Using the RoB tool to assess risk of bias of included studies

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Bias Method Group
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Outlines

- General principles of the RoB tool
- Selection bias
  - Definition / Examples
- Performance bias
  - Definition / Examples
- Detection bias
  - Definition / Examples
- Attrition bias
  - Definition / Examples
- Risk of bias summary
The Risk of Bias Tool

http://www.cochrane-handbook.org/
Chapter 8

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8.3 Tools for assessing quality and risk of bias
8.4 Introduction to sources of bias in clinical trials
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Population

Treatment A  Comparator B

Outcome Assessment  Outcome Assessment

Publication

Bias

Selection bias

Performance bias

Detection bias

Attrition bias

Reporting bias
Population

Randomisation

Treatment A

Comparator B

Blinding of participants and personnel

Blinding of outcome assessors

Outcome Assessment

Outcome Assessment

Publication

Bias

Selection bias

Performance bias

Detection bias

Attrition bias

Reporting bias
The “Risk of Bias” tool

The 7 items

- Sequence generation
- Allocation sequence concealment
- Blinding of participants, personnel
- Blinding of outcome assessment
- Incomplete outcome data
- Selective outcome reporting
- Other sources of bias
The Cochrane “Risk of Bias” tool

- Sequence generation
- Allocation sequence concealment
  
  - Blinding participants and personnel
  - Blinding of outcome assessment  
    *Separate assessment for each outcome*
  - Incomplete outcome data
- Selective outcome reporting
- Other sources of bias
The “Risk of Bias tool” (RoB)
General principles

- **2 steps**
  - What was **reported**
    - Extraction of what was reported in the published report / protocol/ contact with authors
    - Comment
  - **Judgment** relating to the risk of bias
    - Low risk of bias
    - High risk of bias
    - Unclear (judgment is impossible)
The “Risk of Bias tool” (RoB)
General principles. What was reported?

<table>
<thead>
<tr>
<th>Sequence generation.</th>
<th>Low</th>
<th><strong>Quote</strong>: “patients were randomly allocated”. <strong>Comment</strong>: Probably done, since earlier reports from the same investigators clearly describe use of random sequences (Cartwright 1980).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low</td>
<td><strong>Quote</strong>: “double blind, double dummy”; “High and low dose tablets or capsules were indistinguishable in all aspects of their outward appearance. For each drug an identically matched placebo was available”. <strong>Comment</strong>: Probably done</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) (Mortality)</td>
<td>Low</td>
<td><strong>Quote</strong>: “Obtained from medical records” <strong>Comment</strong>: review authors do not believe this will introduce bias.</td>
</tr>
</tbody>
</table>
The “Risk of Bias tool” (RoB)

General principles. Judgment

- **High risk of bias**
  - Bias of sufficient magnitude to have a notable impact on the results

- **Unclear risk of bias**
  - Insufficient details reported
  - Appropriate reporting, but the risk of bias is unknown
Risk of bias versus quality assessment of randomised controlled trials: cross sectional study

Lisa Hartling, assistant professor Maria Ospina, project manager Yuanyuan Liang, research scientist and biostatistician Donna M Dryden, assistant professor Nicola Hooton, project coordinator Jennifer Krebs Seida, project coordinator Terry P Klassen, professor

Table 1 | Inter-rater agreement using risk of bias tool

<table>
<thead>
<tr>
<th>Domain</th>
<th>Risk of bias assessments</th>
<th>Weighted ( \kappa ) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Unclear</td>
</tr>
<tr>
<td>Sequence generation</td>
<td>4</td>
<td>107</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>5</td>
<td>105</td>
</tr>
<tr>
<td>Blinding</td>
<td>16</td>
<td>49</td>
</tr>
<tr>
<td>Incomplete data</td>
<td>25</td>
<td>52</td>
</tr>
<tr>
<td>Selective reporting</td>
<td>16</td>
<td>19</td>
</tr>
<tr>
<td>Other sources of bias</td>
<td>15</td>
<td>85</td>
</tr>
<tr>
<td>Overall risk of bias</td>
<td>61</td>
<td>96</td>
</tr>
</tbody>
</table>
The “Risk of Bias tool” (RoB)

General principles

- Reviewers specifically trained
- Independent duplicate assessment with consensus
- Decisions need to be pre-specified in the protocol
  - Classification of outcomes (subjective / objective)
  - Blinding: successful blinding procedure
  - Missing data
  - Other risk of bias
- Contact authors for missing information
The “Risk of Bias tool” (RoB)

Selection bias

- Sequence generation
- Allocation concealment
Sequence generation
‘Low risk’ of bias

Minimization
Sequence generation

‘High risk’ of bias

- A non-random component in the sequence generation process
  - odd or even date of birth
  - some rule based on date (or day) of admission
  - some rule based on hospital or clinic record number...

- Approaches involving judgment
  - Allocation by judgment of the clinician
  - Allocation by preference of the participant
  - Allocation based on a laboratory test or a series of tests
  - Allocation by availability of the intervention...
Sequence generation
‘Unclear risk’ of bias

- No description of the process
- Incomplete description of the process
  - Blocked randomization reported
  - No reporting of the process of selecting the blocks
    - Random number table
    - Computer random number generator
Allocation concealment

‘Low risk of Bias’

- Participants and investigators enrolling participants could not foresee assignment
  - Central allocation (including telephone, web-based and pharmacy-controlled randomization)
  - Sequentially numbered drug containers of identical appearance
  - Sequentially numbered, opaque, sealed envelopes
Allocation concealment

‘High risk of Bias’

- Participants or investigators enrolling participants could possibly foresee assignments
  - Using an open random allocation schedule
  - Assignment envelopes were used without appropriate safeguards
  - Alternation or rotation
  - Date of birth
  - Case record number

- Any other explicitly unconcealed procedure
“Randomization was by a sequentially numbered computerized randomization algorithm. The allocation to treatment was concealed until study entry.”
Randomization was by a sequentially numbered computerized randomization algorithm. The allocation to treatment was concealed until study entry.

