Cochrane in CORR

Cochrane in CORR®: Industry Sponsorship and Research Outcome

Tahira Devji BSc^{1b}, Jason W. Busse DC, PhD

Importance of the Topic

In the past decade, the number of clinical trials funded by industry has substantially increased in the United States [9]. The drug and device industry now funds six times more clinical trials than the federal govern-

ment [3]. This may be cause for concern, as publication agreements in which industry sponsors constrain academic authors' independence are common [5] and several research articles suggest industry sponsorship is more likely to result in pro-industry findings, pro-industry conclusions, and suppression of negative results [1, 2, 6,

8, 11]. A recent example of industry manipulation involved a randomized trial on low-intensity pulsed ultrasound for tibial shaft fractures. The industry sponsor conducted an unplanned interim analysis and, on the grounds of no difference in effect between treatment and control, discontinued the trial early [4, 13].

This Cochrane review examined 75 articles investigating whether industry funding of drug and device studies is associated with conclusions that are more favorable to the sponsor [10]. The review concluded that industry-sponsored studies reported more favorable efficacy results, similar harm results, more favorable conclusions, and less concordance between study results and conclusions when compared to nonindustry-sponsored studies. Industry-funded trials were also more likely to be at low risk of bias due to blinding.

A note from the Editor-in-Chief:

We are pleased to publish the next installment of Cochrane in CORR®, our partnership between CORR®, The Cochrane Collaboration®, and McMaster University's Evidence-Based Orthopaedics Group. In this column, researchers from McMaster University and other institutions will provide expert perspective on an abstract originally published in The Cochrane Library that we think is especially important.

(Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: MR000033. DOI: [10.1002/14651858.MR000033.pub3](https://doi.org/10.1002/14651858.MR000033.pub3).) Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd. Reproduced with permission. The authors certify that neither they, nor any members of their immediate families, have any commercial associations (such as consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

All ICMJE Conflict of Interest Forms for authors and Clinical Orthopaedics and Related Research® editors and board members are on file with the publication and can be viewed on request.

The opinions expressed are those of the writers, and do not reflect the opinion or policy of CORR® or The Association of Bone and Joint Surgeons®.

Cochrane Reviews are regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library (<http://www.thecochranelibrary.com>) should be consulted for the most recent version of the review.

This Cochrane in CORR® column refers to the abstract available at:

DOI: [10.1002/14651858.MR000033.pub3](https://doi.org/10.1002/14651858.MR000033.pub3).

T. Devji BSc (✉)

Department of Health Research Methods, Evidence and Impact, McMaster University, 1280 Main Street West, Hamilton, ON L8S 4K1, Canada
e-mail: devjits@mcmaster.ca

J. W. Busse DC, PhD

The Michael G. DeGroote Institute for Pain Research and Care, McMaster University, Hamilton, ON L8S 4K1, Canada

Cochrane in CORR

Upon Closer Inspection

This Cochrane review provided consistent evidence for the existence of an industry bias. Most included studies were categorized at high risk of bias; this assessment of risk of bias, however, was based on unvalidated criteria. Many of the included studies lacked information on study conduct and did not control for confounders that could influence the relationship between industry sponsorship and research outcomes. Furthermore, it is not clear if the review accounted for the effects of clustering. The inclusion of multiple reviews may have resulted in shared primary studies contributing more than once to pooled effect estimates, potentially overestimating the association [10]. Despite these limitations, this review provides convincing evidence that industry-sponsored studies are more likely to report more favorable efficacy results than nonindustry-sponsored studies.

This Cochrane review identified a number of important findings in their subgroup analyses. For example, when restricted to studies at low risk of bias, the association between industry sponsorship and favorable results was stronger and industry support was associated with less reporting of harms. A subgroup analysis based on the type of intervention found that industry-funded drug studies were more likely to report favorable results, whereas industry-funded device trials were less likely to report favorable results. Ideally, the authors would have performed meta-regression considering all promising subgroup factors to explore which ones retained significance in an adjusted analysis.

Take-home Messages

This recently published Cochrane review found evidence that industry sponsorship is associated with more favorable results and conclusions, and

this bias is not captured by standard risk-of-bias assessments. The review authors suggest that industry bias may be mediated by choice of comparators (such as placebo vs. current gold standard), dosing and timing of comparisons, choice of outcomes, selective analysis, and selective reporting [7].

When conducting a systematic review and meta-analysis, authors should capture and report the prevalence of industry funding among eligible primary studies and empirically explore, on an outcome-by-outcome basis, whether industry funding is associated with systematic differences in treatment effects. If so, and the subgroup effect is deemed credible based on established criteria [12], we believe review authors should focus on studies that are not funded by industry. If no credible subgroup effect is detected, then review authors can confidentially pool results from studies that are industry funded with those that are not.

