
Conflicts of interest and recommendations in clinical guidelines, opinion pieces, and narrative reviews.

DOI: 10.1002/14651858.MR000040.pub2.

www.cochranelibrary.com
ABSTRACT

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

We will investigate whether:

- Clinical guidelines written by authors with financial or non-financial conflicts of interest are more likely to recommend an intervention;
- Opinion pieces written by authors with financial or non-financial conflicts of interest are more likely to recommend an intervention;
- Narrative reviews written by authors with financial or non-financial conflicts of interest are more likely to recommend an intervention.
**BACKGROUND**

Recommendations related to treatment and diagnostics impact on patient care, especially if they are written by “key opinion leaders” or come from healthcare authorities. Recommendations may appear in multiple types of publications (e.g., clinical guidelines) (Guyatt 2011; U.S. Preventive Services Task Force 2015), as well as in publications where the authors are free to selectively cite studies and interpret their results (e.g., opinion pieces such as editorials and commentaries, and narrative reviews).

Quite often, publications expressing treatment recommendations are authored by key opinion leaders with conflicts of interest related to the pharmaceutical or device industry. For example, in a sample of 150 editorials, Bariani et al. found that 47% of authors declared a financial conflict of interest (Bariani 2013). Even higher proportions of financial conflicts of interest were found among authors of clinical guidelines (87%) and narrative reviews (51%) (Choudhry 2002; Dunn 2016). Furthermore, Xu et al. found that 27% of a sample of committee meetings at the US Food and Drug Administration (FDA) included at least one voting member with financial conflicts of interest (Xu 2017).

Authors may also have non-financial conflicts of interest. For example, if an author of a guideline is also responsible for some of the trials or systematic reviews on which the guideline recommendations are based, this creates an intellectual conflict of interest (Akl 2014). Whereas financial conflicts of interest are relatively simple to characterise (i.e., any financial relationship with a party with an interest in the recommendation), it is more challenging and debated which interests and relationships constitute a non-financial conflict of interest. On one hand, a multitude of interests such as specialist interest, intellectual interest, personal beliefs, and personal relationships can be viewed as non-financial conflicts of interest (The PLoS Medicine Editors 2008; Viswanathan 2014). On the other hand, labelling personal beliefs and theoretical schools of thoughts as conflicts of interest risks muddying the waters since no researcher is interest free or free from intellectual pre-conceptions (Bero 2014; Bero 2016). The lack of consensus regarding what authors and editors view as a non-financial conflict of interest is also reflected in the variation in disclosure policies between journals. Shawwa et al. found that 57% of core clinical journals specifically required disclosure of non-financial conflicts of interest, but that there was large variation in the definition of such conflicts between journals (Shawwa 2016).

Numerous studies have investigated the impact of financial conflicts of interest and interpretation of the results of primary research studies, mainly in clinical trials. In an updated Cochrane Methodology Review, Lundh et al. found an association between industry sponsorship and favourable conclusions in primary research studies (Lundh 2017). This association has been attributed to various factors, including the sponsor’s influence on framing the question, study design, and reporting of results (Bero 2007; Bero 1996). Similarly, the authors of another Cochrane Methodology review found an association between financial conflicts of interest and conclusions in systematic reviews (Hansen 2017). In contrast, few observational studies have investigated the association between conflicts of interest and recommendations in clinical guidelines (Norris 2012), opinion pieces (Bariani 2013), and narrative reviews (Dunn 2016). Furthermore, the evidence from such observational studies has to our knowledge not been synthesised in a systematic review of research methodology.

**Description of the methods being investigated**

This review will identify, analyse, and summarise observational studies that examine the association between authors’ financial and non-financial conflicts of interest and their recommendations expressed in clinical guidelines, opinion pieces (e.g., editorials), and narrative reviews.

**How these methods might work**

Financial conflicts of interest such as honoraria, consultancies, grants, or membership of a speakers’ bureau or advisory board can provide substantial income for physicians and academic researchers. Such relationships may therefore affect how the benefits and harms of the companies’ products are perceived and thereby reflected in researchers’ recommendations. Similarly, non-financial conflicts of interests, such as how authors interpret the results of their own studies, may influence the recommendations for a particular intervention.

