Cochrane Learning live webinar: May 7th 2020: Introduction to RoB2

Introduction to RoB 2
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With special thanks to Jelena Savović, Matthew Page, Roy Elbers, Barney Reeves, Asbjørn Hróbjartsson, Isabelle Boutron, Luke McGuinness, Vincent Cheng and all RoB 2 collaborators
RoB 2: contributors

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Contributors:

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• The original tool was developed with support from a Cochrane Quality Improvement Project grant and its evaluation and early revisions by the Cochrane Methods Innovation Fund
Session outline

- From the original Cochrane risk of bias tool to RoB 2
  - Introductory and historical remarks
  - Why RoB 2?
- An overview of RoB 2
  - Domains of bias covered
  - Specifying the effect of interest
  - Signalling questions and risk of bias judgements
  - Resources available
- Using RoB 2 in a Cochrane Review
- What to write about in a protocol
- Questions
What is bias?

Systematic error or deviation from the truth

- a study may systematically overestimate or underestimate the effect of intervention
  - beyond random error (sampling variation)

- our focus is on **internal validity**
  - whether the result reflects what the study aims to estimate
  - distinct from **external validity** (generalizability): the relevance of the study to external situations
<table>
<thead>
<tr>
<th>Low quality</th>
<th>Poor reporting</th>
<th>Imprecision</th>
</tr>
</thead>
<tbody>
<tr>
<td>• bias can occur in well-conducted studies</td>
<td>• good methods may have been used but not well reported</td>
<td>• error due to sampling variation</td>
</tr>
<tr>
<td>• not all methodological flaws introduce bias</td>
<td>• inappropriate methods may have been used but not clearly described</td>
<td>• reflected in the confidence interval</td>
</tr>
</tbody>
</table>
Quality scales and checklists

- many scales and checklists are available
  - but many include criteria not related to bias
- different scales lead to different conclusions
- **numerical scales are not justified**
  - There is no empirical basis for weighting different items

**Quality scales should not be used in Cochrane**
Assessing risk of bias in included studies

Edited by Julian PT Higgins and Douglas G Altman on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group

Key Points

- Problems with the design and execution of individual studies of healthcare interventions raise questions about the validity of their findings; empirical evidence provides support for this concern.

- An assessment of the validity of studies included in a Cochrane review should emphasize the risk of bias in their results, i.e. the risk that they will overestimate or underestimate the true intervention effect.

- Numerous tools are available for assessing methodological quality of clinical trials. We recommend against the use of scales yielding a summary score.

- The Cochrane Collaboration recommends a specific tool for assessing risk of bias in each included study. This comprises a description and a judgement for each entry in a ‘Risk of bias’ table, where each entry addresses a specific feature of the study. The judgement for each entry involves answering a question, with answers ‘Yes’ indicating low risk of bias, ‘No’ indicating high risk of bias, and ‘Unclear’ indicating either lack of information or uncertainty over the potential for bias.

SUMMARY POINTS

Systematic reviews should carefully consider the potential limitations of the included studies.

The Cochrane Collaboration has developed a new tool for assessing risk of bias in randomised trials.

The tool separates a judgement about risk of bias from a description of the support for that judgement, for a series of items covering different domains of bias.

The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials can cause the effect of an intervention to be underestimated or overestimated. The Cochrane Collaboration’s tool for assessing risk of bias aims to make the process clearer and more accurate.

Randomised trials, and systematic reviews of such trials, provide the most reliable evidence about the effects of healthcare interventions. Provided that there are enough participants, randomisation should ensure that participants in the intervention and comparison groups are similar with respect to both known and unknown prognostic factors. Differences in outcomes of interest between the different groups can then in principle be ascribed to the causal effect of the intervention. Causal inferences from randomised trials can, however, be undermined by flaws in design, conduct, analyses, and reporting, leading to underestimation or overestimation of the true intervention effect (bias). However, it is usually impossible to know the extent to which biases have affected the results of a particular trial.

Systematic reviews aim to collate and synthesise all studies that meet prespecified eligibility criteria, using methods that attempt to minimise bias. To obtain reliable conclusions, review authors must carefully consider the potential limitations of the included studies. The notion of study “quality” is not well defined, but relates to the extent to which its design, conduct, analysis, and presentation were appropriate to answer the research question. Many tools for assessing the quality of randomised trials are available, including scales (which score the trials) and checklists (which assess trials without producing a score). Until recently, Cochrane reviews used a variety of these tools, mainly checklists. In 2005 the Cochrane Collaboration’s methods group embarked on a new strategy for assessing the quality of randomised trials. In this paper we describe the collaboration’s new risk of bias assessment tool, and the process by which it was developed and evaluated.
Have you used the original (2008 or 2011) version of the Cochrane risk of bias tool?
Biases in Randomized Trials

A Conversation Between Trialists and Epidemiologists


Abstract: Trialists and epidemiologists often employ different terminology to refer to biases in randomized trials and observational studies, even though many biases have a similar structure in both types of study. We use causal diagrams to represent the structure of biases, as described by Cochrane for randomized trials, and provide a translation to the usual epidemiologic terms of confounding, selection bias, and measurement bias. This structural approach clarifies that an explicit description of the inferential goal—the intention-to-treat effect or the per-protocol effect—is necessary to assess risk of effects associated with receiving an intervention (placebo effects), may facilitate blinding of outcome assessors, and may improve adherence.