Cochrane in CORR

Appendix

Industry sponsorship and research outcome (Review)

Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L

Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L.
Industry sponsorship and research outcome.
Cochrane Database of Systematic Reviews 2017, Issue 2. Art. No.: MR000033.
DOI: 10.1002/14651858.MR000033.pub3.

www.cochranelibrary.com

Cochrane in CORR

[Methodology Review]

Industry sponsorship and research outcome

Andreas Lundh¹, Joel Lexchin², Barbara Mintzes³, Jeppe B Schroll⁴, Lisa Bero⁵

¹Center for Evidence-Based Medicine, Odense University Hospital and University of Southern Denmark, Odense, Denmark. ²School of Health Policy and Management, York University, Toronto, Canada. ³Charles Perkins Centre and Faculty of Pharmacy, The University of Sydney, Sydney, Australia. ⁴Department of Obstetrics and Gynaecology, Herlev Hospital, Herlev, Denmark. ⁵Charles Perkins Centre and Faculty of Pharmacy, University of Sydney, Sydney, Australia

Contact address: Andreas Lundh, Center for Evidence-Based Medicine, Odense University Hospital and University of Southern Denmark, Sdr. Boulevard 29, Entrance 50 (Videncentret), Odense, 5000, Denmark. andreas.hover.lundh@rsyd.dk.

Editorial group: Cochrane Methodology Review Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 2, 2017.

Citation: Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. *Cochrane Database of Systematic Reviews* 2017, Issue 2. Art. No.: MR000033. DOI: 10.1002/14651858.MR000033.pub3.

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Clinical research affecting how doctors practice medicine is increasingly sponsored by companies that make drugs and medical devices. Previous systematic reviews have found that pharmaceutical-industry sponsored studies are more often favorable to the sponsor's product compared with studies with other sources of sponsorship. A similar association between sponsorship and outcomes have been found for device studies, but the body of evidence is not as strong as for sponsorship of drug studies. This review is an update of a previous Cochrane review and includes empirical studies on the association between sponsorship and research outcome.

Objectives

To investigate whether industry sponsored drug and device studies have more favorable outcomes and differ in risk of bias, compared with studies having other sources of sponsorship.

Search methods

In this update we searched MEDLINE (2010 to February 2015), Embase (2010 to February 2015), the Cochrane Methodology Register (2015, Issue 2) and Web of Science (June 2015). In addition, we searched reference lists of included papers, previous systematic reviews and author files.

Selection criteria

Cross-sectional studies, cohort studies, systematic reviews and meta-analyses that quantitatively compared primary research studies of drugs or medical devices sponsored by industry with studies with other sources of sponsorship. We had no language restrictions.

Data collection and analysis

Two assessors screened abstracts and identified and included relevant papers. Two assessors extracted data, and we contacted authors of included papers for additional unpublished data. Outcomes included favorable results, favorable conclusions, effect size, risk of bias and whether the conclusions agreed with the study results. Two assessors assessed risk of bias of included papers. We calculated pooled risk ratios (RR) for dichotomous data (with 95% confidence intervals (CIs)).

Industry sponsorship and research outcome (Review)

Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

WILEY

Cochrane in CORR

Main results

Twenty-seven new papers were included in this update and in total the review contains 75 included papers. Industry sponsored studies more often had favorable efficacy results, RR: 1.27 (95% CI: 1.17 to 1.37) (25 papers) (moderate quality evidence), similar harms results RR: 1.37 (95% CI: 0.64 to 2.93) (four papers) (very low quality evidence) and more often favorable conclusions RR: 1.34 (95% CI: 1.19 to 1.51) (29 papers) (low quality evidence) compared with non-industry sponsored studies. Nineteen papers reported on sponsorship and efficacy effect size, but could not be pooled due to differences in their reporting of data and the results were heterogeneous. We did not find a difference between drug and device studies in the association between sponsorship and conclusions (test for interaction, $P = 0.98$) (four papers). Comparing industry and non-industry sponsored studies, we did not find a difference in risk of bias from sequence generation, allocation concealment, follow-up and selective outcome reporting. However, industry sponsored studies more often had low risk of bias from blinding, RR: 1.25 (95% CI: 1.05 to 1.50) (13 papers), compared with non-industry sponsored studies. In industry sponsored studies, there was less agreement between the results and the conclusions than in non-industry sponsored studies, RR: 0.83 (95% CI: 0.70 to 0.98) (six papers).

Authors' conclusions

Sponsorship of drug and device studies by the manufacturing company leads to more favorable efficacy results and conclusions than sponsorship by other sources. Our analyses suggest the existence of an industry bias that cannot be explained by standard 'Risk of bias' assessments.

PLAIN LANGUAGE SUMMARY

Industry sponsorship and research outcome

Results from clinical studies on drugs and medical devices affect how doctors practice medicine and thereby the treatments offered to patients. However, clinical research is increasingly sponsored by companies that make these products, either because the companies directly perform the studies, or fully or partially fund them. Previous research has found that pharmaceutical industry sponsored studies tend to favor the sponsors' drugs more than studies with any other sources of sponsorship. This suggests that industry sponsored studies are biased in favor of the sponsor's products.