**Why it is important to do this review**

Recommendations in scientific articles or guidelines and decisions about which interventions are approved and available have substantial impact on the interventions offered to patients. It is therefore important that such recommendations are evidence-based and that bias is minimised. Despite being recognized as an important source of bias, the relationship between conflicts of interest and recommendations for medical interventions has, to our knowledge, not previously been studied in a systematic review. Other reviews have focused on assessing the association of sponsorship and outcomes of original research studies.

**Terminology**

We define ‘financial conflicts of interest’ according to the Institute of Medicine (US) as “a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest” (Institute of Medicine 2008). This would include, for example, employment, research grants, being on a speaker’s bureau, owning stocks, and consultancy work. We focus on financial conflicts of interest related to a drug, device, or medical imaging company. Financial conflicts of interest related to other companies (e.g. tobacco companies) will not be included. We will define ‘drugs’ as medications requiring approval from a regulatory authority as a prescription drug. We will define ‘devices’ according to the Food and Drug Administration (FDA) as instruments used in diagnosis, treatment, or prevention of disease (FDA 2017).

As there is no consensus concerning the definition of non-financial conflicts of interest, we will generally use the definition used by the authors of the included studies. If the authors do not use the term non-financial conflict of interest, we will use the following subcategories: personal and professional relationships (e.g. research collaboration), or intellectual and academic conflicts of interest (e.g. authorship of studies that are part of the evidence base for reaching a particular recommendation) (Akl 2014). We will not focus on studies investigating beliefs (e.g. political or religious), personal experience (e.g. abuse or trauma), or institutional conflicts of interest (Bero 2016). In some cases a relationship can be considered both a
financial and non-financial conflict of interest. For example, a surgeon who uses a particular surgical intervention which he/she then investigates in a clinical guideline. This can be viewed as a financial conflict of interest, because the surgeon might benefit financially if the intervention is recommended. It might also be viewed as a non-financial conflict of interest, because the surgeons use the surgical procedure themselves or may have conducted some of the studies included in the guideline. For this review, we will regard such relationships as non-financial because they differ from what is typically regarded as financial conflicts of interest (i.e. relationships with the drug or device industry).

We use the overall term ‘conflicts of interest’ to refer to both financial and non-financial conflicts of interest.

We use the term ‘clinical guidelines’ to refer to guidelines including committee reports. We define ‘clinical guidelines’ according to the Institute of Medicine as “statements that include recommendations intended to optimise patient care” (Institute of Medicine 2011). We will also use the term ‘clinical guideline’ to refer to ‘committee reports’ such as reports from meetings held in committees, boards, councils, or similar that are established to advise an organisation and provide a recommendation concerning an intervention (e.g. the Food and Drug Administration’s advisory committee on oncological drugs).

We define ‘opinion pieces’ as documents that are not empirical studies in which an author expresses a personal opinion about a specific intervention (e.g. editorials, commentaries, and letters-to-the-editors).

We define ‘narrative reviews’ as literature reviews without a systematic search for literature with clear eligibility criteria.

We use the term ‘documents’ to refer to clinical guidelines, opinion pieces, and narrative reviews included in the observational studies.

We use the term ‘included observational studies’ to refer to the studies we include in this Cochrane methodology review.

We use the term ‘certainty of the Cochrane methodology review evidence’ to refer to the certainty of the body of evidence of this methodology review. This assessment will be inspired by the GRADE approach and done according to the procedure described in the ‘Assessment of the certainty of the Cochrane methodology review evidence’ section (Schünemann 2008).

OBJECTIVES

We will investigate whether:

- Clinical guidelines written by authors with financial or non-financial conflicts of interest are more likely to recommend an intervention;
- Opinion pieces written by authors with financial or non-financial conflicts of interest are more likely to recommend an intervention;
- Narrative reviews written by authors with financial or non-financial conflicts of interest are more likely to recommend an intervention.

METHODS

Criteria for considering studies for this review

Types of studies

We will include observational studies of any design that assess the association between conflicts of interest and recommendations expressed in clinical guidelines, opinion pieces, or narrative reviews concerning drug, device, or diagnostic interventions. If the sample of documents included in an observational study contains a mixture of, for example, clinical guidelines and original research, we will include the observational study, but only include the study in our pooled analyses if we can separate the data for clinical guidelines.

