

Financial conflicts of interest and outcomes and quality of systematic reviews

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[Methodology Protocol]

Financial conflicts of interest and outcomes and quality of systematic reviews

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ABSTRACT

This is a protocol for a Cochrane Review (Methodology). The objectives are as follows:

The primary objectives are to investigate to what degree:

- funding of systematic reviews by drug, device, and imaging companies and authors' other financial conflicts of interest are associated with effect size estimate; and
- funding of systematic reviews by drug, device, and imaging companies and authors' other financial conflicts of interest are associated with conclusions that are favourable to the sponsor.

The secondary objective is to investigate to what degree:

- funding of systematic reviews by drug, device, and imaging companies and authors' other financial conflicts of interest are associated with the methodological quality of systematic reviews as presented by the reviews

BACKGROUND

Description of the problem or issue

Systematic reviews provide a rational basis for developing clinical guidelines for treatment decisions and for planning clinical trials.

Systematic reviews thus have a major impact on how physicians practise medicine, and which treatments are offered to patients (Guyatt 2008). It is therefore essential that such reviews are trustworthy and unbiased.

The pharmaceutical and medical device industry often funds clinical research, most often clinical trials (Chan 2005), but also sys-

tematic reviews. In a random sample of 300 systematic reviews, Page and colleagues found that eight systematic reviews (3%) received funding from a for-profit source (Page 2016). Moreover, the industry might deliberately sponsor systematic reviews in areas where the evidence is uncertain. For example, Ebrahim and colleagues investigated all meta-analyses of clinical trials of antidepressants and found that a third were funded by the industry (Ebrahim 2016). Furthermore, systematic reviews are often produced by authors with financial conflicts of interest (Hakoum 2016), which might also influence the results and conclusions. Numerous studies have been published on the association between industry sponsorship and outcomes of primary research studies, mainly clinical trials. A recent update of a Cochrane Review by Lundh and colleagues investigated the association between industry sponsorship and research outcomes in primary research and reported a clear association between funding source and trial conclusions based on 75 empirical studies (Lundh 2017). In contrast, fewer studies have investigated how industry funding and other financial conflicts of interest impact on results and conclusions of systematic reviews.

Why it is important to do this review

While conflicts of interest generally are associated with more positive conclusions in primary research studies (Lundh 2017), the empirical evidence is less clear with regard to the relationship between conflicts of interest on results and conclusions in systematic reviews. Existing studies investigating the association between industry funding and other financial conflicts of interest on results and conclusions of systematic reviews have, to our knowledge, not been identified, analysed, and summarised in a methodological systematic review. However, the retrospective nature of a systematic review and the subjective element in selecting criteria for studies and outcomes implies a possible greater susceptibility to industry funding and other conflicts of interest as compared with prospective primary clinical research such as randomised trials. This concern is supported by Jørgensen and colleagues, who compared 24 pairs of systematic reviews of the same two drugs used for the same disease, and reported that industry-funded reviews had more favourable conclusions (Jørgensen 2006). However, other studies have reported a less clear association with wide confidence intervals (Yank 2007). A methodological systematic review of all studies is important to provide a summary of results, an explanation for heterogeneity, and a clarification of the risk of bias.

Terminology

We define industry funding as funding of the study, authorship by full-time industry employees, or provision of assistance by industry (e.g. statistical analysis by company statistician, or writing assistance by a medical writer funded by the company or by someone

whose affiliation is not clarified, not even after we have asked the authors and the drug companies that might have been involved). We define other financial conflicts of interest as any relationship among the authors, apart from full-time employment, with a drug, device, or imaging company. For example research grants, being on a speakers' bureau, owning stocks, being on an advisory board, and consultancy work.

We use the term 'Cochrane methodology review' to refer to our present review.

We use the term 'observational studies' to refer to the studies we will include in this Cochrane Methodology Review.

We use the term 'systematic reviews' to refer to the studies included in the observational studies.

We use the term 'risk of bias' to refer to risk of bias in the included observational studies. This assessment will be done according to four pre-specified criteria described in the 'Assessment of risk of bias in included observational studies' section.

We use the term 'methodological quality of the systematic reviews' to refer to the methodological assessment of investigated systematic reviews made by the authors of the included observational studies. For example, Yank and colleagues used a modified version of Oxman 1991's 'Oxman and Guyatt scale' to evaluate their 124 systematic reviews (Yank 2007).

We use the term 'certainty of the Cochrane methodology review evidence' to refer to the quality of the body of evidence of our methodology review. This assessment will be inspired by the GRADE approach and done according to the procedure described in the 'Assessment of certainty of the Cochrane methodology review evidence' section (Schünemann 2011).

