BMJ - Decision on Manuscript ID BMJ.2016.034967.R1

Body: 29-Dec-2016

Dear Dr. Yavchitz:

Manuscript ID BMJ.2016.034967.R1 entitled "Impact of searching clinical trial registries in systematic reviews of pharmaceutical treatments" which you submitted to BMJ,

Thank you for sending us your paper. We are pleased to say that we would like to publish it in the BMJ as long you are willing and able to address the comments from the reviewers.

We are looking forward to reading the revised manuscript and, we hope, making a final acceptance decision.

Please note that the BMJ might choose to shorten content or replace or re-size images for the print issue.

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https://mc.manuscriptcentral.com/bmj?URL_MASK=48709c7108704f1eb2308638c2bbc9f0

Yours sincerely

Jose Merino
jmerino@bmj.com,

REFEREE 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

Additional Questions:
Please enter your name: Matthew 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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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.

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
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.

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.

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.

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)?

Discretionary revision

p5 line 1 The authors should describe what searching trials registries impacts upon. For example, on the results.

p10 line 1 Meta-analyses.

p13 line 9-11 48+11+44 = 103, but it is reported that 107 systematic reviews searched registries. The authors should explain this discrepancy.

p18 line 3-15 This paragraph seems to detailed. The authors should consider shortening it.

p20 line 18-23 The authors should consider shortening this section as this seems just to be a repetition of the results.

Table 2 and elsewhere in manuscript. I would suggest using harms instead of safety. Similar to CONSORT and PRISMA guidelines.

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.

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 Evidencebased Medicine, Odense University Hospital, Denmark

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
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)

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%.

Additional Questions:
Please enter your name: Julie Morris

Job Title: Head of Medical Statistics

Institution: UHSM

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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Items to include with your revision (see http://www.bmj.com/about-bmj/resources-authors/article-types/research):

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i. For a clinical trial: Absolute event rates among experimental and control groups; RRR (relative risk reduction); NNT or NNH (number needed to treat or harm) and its 95% confidence interval (or, if the trial is of a public health intervention, number helped per 1000 or 100,000.)
ii. For a cohort study: Absolute event rates over time (eg 10 years) among exposed and non-exposed groups; RRR (relative risk reduction.)
iii. For a case control study:OR (odds ratio) for strength of association between exposure and outcome.
iv. For a study of a diagnostic test: Sensitivity and specificity; PPV and NPV (positive and negative predictive values.)
v. For a systematic review and/or meta-analysis: Point estimates and confidence intervals for the main results; one or more references for the statistical package(s) used to analyse the data, eg RevMan for a systematic review. There is no need to provide a formal reference for a very widely used package that will be very familiar to general readers eg STATA, but please say in the text which version you used. For articles that include explicit statements of the quality of evidence and strength of recommendations, we prefer reporting using the GRADE system.

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g. Footnotes and statements

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Date Sent: 29-Dec-2016