We will include observational studies if the authors use the term financial conflicts of interest or the term non-financial conflicts of interest. If the authors do not use the term non-financial conflicts of interest, we will include the observational study if it concerns intellectual, academic, professional, or specialist interests and personal or professional relationships.

Studies in all languages will be eligible.

We will exclude observational studies concerning financial conflicts of interest not related to the device, drug, or medical imaging industry (e.g. tobacco or nutrition industry).

We will exclude observational studies concerning beliefs (e.g. religious) or personal experiences (e.g. suffering from the medical condition), even if the original authors defined this as non-financial conflicts of interest.

We will exclude observational studies concerning membership of certain groups (i.e. gender or ethnicity) even if the original authors defined this as non-financial conflicts of interest.

We will exclude observational studies concerning both financial and non-financial conflicts of interest at the level of an institution.

We will exclude studies concerning conflicts of interest related to committee reports for grants.

Types of data

We will include dichotomous (e.g. number of events) or continuous data (e.g. percentages) on the association between conflicts of interest and favourability of recommendations. These types of data will include, for example, odds ratios, 95% confidence intervals, and p-values.

Types of methods

We will investigate financial and non-financial conflicts of interest. Thus, we will compare favourability of recommendations between documents with and without conflicts of interest.

Types of outcome measures

Primary outcomes

The primary outcomes will be direction of recommendations in clinical guidelines, opinion pieces, and narrative reviews. We define ‘favourable recommendations’ according to the definitions used by the authors of the observational studies.
Search methods for identification of studies

Electronic searches
PubMed, Embase, and the Cochrane Methodology Register will be searched. We will search Web of Science for studies that cite any of the observational studies that we include.

Search strategy
Our search strategy is based on search terms used in a PubMed search from two other Cochrane Methodology Reviews (Lundh 2017; Hansen 2017) on financial conflicts of interest in primary research studies and systematic reviews, and tailored for this review (Appendix 1). The strategy will be adapted for and applied to Embase and The Cochrane Methodology Register.

Searching other resources
Grey literature
Our electronic search in the Cochrane Methodology Register will identify relevant grey literature as the database includes conference abstracts. We will search for conference abstracts from Peer Review Congresses (American Medical Association 2017), Cochrane Colloquia (Cochrane Community 2017), and Evidence Live (Centre for Evidence-Based Medicine 2017). We will search PROSPERO for registered systematic reviews and the ProQuest database for dissertations and theses.

Additional searches
We will use Google Scholar to search for additional eligible observational studies. We will base our search on core search terms from the search strategy defined in Appendix 1 and screen the first 20 records for each search. Other sources of data will include the files of the authors of this review and checking reference lists of included 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 AWJ) will independently assess potentially eligible observational studies based on full text. Any disagreements will be resolved by discussion and arbitration when needed by the third review author (AL).

Reasons for exclusion of potentially eligible observational studies will be described in the final report in the 'Characteristics of excluded studies Table'. Papers published in languages other than English will be translated when feasible.

Data extraction and management
Two review authors (CH and AWJ/ML) will extract data from included observational studies, independently. Any difference in data extraction will be resolved with arbitration when needed by a third review author (AH). If necessary, we will contact authors of the observational studies for information or data relevant for the review that were not clear from the reporting of the observational study (Young 2011). For each included observational study, we will search for published protocols. If not published or otherwise available online, we will ask authors for their protocols. Data on study characteristics and outcome data will be extracted on the following:

Study characteristics
- Title
- Name of first author
- Name of journal
- Year published
- Primary aim of the study
- Design of study: cohort, cross-sectional study, systematic review or meta-analysis, or other
- Study domain - category: clinical guideline, committee report, opinion pieces, narrative review, or mixed
- Sample description including document type, disease area, and region (specific country or international). For example, European clinical guidelines on treatment of hypertension
- Strategy used to collect sample: for example search of PubMed. Date of sample and time period covered
- Definition of clinical guidelines, committee reports, opinion pieces, or narrative reviews used in the observational study. Verbatim extraction
- Number of included documents (separate data for clinical guidelines, opinion pieces, and narrative reviews) examined in the observational study
- Types of documents included in the observational study. Verbatim extraction
- Types of documents included in the observational study (drug, device, medical imaging)

