trial registry. Among the 116 systematic reviews without a search, 95 reported relevant information in order to conduct an additional search of trial registries. By searching registries the authors identified 122 additional trials for 41 (43%) systematic reviews. However, only 45 trials contained sufficient information for inclusion in meta-analysis in 14 of the systematic reviews. Inclusion of data lead to changes in summary effect estimates from 0 to 29%.

The study is generally is novel, uses appropriate methodology and is generally well reported. Nevertheless, I have some comments which I have addressed below.

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 (Obstet Gynecol 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.

p8 para 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 Clin Epidemiol 2015). This would likely have lead to additional data being included. The authors should address this in their discussion.

p11 para 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.

p12 para 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.

p12 para 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. 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. 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.

p14 para 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.

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.

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).

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?

p6 para 1 +2 The authors should consider having a subheading for the 'search' and one for 'inclusion/exclusion criteria'.

p8 para 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.

p11 para 1 line 1 I suggest 'included' instead of 'selected'.

p15 para 2 line 7 107 of 223 is 48% not 47%.

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.

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.

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

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?

Appendix 3 The layout of this appendix is unreadable.

Language: Acceptable.

Stat review: Does not need to be reviewed by a statistician.

Conflicts of interest: None.

Additional Questions:
Please enter your name: Andreas Lundh

Job Title: Postdoc and Fellow

Institution: Centre of Evidence-based Medicine

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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