

## Highlights

- Methods to assess risk of bias in a way that is reliable, reproducible and transparent to readers, have evolved over time.
- Viswanathan et al. recently provided updated recommendations for assessing risk of bias in systematic reviews of health care interventions.
- We comment on their recommendations, and discuss new tools in development that we, as co-convenors and coordinators of the Cochrane Bias Methods Group, are leading, which complement the methods recommended.

# Assessing risk of bias in studies that evaluate health care interventions: recommendations in the misinformation age

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## Abstract

Methods to assess risk of bias in a way that is reliable, reproducible and transparent to readers, have evolved over time. Viswanathan et al. recently provided updated recommendations for assessing risk of bias in systematic reviews of health care interventions. We comment on their recommendations, and discuss new tools in development that we, as co-convenors and coordinators of the Cochrane Bias Methods Group, are leading, which complement the methods recommended.

**Keywords:** Bias; Methodology; Quality; Randomized trials; Non-randomized studies; Systematic reviews

## 1. Introduction

There is empirical evidence that flaws in the design and conduct of intervention studies are associated with biased estimates of treatment benefits and harms (1, 2). Failure to consider potential biases can lead to the adoption of ineffective and unsafe interventions in clinical practice. The ability to assess the trustworthiness of research results is therefore an indispensable skill, which is becoming even more valuable in this age of misinformation and “alternative facts” (3, 4). International guidance for the conduct and reporting of systematic reviews suggests that the assessment of the risk of bias in the included studies is a key feature of a credible evidence synthesis (5-8). However, the methods required to assess risk of bias in a way that is reliable, reproducible and transparent to readers, have evolved over time (9).

In this issue of the *Journal of Clinical Epidemiology*, Viswanathan et al. describe recommendations for assessing risk of bias in randomized and non-randomized studies that evaluate health care interventions (10). The guidance updates that provided in 2012 and included in the United States *Agency for Healthcare Research & Quality (AHRQ) Methods Guide for Comparative Effectiveness Reviews* (11). We comment on the recommendations, and discuss new tools in development that we, as co-convenors and coordinators of the Cochrane Bias Methods Group, are leading, which complement the methods recommended.

## 2. Summary of the recommendations by Viswanathan et al.

Viswanathan et al. (10) provide the following key suggestions for assessing risk of bias in randomized trials and non-randomized studies of interventions (NRSI). Risk of bias assessment should be separated from assessment of other issues, such as precision of effect estimates, applicability, and conflicts of interest in included studies. Methods for assessing risk of bias should be pre-specified in the review protocol. When selecting risk of bias domains to assess, systematic reviewers should

consider domains included in the framework underpinning the ROBINS-I (Risk Of Bias In Non-randomized Studies of Interventions) tool (12). That is, reviewers should consider problems arising from the randomization process in randomized trials, and bias due to confounding, selection of participants and misclassification of interventions in NRSI, along with bias due to deviations from intended interventions, missing data, measurement of outcomes, and selective outcome reporting in both randomized trials and NRSI. Methods to reduce uncertainty in assessments should be used, such as assessment of studies by two authors independently, or some combination of human effort with machine automation (e.g. human review of assessments made by machine learning methods). Domain-level judgements with supporting details (e.g. quotes of methods reported) should be presented in lieu of numerical “quality scores”, to aid transparency and reproducibility of assessments (10).

### **3. Comparison with the approach advocated by the Cochrane Bias Methods Group co-convenors**

To a considerable extent, Viswanathan et al. (10) provide an endorsement of generally accepted principles for risk of bias assessment that have been developed and refined by methodological researchers often associated with Cochrane. The recommendations described above are largely consistent with the 2011 Cochrane Handbook recommendations (7) and the frameworks used to develop the ROBINS-I tool (12) and the revised Cochrane tool for assessing risk of bias in randomized trials (RoB 2.0) (13). However, there are several areas where we propose alternative recommendations.

Viswanathan et al. (10) suggest that systematic reviewers consider assessing risk of bias on a per-outcome basis, given that some outcomes in a study may be more prone to bias than others (e.g. the risk of bias in effect estimates for all-cause mortality and patient-reported pain are likely to differ in a trial that cannot blind participants to the assigned intervention). We agree with this sentiment, but

think it should go one step further in recommending result-level assessments, which are even more specific than outcome-level assessments. For example, if two results are available for a single outcome, such as pain, one adjusted for confounders and the other not, the risk of bias may differ for the two results. Therefore, consistent with the ROBINS-I (12) and RoB 2.0 (13) tools, we encourage reviewers to make assessments specific to a particular result.