Conflicts of interest and outcome data
- Definition of financial conflicts of interest used in the observational study. Verbatim extraction
- Definition of non-financial conflicts of interest used in the observational study. Verbatim extraction
- Types of financial conflicts of interest investigated, potential categories are:
  * Funding
  * Grant
  * Honorarium
  * Consulting
  * Speakers bureau
- Types of non-financial conflicts of interest investigated, potential categories are:
  * Academic or intellectual
  * Professional or specialist
  * Personal or professional relationships
- Definition of favourable recommendations used by the authors of the observational study. Verbatim extraction
- Definition of primary analysis used in the observational study. Verbatim extraction
- Total number of documents with and without conflicts of interest. Stratified by types of document (i.e. clinical guideline, opinion piece, narrative review) and type of conflicts of interest (i.e. financial and non-financial)
- Number of documents with and without conflicts of interest with favourable recommendations stratified by types of documents (i.e. clinical guideline, opinion piece, narrative review) and type of conflicts of interest (i.e. financial and non-financial)
• Any data on estimates of the association between financial and non-financial conflicts of interest and recommendations in clinical guidelines, opinion pieces, and narrative reviews (for example, adjusted effect estimates and confidence intervals).

The full plan for data extraction is shown in Appendix 2.

Assessment of risk of bias in included studies

As there are no published assessment tools for investigating bias in these types of studies, we have developed our own criteria based on criteria use in previous Cochrane Methodology Reviews on financial conflicts of interest in primary research studies and systematic reviews (Lundh 2017; Hansen 2017).

Two review authors (CH and AWJ/ML) will independently review observational studies for risk of bias. Any disagreements will be resolved by discussion and arbitration when needed by a third review author (AH). We will contact authors of the observational studies for additional information when information is not clear from the reporting. We will use the following criteria:

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

• Whether there was a risk of bias in the coding of conflicts of interest (low risk of bias may, for example, include a coding done by two or more assessors based on multiple sources).

• Whether there was a risk of bias in the coding of recommendations (low risk of bias may, for example, include a coding done by two or more assessor blinded to the status of conflicts of interest).

• Whether there was a risk of bias in the comparability of investigated documents (low risk of bias may, for example, include documents with and without conflicts of interest discussing the same treatment used in similar groups of patients).

In assessing risk of bias, our primary aim is to differentiate between observational 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.

Dealing with missing data

Authors of the included observational studies will be contacted in an attempt to obtain unpublished data (Young 2011). For example, if a study includes both opinion pieces and original research, but does not report the results separately, we will try to obtain data for the opinion pieces.

Assessment of heterogeneity

Statistical heterogeneity will be described using the I² statistic. We define substantial heterogeneity as I²>50%.

To further address statistical heterogeneity, we will calculate prediction intervals for our primary outcomes. A prediction interval presents the expected range of true effects in similar studies, is not influenced by sample size, and shows whether the study effects are dispersed over a wide range (IntHout 2016). A prediction interval thereby shows the range of risk ratios that can be expected from similar studies, and, thus, a broad prediction interval indicates heterogeneity and uncertainty. To calculate prediction intervals, we will use the formula presented by Riley et al (Riley 2011) (Appendix 3).

Data synthesis

We plan to calculate pooled risk ratios with 95% confidence intervals using random-effects models. We will compare recommendations between documents with and without conflicts of interest. In our primary analyses, we will analyse financial and non-financial conflicts of interests separately, and analyse clinical guidelines, opinion pieces, and narrative reviews separately. In our primary analyses, we will use the definitions and coding of recommendations, conflicts of interest, clinical guidelines, opinion pieces, and narrative reviews used by the authors of the observational studies. If meta-analysis is not meaningful (e.g. due to considerable methodological and clinical heterogeneity between studies), the results will be reported qualitatively.

If the authors of the observational studies measure the outcome by using a scale (e.g. highly positive, positive, neutral, negative, and highly negative (Bariani 2013)) and dichotomise this scale into two categories (e.g. recommending and not recommending), we will use the dichotomising strategy of the authors of the observational studies. If the authors do not dichotomise the outcome, we will try to dichotomise it based on what is done in the majority of observational studies.