Widespread use of masking and of intention-to-treat analyses became established by regulatory requirements, which privileged intention-to-treat analyses of double-blind placebo-controlled RCTs to assess the efficacy of drugs before licensing. However, masking is sometimes not feasible (e.g., in surgical trials), and may not even be desirable (e.g., in
Some issues raised with existing tool

- Used simplistically: guidance not followed
- Used inconsistently: domains added or removed
- Modest agreement rates
- Overuse of “unclear” judgement, itself ambiguous
- Some domains too complex, particularly incomplete outcome data and selective reporting
- Challenges with unblinded trials
- Not well suited to cross-over trials or cluster-randomized trials
- No overall risk of bias judgement
Why a new version?

More appropriate
- more comprehensive
- versions appropriate to cluster-randomized trials, cross-over trials

More usable and (we hope) reliable
- more structure to improve consistency
- clearer guidance; in-built help in reaching judgements

More current
- incorporates developments in the science (particularly missing data, unblinded trials)

More useful
- overall risk of bias judgement feeds into sensitivity analyses/exploration of heterogeneity
- allied to ROBINS-I for non-randomized studies
**RoB 2: a revised tool for assessing risk of bias in randomised trials**

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Assessment of risk of bias is regarded as an essential component of a systematic review on the effects of an intervention. The most commonly used tool for randomised trials is the Cochrane risk-of-bias tool. We updated the tool to encompass tools developed in the effect of intervention that would be observed in a large randomised trial without any bias. Quality is not well defined and can include study characteristics (such as performing a sample size calculation) that are not inherently related to bias in the study’s results. The RoB 2 tool considers biases arising at different stages of a trial (known as bias domains), which were chosen on the basis of both empirical evidence and theoretical considerations. Assessments of risk of bias are not rated.

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**RoB 2 tool**

A revised Cochrane risk of bias tool for randomized trials

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**SUMMARY POINTS**

- Assessment of risk of bias is an essential component of a systematic review on the effects of an intervention.
- The most commonly used tool for randomised trials is the Cochrane risk-of-bias tool.
- We updated the tool to encompass tools developed in the effect of intervention that would be observed in a large randomised trial without any bias.
- Quality is not well defined and can include study characteristics (such as performing a sample size calculation) that are not inherently related to bias in the study’s results.
- The RoB 2 tool considers biases arising at different stages of a trial (known as bias domains), which were chosen on the basis of both empirical evidence and theoretical considerations.
- Assessments of risk of bias are not rated.

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**Citing the tool**

The revised tool may be cited as:


**Other publications**

• assess key results from each included study for **risk of bias**
  – can’t measure the presence of bias
  – look for methods shown to minimize risk
  – … and evidence that the study ran successfully

• **risk of bias** is a property of a **result**
  – rather than of a **study**, or an **outcome**
  – if there is no result from a study, the result of the synthesis (meta-analysis) may be at risk of bias because of **Missing Evidence**
  • see **reporting bias; RoB ME tool**
Outcome domain: e.g. depression
Outcome measure: e.g. Beck depression inventory
Timepoint: e.g. 12 weeks
Outcome data: Measurement in all participants
Result: Analysis to compare groups
RoB 2 this
Overview of RoB 2

- fixed set of five **bias domains**
  - all are mandatory, and none can be added
  - (there is an additional domain in versions for cross-over trials and cluster-randomized trials)
- includes an **overall risk of bias**
  - used to guide analysis and interpretation
- important distinction between **effects of interest**
- funding and vested interests should be examined separately, and used to inform RoB 2 assessments
  - see **TACIT** (Tool for Addressing Conflicts of Interest in Trials)
Risk of bias assessment for a specific result

1. Specify result being assessed
2. Specify effect of interest
3. List sources of information used to inform assessment
4. Answer signalling questions
5. Judge risk of bias for each domain
6. Judge overall risk of bias for the result

For the synthesis
Integrate judgement(s) into results and conclusions
  e.g. stratify meta-analysis by overall risk of bias judgement
Risk of bias in randomized trials