This review is an update of a previous review that looked at sponsorship of drug and device studies. The primary aim of the review was to find out whether the published results and overall conclusions of industry sponsored drug and device studies were more likely to favor the sponsors' products, compared with studies with other sources of sponsorship. The secondary aim was to find out whether such industry sponsored studies used methods that increase the risk of bias, again compared with studies with other sources of sponsorship. In this update, we carried out a comprehensive search of all relevant papers of empirical studies published from 2010 to February 2015 and included 27 new papers, yielding a total of 75 papers included in our review.

Industry sponsored drug and device studies more often had efficacy results that were favorable to the sponsors' products, (risk ratio (RR): 1.27, 95% confidence interval (CI): 1.17 to 1.37), similar harms results (RR: 1.37, 95% CI: 0.64 to 2.93) and favorable overall conclusions (RR: 1.34, 95% CI: 1.19 to 1.51), compared with non-industry sponsored drug and device studies. We did not find a difference between industry and non-industry sponsored studies with respect to standard methodological factors that may increase the risk of bias, except for blinding: industry sponsored studies reported satisfactory blinding more often than non-industry sponsored studies. In industry sponsored studies, there was less agreement between the results and the conclusions than in non-industry sponsored studies, RR: 0.83 (95% CI: 0.70 to 0.98). We did not find a difference between drug and device studies in the association between sponsorship and conclusions. Our analysis suggests that industry sponsored drug and device studies are more often favorable to the sponsor's products than non-industry sponsored drug and device studies due to biases that cannot be explained by standard 'Risk of bias' assessment tools.

Cochrane in CORR

References

1. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: A systematic review. *JAMA*. 2003;289:454–465.
2. Bhandari M, Busse JW, Jackowski D, Montori VM, Schünemann H, Sprague S, Mears D, Schemitsch EH, Heels-Ansdell D, Devereaux PJ. Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials. *Can Med Assoc J*. 2004;170:477–480.
3. Ehrhardt S, Appel LJ, Meinert CL. Trends in national institutes of health funding for clinical trials registered in ClinicalTrials.gov. *JAMA*. 2015;314:2566–2567.
4. Griffin XL. Low intensity pulsed ultrasound for fractures of the tibial shaft. *BMJ*. 2016;355:i5652.
5. Kasenda B, von Elm E, You JJ, Blümle A, Tomonaga Y, Saccilotto R, Amstutz A, Bengough T, Meerpohl JJ, Stegert M, Olu KK, Tikkinen KA, Neumann I, Carrasco-Labra A, Faulhaber M, Mulla SM, Mertz D, Akl EA, Bassler D, Busse JW, Ferreira-González I, Lamon-tagne F, Nordmann A, Gloy V, Raatz H, Moja L, Ebrahim S, Schandelmaier S, Sun X, Vandvik PO, Johnston BC, Walter MA, Burnand B, Schwenkglenks M, Hemkens LG, Bucher HC, Guyatt GH, Briel M. Agreements between industry and academia on publication rights: A retrospective study of protocols and publications of randomized clinical trials. *PLoS Med*. 2016;13:e1002046.
6. Lexchin J, Bero LA, Djulbegovic B, Clark O. Pharmaceutical industry sponsorship and research outcome and quality: Systematic review. *BMJ*. 2003;326:1167–1170.
7. Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. *Cochrane Database Syst Rev*. 2017;2:MR000033.
8. Melander H, Ahlqvist-Rastad J, Meijer G, Beermann B. Evidence b(i)ased medicine—selective reporting from studies sponsored by pharmaceutical industry: Review of studies in new drug applications. *BMJ*. 2003;326:1171–1173.
9. Moses H 3rd, Matheson DH, Cairns-Smith S, George BP, Palisch C, Dorsey ER. The anatomy of medical research: US and international comparisons. *JAMA*. 2015;313:174–189.
10. Senn SJ. Overstating the evidence: Double counting in meta-analysis and related problems. *BMC Med Res Methodol*. 2009;9:10.
11. Stamatakis E, Weiler R, Ioannidis J. Undue industry influences that distort healthcare research, strategy, expenditure and practice: A review. *Eur J Clin Invest*. 2013;43:469–475.
12. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ*. 2010;340:c117.
13. TRUST Investigators writing group, Busse JW, Bhandari M, Einhorn TA, Schemitsch E, Heckman JD, Tornetta P 3rd, Leung KS, Heels-Ansdell D, Makosso-Kallyth S, Della Rocca GJ, Jones CB, Guyatt GH. Re-evaluation of low intensity pulsed ultrasound in treatment of tibial fractures (TRUST): Randomized clinical trial. *BMJ*. 2016;355:i5351.