If the observational studies contain a mixture of documents and original research (e.g. clinical trials) and the authors cannot provide us with separate data, we will report the observational study qualitatively.

Subgroup analysis and investigation of heterogeneity

We plan to conduct the following subgroup analyses for our primary analyses:

1. Documents stratified by different types of financial conflicts of interest (e.g. funding, investigator, grants, honorarium, consulting, speaker’s bureau, equity/stock, gifts

2. Clinical guidelines following methodological procedures (e.g. GRADE (Guyatt 2011) or USPSTF (U.S. Preventive Services Task Force 2015)) versus clinical guidelines not following methodological procedures versus committee reports. For the division of documents, we will rely on the coding done by the authors of the included observational studies

3. Observational studies assessed as high risk of bias versus observational studies assessed as low risk of bias

Sensitivity analysis

We plan to conduct the following sensitivity analyses for our primary analyses:

1. Excluding documents with unclear or undeclared conflicts of interest for observational studies where data is available

2. Excluding neutral recommendations from the category of ‘not recommending’ for observational studies where data is available

3. Excluding all observational studies which declare a relevant conflict of interest. For example, if one of the included observational studies is funded by a pharmaceutical company, we will exclude this study and re-analyse our data
4. Re-analysing our primary analyses using fixed-effect meta-analyses, if applicable

We plan to conduct all analyses in Review Manager (RevMan 5.3).

Assessment of the certainty of the evidence

We will assess the certainty of the evidence for each of our primary outcomes as high, moderate, low, or very low. Inspired by the GRADE approach, we will base the initial assessment on the study design of the observational studies assessing each primary outcome. In the traditional GRADE approach, observational studies are graded as low certainty and randomised trials as high certainty (Guyatt 2011; Schünemann 2008). However, observational studies would be the appropriate study design for inclusion in our review and, therefore we will regard observational studies as moderate certainty and up- or downgrade in accordance with our assessment of the GRADE domains.

We will assess the following criteria for downgrading the certainty: limitations in the study design, indirectness of evidence, inconsistency of results, imprecision of results, and publication bias. We will assess the following criteria for upgrading the certainty of the methodology review evidence: large effect, dose-response gradient, and plausible confounding could increase confidence in estimated effects (Guyatt 2011).

The certainty of the evidence in our review will be assessed by two review authors (CH and AL) independently and final agreement will be discussed by all review authors.

ACKNOWLEDGEMENTS

We thank Gloria Won, from UCSF Medical Center at Mount Zion, for developing our initial search strategy for an earlier version of this protocol. We thank Herdis Foverskov, from The Medical Research Library at Odense University Hospital, for valuable help in developing and adjusting the search strategies.
REFERENCEs

Additional references

Akl 2014

American Medical Association 2017

Bariani 2013

Bero 1996

Bero 2007

Bero 2014
Bero L. What is in a name? Nonfinancial influences on the outcomes of systematic reviews and guidelines. *Journal of Clinical Epidemiology* 2014;67(11):1239-41. [DOI: 10.1016/j.jclinepi.2014.06.015]

Bero 2016

Centre for Evidence-Based Medicine 2017

Choudhry 2002

Cochrane Community 2017

Dunn 2016

FDA 2017

Guyatt 2011

Hansen 2017

Horsley 2011

Institute of Medicine 2009

Institute of Medicine 2011

IntHout 2016
Appendix 1. PubMed search strategy

Block 1A: drug, device, and imaging industry

1. Drug Industry (MeSH)
2. Manufacturing Industry (MeSH)


4. Personal[Title] OR self-reported[Title] OR selfreported[Title] OR author[Title] OR authors[Title] OR authorship[Title] OR committee[Title] OR board[Title] AND (member[Title] OR members[Title]) OR voting[Title] OR votings[Title] OR financial[Title] OR finance[Title]

5. 1 OR 2 OR 3 OR 4

Block 1B: financial conflicts of interest

6. Conflict of interest (MeSH)
7. Financial support (MeSH)
8. Research support as topic (MeSH)

9. (Conflict[Title/Abstract] OR conflicts[Title/Abstract] OR conflicting[Title/Abstract]) AND (interest[Title/Abstract] OR interests[Title/Abstract])
Conflicts of interest and recommendations in clinical guidelines, opinion pieces, and narrative reviews (Protocol)