Bias arising from the randomization process

Bias due to deviations from intended intervention

Bias due to missing outcome data

Experimental

Comparator

Outcome

Bias in measurement of the outcome

1.02 3.87
2.20 4.32
1.38 5.44

Bias in selection of the reported result
The effect of interest

Scenario: trial of screening for colorectal cancer
- people individually randomized to receive invitation to attend screening
- 55% of patients in the intervention arm attend screening
- all patients followed up for 10 years

We could be interested in either or both of:

- the **effect of assignment to intervention**
  - of most interest to a policymaker considering whether to introduce a screening programme
  - the ‘intention-to-treat’ (ITT) effect

- the **effect of adhering to intervention**
  - of most interest to a patient deciding whether to be screened
  - the ‘per-protocol’ effect
Signalling questions and judgements

- **signalling questions** increase transparency
  - support each one with evidence/quotes/explanation

- algorithms map answers to signalling questions onto **risk of bias judgements**
  - ‘**Low risk of bias**, ‘**Some concerns**, ‘**High risk of bias**’
  - “Probably yes” = “Yes”, and “Probably no” = “No”
  - algorithms can be overridden

- a ‘High risk of bias’ judgement in any one domain puts the result at high risk of bias
Bias arising from the randomization process

1.1 Was the allocation sequence random?
   - Yes / Probably yes / Probably no / No / No information

1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?
   - Yes / Probably yes / Probably no / No / No information

1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?
   - Yes / Probably yes / Probably no / No / No information
Illustration of algorithm: Domain

1.1 Allocation sequence random?

1.2 Allocation sequence concealed?

1.3 Baseline imbalances suggest a problem?

Low risk

Some concerns

High risk
## Suggested overall risk of bias judgement

<table>
<thead>
<tr>
<th>Domain 1</th>
<th>Domain 2</th>
<th>Domain 3</th>
<th>Domain 4</th>
<th>Domain 5</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Low</td>
<td>Some concerns</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
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<tr>
<td>High</td>
<td>Low</td>
<td>Some concerns</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Some concerns</td>
<td>Some concerns</td>
<td>Some concerns</td>
<td>Low</td>
<td>Some concerns</td>
<td>High?</td>
</tr>
</tbody>
</table>

**Discretionary override**
Cluster-randomized trials

Adapted tool addresses issues that differ compared with individually-randomized trials, e.g.:

- Bias arising from the timing of identification and recruitment of participants (additional domain)
- Outcome data may be missing for cluster or individuals within clusters
- Outcome assessors may not be aware that a trial is taking place
Crossover trials
(with thanks to Tianjing Li)

Parallel-groups design

Randomization

Society Cafe

Little Victories Cafe
Crossover design

Crossover trials
(with thanks to Tianjing Li)
Issues addressed in adapted tool for crossover trials

- Bias due to period effects
- Bias due to carryover effects
- Selective reporting of first period data
Incorporating findings into a review

- Options include
  - narrative only
  - stratified analysis
  - restrict primary analysis to studies at low risk (or ‘low risk’ and ‘some concerns’)
  - explore the impact further

- More about this in webinar 7

Address risk of bias outcome by outcome
Resources available
• **Chapter 7** explains risk of bias issues in general

• **Chapter 8** provides a brief overview of the RoB 2 tool

• **MECIR** items summarize *Handbook* guidance
Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne on behalf of the RoB2 Development Group

22 August 2019

Dedicated to Professor Douglas G Altman, whose contributions were of fundamental importance to development of risk of bias assessment in systematic reviews

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Additional Domain: Bias arising from the timing of identification and recruitment of participants

Additional Domain: Cross-over trials (individually randomized)

Add issues related to carry over and period effects

Cochrane Handbook Chapter 23: Including variants on randomized trials

- Interim guidance is available via the RoB 2.0 pilot
Excel tool

Online platform (later in 2020)

robvis

https://bit.ly/36Bku8L

The recommended way to do RoB 2 assessments at the moment
Other Cochrane resources

- Interactive learning module
- Standard author training materials currently being updated
- RoB 2 Pilot Starter Pack
RoB 2 in Cochrane reviews

RoB 2 Implementation

- Pilot
- RevMan Web

Protocol considerations
• Gradual, supported rollout across 2019/2020

• RoB2 pilot
  – Review teams
  – CRGs

• Publication
  • RevMan 5
  • RevMan Web
CRG / Author team join the Pilot

Protocol assessment

Kick off call

Monthly web clinics

Methods Support Unit

CRG
MSU
Authors
Implementation team
RevMan Web developers

RoB 2 pilot
## RoB 2 pilot

### Progress

<table>
<thead>
<tr>
<th></th>
<th>Pilot</th>
<th>Joining the pilot</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>18 reviews</td>
<td>22 reviews</td>
<td>40 reviews</td>
</tr>
<tr>
<td></td>
<td>16 CRGs</td>
<td>8 CRGS</td>
<td>23 CRGs</td>
</tr>
</tbody>
</table>
RevMan 5 ✗ RevMan Web ✔