OBJECTIVES

The primary objectives are to investigate to what degree:

- funding of systematic reviews by drug, device, and imaging companies and authors' other financial conflicts of interest are associated with effect size estimate; and
- funding of systematic reviews by drug, device, and imaging companies and authors' other financial conflicts of interest are associated with conclusions that are favourable to the sponsor.

The secondary objective is to investigate to what degree:

- funding of systematic reviews by drug, device, and imaging companies and authors' other financial conflicts of interest are associated with the methodological quality of systematic reviews as presented by the reviews

METHODS

Criteria for considering studies for this review

Types of studies

We will include observational studies of any study design that investigate samples of systematic reviews with and without industry funding or other financial conflicts of interests. We define systematic reviews according to definitions used by the authors of included observational studies. If the sample of systematic reviews included in the observational study contains meta-analyses that did not use a systematic literature review, we will include the study and assess this in our 'Risk of bias' assessment. For observational studies to be eligible, they must have investigated at least one of the primary or secondary outcomes described below. If the sample of investigations included in the observational study contains a mixture of systematic reviews and other study designs (e.g. randomised trials or clinical guidelines), we will include the observational study if separate data for the group of systematic reviews is available. If not reported in the study, we will request the data from the authors (unless the number of systematic reviews is regarded as too small to be informative). Observational studies in all languages will be eligible.

Types of data

We will include dichotomous and continuous data on the association between industry funding and outcomes. Furthermore, we will include dichotomous and continuous data on the association between other financial conflicts of interest and outcomes. These types of data will include, for example, events, odds ratios, percentages, 95% confidence intervals, and P values.

Types of methods

We will include observational studies that quantitatively compare outcomes or methodological quality of systematic reviews funded by drug, device, or imaging companies or written by authors with conflicts of interest, with systematic reviews that have other sources of funding or are written by authors without conflicts of interest.

Types of outcome measures

Primary outcomes

We will include two primary outcomes.

1. Effect size estimates (e.g. relative risks or standardised mean difference) for efficacy and harms separately.
2. Favourable conclusions (e.g. whether the experimental intervention is recommended without reservations ([Jorgensen 2008](#))).

We define 'favourable conclusions' according to the definitions used by authors of the observational studies.

Secondary outcomes

We will include one secondary outcome.

1. The methodological quality of the systematic reviews presented in the observational studies according to the definitions used by the authors. This type of data would be measured, for example, by the 9-item Oxman and Guyatt scale that measures different aspects of methodological quality ([Oxman 1991](#)). Thus, this type of data would include data from the components of different methodological quality scales (i.e. how many systematic reviews with and without industry funding or other financial conflicts of interest that fulfilled each item in the scales).

Search methods for identification of studies

Electronic searches

We will search PubMed, Embase, and the Cochrane Methodology Register. We will search Web of Science for studies that cite any of the observational studies that are eligible for our review. We will use the strategy shown in Appendix 1 for PubMed and adapt this strategy for the other databases.

Searching other resources

Grey literature

Our electronic search in the Cochrane Methodology Register will identify relevant grey literature, as the database includes conference abstracts. In addition, we will search proceedings from Peer Review Congresses and Cochrane Colloquia. Furthermore, we will search PROSPERO for registered systematic reviews and the ProQuest Dissertation and Theses database for dissertation theses related to our topic of interest. Finally, we will search Google Scholar for eligible unpublished studies.

Reference lists

Other sources of data will include searches of reference lists of the observational studies ([Horsley 2011](#)).

Data collection and analysis

Selection of studies

One review author (CH) will screen titles and abstracts of all retrieved records for obvious exclusions. Two review authors (CH and KR) will independently assess potentially eligible studies based on full text. We will resolve any disagreements by discussion; and, if

necessary, by arbitration provided by another review author (AL). Reasons for exclusion of potentially eligible studies will be described in the final report in the 'Characteristics of excluded studies' table. Non-English studies will be translated when feasible.

Data extraction and management

Two review authors (CH and AL) will independently extract data from included observational studies. We will resolve any disagreement in data extraction by discussion; and, if necessary, by arbitration provided by another review author (AH). All data will be extracted into a pilot-tested data sheet.

If necessary, we will contact the authors of the observational studies for information that is unclear from the reporting of the original studies.

Data will be extracted on the following.