In addition, we have some concerns with the suggestion that systematic reviewers should select “...the most important categories of bias for the outcome(s) and topic at hand” (10). This suggests that domains already included in existing tools could be modified on a per-review basis, with particular domains added or removed based on the preference of the systematic reviewer.

Modification of existing tools occurs frequently in practice; for example, in an audit of 100 Cochrane reviews published in 2014, the domains, “blinding of participants and caregivers” and “blinding of outcome assessors” had been omitted from the Cochrane risk of bias tool (14) in 38% and 35% of reviews, respectively (15). In our view, such modifications are inadvisable; allowing users to remove certain domains that they deem not applicable (e.g. because it is not possible to blind participants to the intervention) means that important bias domains are ignored inappropriately. Likewise, review authors should not add additional domains to these tools. Both ROBINS-I (12) and RoB 2.0 (13) include a fixed set of mechanistically defined bias domains, selected based on empirical evidence and wide consultation with methodologists, statisticians, epidemiologists, trialists and systematic reviewers. The included domains are intended to cover all issues that might lead to risk of bias in all NRSI and trials, respectively.

#### **4. Unresolved issues in risk of bias assessment**

There are several unresolved issues in assessing risk of bias in studies. The suggested move from study-level to results-level assessments begs several questions, including: how many results in each

study should be assessed? And if not all results need to be assessed, which should be prioritised?

And how can this new approach to risk of bias assessment be incorporated into the data collection process? In addition, systematic reviewers are advised to consider not only the risk of bias, but also the direction of the bias (i.e. which of the interventions being compared is the bias predicted to favour). However, there is currently very little guidance as to how to reach such judgements. Also, whether and if so, how, to take account of risk of bias in meta-analyses, is an issue of ongoing research (2, 16). We anticipate that guidance for risk of bias assessment will need to be updated in future once these issues are resolved.

## **5. New tools in development**

We are leading or involved in the development of two tools which will complement the assessment of risk of bias in included studies. The first is a new Tool for Addressing Conflicts of Interest in Trials (TACIT). There has long been concern that trial stakeholders' conflicts of interests may have influenced the design, conduct, analysis or reporting of an individual trial (17), yet this issue is poorly addressed in existing systematic reviews (15). The TACIT tool is intended to facilitate gathering and processing of information related to conflicts of interest. Such information may inform the assessment of the core domains of the risk of bias tool (e.g. selective reporting of outcomes) and assessment of the certainty of the evidence of the review result.

The second initiative is a new tool to assess the risk that a synthesis is affected by reporting biases, which can arise when some evidence is missing because of the nature of the findings (e.g. results that are unfavourable to the experimental intervention are not reported) (18). This tool will guide users to consider risk of bias in a synthesis due to both selective publication of whole studies and selective non-reporting of outcomes within study reports, given that both practices lead to the same consequence: evidence missing from the synthesis (19). The tool will complement the ROBINS-I (12)

and RoB 2.0 (13) tools, which include a domain for assessing the risk of bias in selection of a fully reported result, but no mechanism to assess risk of bias due to selective non-reporting.

Once completed, we will provide links to these tools on the Cochrane Bias Methods Group website (<http://methods.cochrane.org/bias/>). In addition, readers should look out for Version 6 of the *Cochrane Handbook for Systematic Reviews of Interventions*, scheduled for release in late 2018, which will provide updated guidance for the assessment of risk of bias, conflicts of interest and reporting biases in systematic reviews of interventions (<http://training.cochrane.org/handbook>).

## 6. Conclusion

The assessment of the risk of bias in studies that evaluate health care interventions should be considered a routine procedure in evidence syntheses. Doing so should help health care decision makers sift evidence that is trustworthy from that which is not. Methods for assessment should continue to evolve, based on the findings of new empirical evidence of bias and perceived usability by systematic reviewers.

## Competing Interests

We have read the journal's policy and the authors of this manuscript have the following competing interests: MJP, IB and AH were members of the core group who developed the RoB 2.0 tool for assessing risk of bias in randomized trials. IB, DGA and AH participated in the development of the ROBINS-I tool for assessing risk of bias in non-randomized studies of interventions. MJP, IB and AH are leading or contributing to the development of new tools for assessing risk of reporting biases in systematic reviews, and conflicts of interest in randomized trials. MJP, IB, DGA and AH are co-convenors of the Cochrane Bias Methods Group, and CH is coordinator of the Group. The views



expressed in this manuscript are those of the authors and not necessarily those of Cochrane or its registered entities, committees, or working groups.

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### **Author Contributions**

All authors declare that they meet the ICMJE conditions for authorship. MJP wrote the first draft of the manuscript. All authors contributed to revisions of the manuscript. All authors approved the final version of the submitted manuscript.

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