RMW Knowledge Base / Assessing risk of bias
How to use Risk of bias 2.0 (RoB 2.0) tool in RevMan Web

RMW knowledgebase:
https://documentation.cochrane.org/revman-kb
RevMan Web

Investigate sensitivity - 1.1 Headache

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Caffeine</th>
<th>Decaf</th>
<th>Risk ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Amore-Coffea 2000</td>
<td>2</td>
<td>31</td>
<td>10</td>
</tr>
<tr>
<td>Delicioza 2004</td>
<td>10</td>
<td>40</td>
<td>9</td>
</tr>
<tr>
<td>Kahve-Paradiso 2002</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Mama-Kaffa 1999</td>
<td>12</td>
<td>53</td>
<td>9</td>
</tr>
<tr>
<td>Morrocona 1998</td>
<td>3</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Norscafe 1998</td>
<td>19</td>
<td>68</td>
<td>9</td>
</tr>
<tr>
<td>Ochlaflazza 1998</td>
<td>4</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>Piazza-Allerta 2003</td>
<td>8</td>
<td>35</td>
<td>6</td>
</tr>
</tbody>
</table>

Total (95% CI) | 277 | 290 | 100.0% | 1.31 [0.92, 1.87] |

Total events: 58, 46
Heterogeneity: CHI² = 8.68, df = 6 (P = 0.19); I² = 34%
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not applicable

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions: Headache
(C) Bias due to missing outcome data: Headache
(D) Bias in measurement of the outcome: Headache
(E) Bias in selection of the reported result: Headache
(F) Overall bias: Headache

How to join the RoB 2 pilot

Author teams

Contact your:

• CRG

CRG teams

Contact your:

• Network Associate Editor

• Method Support Unit

Protocol – Methods

• Criteria for considering studies for this review
  - Types of studies
  - Types of participants
  - Types of interventions
  - Types of outcomes

• Search methods for identification of studies
  - Electronic
  - Other

• Data collection and analysis
  - Selection of studies
  - Data extraction and management
  - Assessment of risk of bias in included studies
  - Measures of treatment effect
  - Unit of analysis issues
  - Dealing with missing data
  - Assessment of heterogeneity
  - Assessment of reporting biases
  - Data synthesis
  - Subgroup analysis and investigation of heterogeneity
  - Sensitivity analysis
  - Summary of findings and assessment of the certainty of the evidence
Protocol – Methods

- Criteria for considering studies for this review
  - Types of studies
  - Types of participants
  - Types of interventions
  - Types of outcomes

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Data collection and analysis
- Selection of studies
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Implications for RoB 2
RoB 2 has implications
<table>
<thead>
<tr>
<th>Types of studies</th>
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</thead>
<tbody>
<tr>
<td><strong>Randomized trials</strong></td>
<td>![Check]</td>
<td></td>
</tr>
<tr>
<td><strong>Cluster-randomized trials</strong></td>
<td>![Question]</td>
<td></td>
</tr>
<tr>
<td><strong>Crossover trials</strong></td>
<td>![Question]</td>
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</tbody>
</table>

**Rationale:** Implications for which variants of the RoB 2 tool you will use
Assessment of risk of bias in included studies

For all users of RoB 2:

1. State RoB 2 will be used and provide a reference to it
2. State which results will be assessed
   - Usually those in SoF table
3. State effect of interest
   - Your choice
4. State plans for design variants (cluster-rand., crossover) if needed
5. Detail assessors (how many? who? independently? consensus?)
6. List the domains in the tool (these can’t be modified)
7. List the judgement options: High, Low, Some concerns; overall RoB
8. Storage and presentation of assessments (inc. consensus decisions)
Primary analysis
• all ‘at Low risk of bias overall’?
• stratified analyses?

Secondary analysis
• sensitivity analyses?
• advanced: bias adjustment?

Does RoB 2 explain heterogeneity?
• subgroup analyses
• meta-regression

Certainty of the evidence
• RoB 2 will feed directly into GRADE

Rationale: All methods in Cochrane systematic reviews are pre-specified to minimize bias
Acknowledgements to

- Ella Flemyng  
  Cochrane Central
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  Executive Methods Team
- Froeks Kamminga
- Andrew Anglemeyer
- Kayleigh Kew
- Rebecka Hall  
  RevMan Web team

More information:

https://methods.cochrane.org/our-team
RevMan Web  https://documentation.cochrane.org/revman-kb
Cochrane online RevMan training https://bit.ly/2SFKZWa