Basic characteristics

- Title.
- Year published.
- Name of first author.
- Name of journal.
- Primary aim of the study.
- Study design used in the paper (cohort, cross-sectional, systematic review or meta-analysis, other).
- Sample strategy used to locate systematic reviews or meta-analyses (e.g. search of PubMed and time period covered).
Verbatim extraction.
- Types of publications (published/unpublished) included in the systematic reviews of meta-analyses. Verbatim extraction.
- Types of publications included in the systematic reviews and meta-analyses (published only, published and unpublished, not described).
- Definition of systematic reviews or meta-analyses used in the paper. Verbatim extraction.
- Number of systematic reviews or meta-analyses included in the paper.
- Types of studies included in systematic review or meta-analysis (e.g. clinical trials or cohort studies).

Outcome data

- Definition of industry funding used in the paper. Verbatim extraction.
- Definition of conflicts of interest used in the paper. Verbatim extraction.
- Definition of effect size estimates used in the paper. If the authors do not investigate 'effect size estimates' but instead 'favourable results' (e.g. based on statistical significance), we will extract this definition. Verbatim extraction.
- Definition of favourable conclusions used in the paper. Verbatim extraction.

- Definition of methodological quality of the systematic reviews used in the paper. Verbatim extraction.
- Definition of primary analysis used in the paper. Verbatim extraction.
- Data on estimates of the association between industry funding and effect size estimates. If the authors do not investigate 'effect size estimates' but instead 'favourable results' (e.g. based on statistical significance), we will extract this information.
- Data on estimates of the association between financial conflicts of interest and effect size estimates. If the authors do not investigate 'effect size estimates' but instead 'favourable results' (e.g. based on statistical significance), we will extract this information.
- Data on estimates of the association between industry funding and conclusions.
- Data on estimates of the association between financial conflicts of interest and conclusions.
- Data on estimates of the association between industry funding and methodological quality of the systematic reviews.
- Data on estimates of the association between financial conflicts of interest and methodological quality of the systematic reviews.

Data for informing subgroup analyses or reflection on heterogeneity

- Types of interventions included in systematic reviews or meta-analyses. Verbatim extraction.
- Types of interventions included in systematic reviews of meta-analyses (drug, device, imaging, mixed).
- Study domain (i.e. topic of interest) of systematic reviews. Verbatim extraction.
- Study domain coded (specific disease, specific therapy, mixed domain).
- Data on estimates of the association between different degrees of industry funding (e.g. mild, moderate, and severe) and effect size estimates. If the authors do not investigate 'effect size estimates' but instead 'favourable results' (e.g. based on statistical significance), we will extract this information.
- Data on estimates of the association between different degrees of financial conflicts of interest (e.g. mild, moderate, and severe) and effect size estimates. If the authors do not investigate 'effect size estimates' but instead 'favourable results' (e.g. based on statistical significance), we will extract this information.
- Data on estimates of the association between different degrees of industry funding (e.g. mild, moderate, and severe) and conclusions.
- Data on estimates of the association between different degrees of financial conflicts of interest (e.g. mild, moderate, and severe) and conclusions.

Additional data

- Declaration of funding source and other conflicts of interest in the study. Verbatim extraction.
- Additional relevant data.

Assessment of risk of bias in included studies

Since there are no validated criteria for assessing risk of bias in these types of studies, we plan to use a set of criteria similar to criteria developed for a Cochrane Protocol and a previous Cochrane Review by one of the authors of this review (Lundh 2013; Lundh 2017). Two review authors (CH and AL) will independently assess risk of bias. We will resolve any disagreements by discussion; or by arbitration, when needed, provided by a third review author (AH). We will categorise each component as high risk of bias, low risk of bias, or unclear. We will use the following criteria.

1. Whether there was a risk of bias in the study inclusion process (low risk of bias may, for example, include clear inclusion criteria with two or more assessors independently selecting studies).

2. Whether there was a risk of bias in the coding of sponsorship, conflicts of interest, and outcomes (low risk of bias may, for example, include a coding done by two or more assessors).

3. Whether there was a risk of bias in the comparability of systematic reviews.

- i) Whether the groups of systematic reviews with and without industry funding and other financial conflicts of interest were comparable by design (e.g. same intervention, same disease, same outcomes, and conducted at a comparable time).

- ii) Whether the groups of systematic reviews with and without industry funding and other financial conflicts of interest were comparable by analysis (e.g. controlled for differences in study characteristics using regression analysis).

Our aim is primarily to differentiate between studies with higher and lower risk of bias. Thus we will code, by default, a study as low risk of bias if all criteria are assessed as low risk of bias; otherwise, we will code it as high/unclear.

Dealing with missing data

We will contact authors of the observational studies in an attempt to obtain missing data on our primary and secondary outcomes.

Assessment of heterogeneity

We will assess statistical heterogeneity using the I^2 statistic.