10. (Competing[Title/Abstract] OR vested[Title/Abstract]) AND (interest[Title/Abstract] OR interests[Title/Abstract])


14. 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13

**Block 2A: non-financial, personal, and academic**

15. Non-financial[Title/Abstract] OR nonfinancial[Title/Abstract]

16. Personal[Title] OR individual[Title] OR self-reported[Title] OR selfreported[Title] OR author[Title] OR authors[Title] OR authorship[Title]


18. 15 OR 16 OR 17

**Block 2B: non-financial conflicts of interest**

19. Conflict of interest (MeSH)

20. Conflict[Title] OR conflicts[Title] OR conflicting[Title] OR competing[Title] OR vested[Title]

21. Relation[Title] OR relations[Title] OR relationship[Title] OR relationships[Title]

22. Interest[Title] OR interests[Title]

23. 19 OR 20 OR 21 OR 22

**Block 3: clinical guidelines, opinion pieces, and narrative reviews**


Conflicts of interest and recommendations in clinical guidelines, opinion pieces, and narrative reviews (Protocol)

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
29. Guidelines as Topic (MeSH)

30. Health Planning Guidelines (MeSH)

31. (Clinical[Title] OR clinic[Title] OR health[Title] OR practice[Title]) AND (guideline[Title] OR guidelines[Title] OR recommendation[Title] OR recommendations[Title])


33. 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32

Combined searches

35. 5 AND 14

36. 19 AND 24

37. (35 OR 36) AND 34

Appendix 2. Data extraction

Study characteristics

- Title
- Name of first author
- Name of journal
- Year published
- Primary aim of the study
- Design of study: cohort, cross-sectional study, systematic review or meta-analysis, or other
- Study domain - category: clinical guideline, committee report, opinion pieces, narrative review, or mixed
- Sample description: for example, clinical guidelines on treatment of hypertension
- Strategy used to collect sample: for example search of PubMed. Time period covered
- Definition of clinical guidelines, committee reports, opinion pieces, or narrative reviews used in the observational study. Verbatim extraction
- Number of included documents (separate data for clinical guidelines, opinion pieces, and narrative reviews) examined in the observational study
- Types of documents included in the observational study. Verbatim extraction
- Types of documents included in the observational study (drug, device, medical imaging)

Conflict of interest and outcome data

- Definition of financial conflicts of interest used in the observational study. Verbatim extraction
- Definition of non-financial conflicts of interest used in the observational study. Verbatim extraction
- Types of financial conflicts of interest investigated, potential categories are:
  * Funding;
  * Grant;
  * Honorarium;
  * Consulting;
  * Speakers bureau;
- Types of non-financial conflicts of interest investigated, potential categories are:
  * Personal beliefs
  * Receiving income as part of employment
- Definition of favourable recommendations used by the authors of the observational study. Verbatim extraction
- Definition of primary analysis used in the observational study. Verbatim extraction
- Total number of documents with and without conflicts of interest. Stratified by types of document (i.e. clinical guideline, opinion piece, narrative review) and type of conflicts of interest (i.e. financial and non-financial)
• Number of documents with and without conflicts of interest with favourable recommendations stratified by types of documents (i.e. clinical guideline, opinion piece, narrative review) and type of conflicts of interest (i.e. financial and non-financial)
• Any data on estimates of the association between financial and non-financial conflicts of interest and recommendations in clinical guidelines, opinion pieces, and narrative reviews (for example, adjusted effect estimates and confidence intervals).

Data for informing subgroup analyses or reflection on heterogeneity

• Total number of documents with conflicts of interest and number with favourable recommendations. Stratified by document type (i.e. clinical guidelines, opinion pieces, and narrative reviews) and category of financial conflicts of interest (e.g. investigator, grants, honorarium, consulting, speaker’s bureau, equity/stock, gifts)
• Total number of documents without conflicts of interest and number with favourable recommendations
• Any data on the association between each category of financial conflicts of interest and favourable recommendations
• Total number of clinical guidelines following methodological procedures with and without conflicts of interest and number with favourable recommendations. Stratified by type of conflicts of interest (i.e. financial and non-financial)
• Total number of clinical guidelines not following methodological procedures with and without conflicts of interest and number with favourable recommendations. Stratified by type of conflicts of interest (i.e. financial and non-financial)
• Total number of committee reports with and without conflicts of interest and number with favourable recommendations. Stratified by type of conflicts of interest (i.e. financial and non-financial)
• Any data on the association between conflicts of interest and favourable recommendations for clinical guidelines following methodological procedures, clinical guidelines not following methodological procedures, and committee reports, separately

Data for performing sensitivity analyses

• Total number of documents with and without conflicts of interest and number of documents in each group with favourable recommendations, when excluding documents with unclear or undeclared conflicts of interest. Stratified by document type (i.e. clinical guidelines, opinion pieces, and narrative reviews) and type of conflicts of interest (i.e. financial and non-financial)
• Any data on the association between conflicts of interest and favourable recommendations, when excluding documents with unclear or undeclared conflicts of interest
• Total number of documents with and without conflicts of interest and number of documents in each group with favourable recommendations, when excluding documents with neutral recommendations. Stratified by document type (i.e. clinical guidelines, opinion pieces, and narrative reviews) and type of conflicts of interest (i.e. financial and non-financial)
• Any data on the association between conflicts of interest and favourable recommendations, when excluding documents with neutral recommendations

Additional data

• Additional relevant information
• Conflicts of interest statement in the observational study. Verbatim extraction

Appendix 3. Calculation of prediction intervals

To calculate prediction intervals, we will use the formula presented in an article by Riley et al (Riley 2011):

\[ \hat{u} - t_{k-2} \cdot \sqrt{T^2 + SE(\hat{u})^2}, \hat{u} + t_{k-2} \cdot \sqrt{T^2 + SE(\hat{u})^2} \]

Where \( \hat{u} \) is the estimate of the average effect measure across studies, \( SE(\hat{u}) \) is the standard error of \( \hat{u} \), \( T \) is the estimate of between-study standard deviation, and \( t_{k-2} \) is the \( 100(1-(\alpha/2)) \) percentile of the \( t \)-distribution with \( k-2 \) degrees of freedom, where \( k \) is the number of observational studies in the meta-analysis and is 0.05 to give a 95% prediction interval (Riley 2011). To meet the assumption on normal distribution, the prediction interval is derived on the natural log scale (Riley 2011). As \( T^2 \) is already a measure for the heterogeneity for \( \ln(\text{RR}) \), this will be used directly in the calculation (IntHout 2016).

WHAT'S NEW

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 October 2019</td>
<td>Amended</td>
<td>This protocol was re-published in October 2019 to generate a new citation, reflecting the change in title and authorship from the original version (Lundh A, Jørgensen AW, Bero L. Association between personal conflicts of interest and recommendations</td>
</tr>
</tbody>
</table>


**CONTRIBUTIONS OF AUTHORS**

AL conceived the idea for the study. The protocol was developed primarily by CH, AH, and AL. LB, KJJ, and AWJ contributed. CH and ML/AWJ will assess studies for inclusion; CH and ML/AWJ will extract data and assess studies for risk of bias. CH will perform the data analysis, and all authors will participate in data interpretation. CH will write the draft review and all authors will contribute in revising the review.

**DECLARATIONS OF INTEREST**

We declare that we have no conflicts of interest.

**SOURCES OF SUPPORT**

**Internal sources**

- Center for Evidence-Based Medicine, Odense University Hospital and University of Southern Denmark, Denmark.
  
  CH, AH, and AL are personally salaried by this institution during the period of the review

- The Nordic Cochrane Centre, Rigshospitalet, Copenhagen, Denmark.
  
  CH and KJJ are personally salaried by this institution during the period of the review

- Charles Perkins Centre and Faculty of Pharmacy, University of Sydney, Sydney, Australia.
  
  LB is personally salaried by this institution during the period of the review

- Otorhinolaryngology and Head & Neck Surgery, Aarhus, Denmark.
  
  AWJ is personally salaried by this institution during the period of the review

- Department of Infectious Diseases, Hvidovre Hospital, Copenhagen, Denmark.
  
  AL is personally salaried by this institution during the period of the review

**External sources**

- No sources of support supplied

---

Conflicts of interest and recommendations in clinical guidelines, opinion pieces, and narrative reviews (Protocol)

Copyright © 2019 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.