Data synthesis

The main analyses will assess the associations between industry funding, including other financial conflicts of interest, and effect size estimates and conclusions, according to the definitions used by the authors. Furthermore, we will assess the association between

industry funding including conflicts of interest and methodological quality of the systematic reviews in a separate analysis. For methodological quality of the systematic reviews, we plan to pool similar items across the different methodological quality tools used by the observational studies. Thus we plan to pool items on search methods, selection of studies, risk of bias assessments, methods used to combine findings from included studies, whether the conclusions were supported by the data, and whether the results were interpreted in light of risk of bias.

We plan to calculate pooled risk ratio estimates with 95% confidence intervals for each analysis. We define substantial heterogeneity as I^2 greater than 50%. Due to the anticipated methodological heterogeneity between the observational studies (e.g. definition of industry funding and conflicts of interests and study domains) we will use a random-effects model as default. If meta-analysis is not meaningful, the results will be reported descriptively. All analyses will be conducted in Review Manager 5 (RevMan 5).

Subgroup analysis and investigation of heterogeneity

We plan to conduct the following subgroup analyses for our primary outcomes.

1. We hypothesise that the association of industry funding including other financial conflicts of interest and favourable outcomes may be larger in studies with high risk of bias. We will compare observational studies with high versus low risk of bias.

2. We plan to compare Cochrane Reviews with non-Cochrane systematic reviews.

3. We will compare observational studies sampling systematic reviews of drugs with observational studies sampling systematic reviews of devices or medical imaging, as the mechanisms of influencing study outcomes may differ between the industries.

4. We will compare different degrees of industry funding and other financial conflicts of interest (e.g. mild, moderate, and severe) according to the definitions used by the authors of the observational studies. If possible, we will analyse this both within observational studies in a stratified analysis and between observational studies in a subgroup analysis.

Sensitivity analysis

The following sensitivity analyses will be done for our primary outcomes in order to test their robustness.

1. We plan to compare systematic reviews restricting the industry group to industry funding only (i.e. excluding systematic reviews with conflicts of interest according to our definition).

2. We plan to compare systematic reviews restricting the industry group to financial conflicts of interest only (i.e. excluding systematic reviews with industry funding according to our definition).

3. We plan to re-analyse all primary outcomes restricting our analyses to included observational studies without industry

funding or other financial conflicts of interest according to the declarations.

4. We plan to re-analyse all primary outcomes based on a fixed-effect model, if applicable.

Assessment of certainty of the Cochrane methodological review evidence

We will grade the certainty of the Cochrane methodology review evidence for each of our outcomes as high, moderate, low, or very low. Inspired by the GRADE approach, we will base the initial judgement on the study design of the observational studies assessing each outcome. In the traditional GRADE approach for studies of the effects of interventions, observational studies of any study design are graded as low certainty and randomised trials are graded as high certainty at the outset (Guyatt 2011; Schünemann 2011). However, observational studies would be the appropriate study design for inclusion in our review and, therefore, they will begin as moderate certainty and be up- or down-graded in accordance with our assessment of their performance against the GRADE domains. We will assess the following criteria for downgrading the certainty of the methodology review evidence: limitations in the design (i.e. if and how much the risk of bias in included observational studies is likely to influence the results) (Guyatt 2011a);

indirectness of evidence (i.e. whether the definitions of industry funding, conflicts of interest, effect size, and favourable conclusions in the observational studies differ from the ones investigated in this methodology review) (Guyatt 2011b); inconsistency of results (i.e. whether the observational studies yield different estimates) (Guyatt 2011c); imprecision of results (i.e. whether the observational studies include few systematic reviews and thus have wide confidence intervals) (Guyatt 2011d); and publication bias (Guyatt 2011e). Finally, we will assess the following criteria for upgrading the certainty of the methodology review evidence: large magnitude of effect; dose-response gradient (i.e. more drastic conflicts of interests are associated with larger differences in effect); and plausible confounding, which can increase confidence in estimated effects (i.e. whether all unaccounted confounders and biases would result in underestimating the effect, which in this case seems unlikely) (Guyatt 2011f).

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* Indicates the major publication for the study

APPENDICES

Appendix I. PubMed search strategy

Block 1: drug, device, and imaging industry

1. Drug Industry (MeSH)
2. (Drug [Title/Abstract] OR drugs[Title/Abstract] OR pharmaceutical[Title/Abstract] OR pharmaceutic [Title/Abstract] OR pharmacological[Title/Abstract] OR pharma*[Title/Abstract] OR biotech*[Title/Abstract] OR biopharma*[Title/Abstract] OR biomed*[Title/Abstract] OR device[Title/Abstract] OR devices[Title/Abstract] OR imaging[Title/Abstract] OR for-profit[Title/Abstract]) OR private[Title/Abstract] AND (industry[Title/Abstract] OR industries[Title/Abstract] OR company[Title/Abstract] OR companies[Title/Abstract] OR manufacturer[Title/Abstract] OR manufacturers[Title/Abstract] OR organisation[Title/Abstract] OR organisations[Title/Abstract] OR organization[Title/Abstract] OR organizations[Title/Abstract] OR agency[Title/Abstract] OR agencies[Title/Abstract] OR sector[Title/Abstract] OR sectors[Title/Abstract])
3. Health[Title/Abstract] AND (industry[Title/Abstract] OR industries[Title/Abstract])
4. 1 OR 2 OR 3

Block 2: conflicts of interest and industry funding

5. Conflict of interest (MeSH)
6. Financial support (MeSH)

7. Research support as topic (MeSH)
8. (Conflict[Title/Abstract] OR conflicts[Title/Abstract] OR conflicting[Title/Abstract]) AND (interest[Title/Abstract] OR interests[Title/Abstract])
9. (Competing[Title/Abstract] OR vested[Title/Abstract]) AND (interest[Title/Abstract] OR interests[Title/Abstract])
10. (Industry[Title/Abstract] OR industries[Title/Abstract] OR company[Title/Abstract] OR companies[Title/Abstract] OR manufacturer[Title/Abstract] OR manufacturers[Title/Abstract] OR finance[Title/Abstract] OR financial[Title/Abstract]) AND (funded[Title/Abstract] OR funding[Title/Abstract] OR sponsor[Title/Abstract] OR sponsors[Title/Abstract] OR sponsorship[Title/Abstract] OR sponsoring[Title/Abstract] OR support[Title/Abstract] OR supported[Title/Abstract] OR finance[Title/Abstract] OR financial[Title/Abstract] OR involvement[Title/Abstract] OR involving[Title/Abstract] OR payment[Title/Abstract] OR payments[Title/Abstract] OR relationship[Title/Abstract] OR relationships[Title/Abstract] OR relation[Title/Abstract] OR relations[Title/Abstract] OR tie[Title/Abstract] OR ties[Title/Abstract])
11. Industry-funded[Title/Abstract] OR industry-funding[Title/Abstract] OR industry-sponsor*[Title/Abstract] OR company-funded[Title/Abstract] OR company-funding[Title/Abstract] OR company-sponsor*[Title/Abstract] OR industry-support[Title/Abstract] OR industry-supported[Title/Abstract] OR company-support[Title/Abstract] OR company-supported[Title/Abstract]
12. (Commercial-academic[Title/Abstract] OR academic-industry[Title/Abstract] OR commercial-industry[Title/Abstract] OR physician-industry[Title/Abstract]) AND (interface[Title/Abstract] OR interfaces[Title/Abstract] OR interaction[Title/Abstract] OR interactions[Title/Abstract] OR relationship[Title/Abstract] OR relationships[Title/Abstract] OR relation[Title/Abstract] OR relations[Title/Abstract])
13. 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12

Block 3: systematic reviews or meta-analyses

14. Review Literature as Topic (MeSH)
15. Meta-Analysis as Topic (MeSH)
16. Meta-analy*[Title/Abstract] OR metaanal*[Title/Abstract]
17. Meta[Title/Abstract] AND analy*[Title/Abstract]
18. (Systematic[Title/Abstract] OR systematically[Title/Abstract] OR systematical[Title/Abstract] OR Cochrane[Title/Abstract] OR literature[Title/Abstract] OR literatures[Title/Abstract]) AND (review[Title/Abstract] OR reviews[Title/Abstract] OR overview[Title/Abstract] OR overviews[Title/Abstract])
19. 14 OR 15 OR 16 OR 17 OR 18

Combined searches

18. 4 AND 13 AND 19

CONTRIBUTIONS OF AUTHORS

AL conceived the idea for the study. The protocol was developed primarily by CH, AH, AL; and PG contributed. CH, AL, and TFF developed the search strategy. CH and KR will include studies, and CH and AL will extract data and assess the risk of bias. All authors will participate in data analysis and writing of the review.

DECLARATIONS OF INTEREST

PG is co-author of two of the eligible observational studies. PG is not involved in the study inclusion and data extraction processes of this methodology review.

The review authors have no other relevant interests.

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Internal sources

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CH, AL, and AH are personally salaried by the institution during the period of this review.
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CH, KR, and PG are personally salaried by the institution during the period of this review.

External sources

- No sources of support supplied