Sequence generation: low risk of bias
Allocation concealment: unclear risk of bias
Combined Intraarterial/Intravenous Thrombolysis for Acute Ischemic Stroke


Pretreatment examination revealed 45 eligible patients who presented with a severe but stable hemispheric syndrome who were then randomized to either the thrombolysis or control group, one after another, according to the order of admission. After informed consent requirements were completed, only 12 patients remained in the thrombolysis group whereas 33 patients were included in the conventional treatment, or control, group. Base-
Combined Intraarterial/Intravenous Thrombolysis for Acute Ischemic Stroke  


Pretreatment examination revealed 45 eligible patients who presented with a severe but stable hemispheric syndrome who were then randomized to either the thrombolysis or control group, one after another, according to the order of admission. After informed consent requirements were completed, only 12 patients remained in the thrombolysis group whereas 33 patients were included in the conventional treatment, or control, group. Base-

Sequence generation: high risk of bias
Allocation concealment: high risk of bias
Twenty patients each were randomly assigned to standard face mask oxygen, CPAP, or bilevel ventilation. The randomisation sequence was generated using random numbers produced by Microsoft Excel. Assignments were concealed in an opaque envelope, which was then further concealed within another. Once enrolled within the study it was impossible to mask treatment allocation. We aimed to enrol 60 consecutive eligible patients.
Twenty patients each were randomly assigned to standard face mask oxygen, CPAP, or bilevel ventilation. The randomisation sequence was generated using random numbers produced by Microsoft Excel. Assignments were concealed in an opaque envelope, which was then further concealed within another. Once enrolled within the study it was impossible to mask treatment allocation. We aimed to enrol 60 consecutive eligible patients.
Randomisation and masking

We randomised participants using an independent telephone randomisation system that included a minimisation algorithm balancing for sex (male, female), age (16–18 years, 19–34 years, and >34 years), educational level (to age ≤16 years, >16 years), and Fagerstrom score for nicotine addiction (≤5, >5). The system automatically generated intervention or control group texts according to the allocation. Researchers who gathered data and undertook laboratory analyses were masked to treatment allocation.
Randomisation and masking

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Sequence generation: low risk of bias
Allocation concealment: low risk of bias
The “Risk of Bias tool” (RoB)
Performance and detection bias

Performance Bias

Detection Bias

Blinding of participants and personnel

Blinding of outcome assessor
The “Risk of Bias tool” (RoB)
Who is blinded?

ORIGINAL ARTICLES

Specific instructions for estimating unclearly reported blinding status in randomized trials were reliable and valid

Elie A. Akl\textsuperscript{a,b,c,*}, Xin Sun\textsuperscript{c,d}, Jason W. Busse\textsuperscript{c,e}, Bradley C. Johnston\textsuperscript{c}, Matthias Briel\textsuperscript{c,f}, Sohail Mulla\textsuperscript{c}, John J. You\textsuperscript{c,g}, Dirk Bassler\textsuperscript{h}, Francois Lamontagne\textsuperscript{i}, Claudio Vera\textsuperscript{j}, Mohamad Alshurafa\textsuperscript{c}, Christina M. Katsios\textsuperscript{g}, Diane Heels-Ansdell\textsuperscript{c}, Qi Zhou\textsuperscript{c}, Ed Mills\textsuperscript{c}, Gordon H. Guyatt\textsuperscript{c,g}
The “Risk of Bias tool” (RoB)

Who is blinded?

No explicit statement about blinding status of patients, healthcare providers, data collectors and outcome adjudicator

- Probably blinded
  - Placebo controlled drug trial
  - Active control drug trial with mention « double dummy » or identical

- Probably not blinded
  - Active control drug trial no with mention « double dummy » ...
  - Non drug trial
The “Risk of Bias tool” (RoB)

Who is blinded?

<table>
<thead>
<tr>
<th>Reporting as “single”, “double”, “triple” blind</th>
</tr>
</thead>
</table>

- **Single blind**
  - Use the best judgment to assign « probably blinded » to 1 group et « probably not blinded » to the other

- **Double blind or triple blind**
  - Probably blinded for patients, care providers, data collectors, outcome assessor.
### The “Risk of Bias tool” (RoB)

#### Who is blinded?

Agreement between the consensus using the specific coding scheme and contact of authors

<table>
<thead>
<tr>
<th>Role</th>
<th>Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>98.2%</td>
</tr>
<tr>
<td>Care Providers</td>
<td>100%</td>
</tr>
<tr>
<td>Data collectors</td>
<td>96.3%</td>
</tr>
<tr>
<td>Outcome adjudicator/assessor</td>
<td>93.6%</td>
</tr>
</tbody>
</table>
The “Risk of Bias tool” (RoB)
What is the blinding procedure?

- **Assessment of zinc treatment for common cold**\(^1,2\)
  - Specific taste and aftertaste of zinc
  - Hunches: « anything tasting as bad as zinc and with as much aftertaste as zinc must be a good medicine »
  - Success of blinding was questionnable

- **Beta Blocker Heart Attack Study trial**\(^3\)
  - Comparison of propanolol and placebo
  - Heart rate change was a major cause of treatment identification

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1) Desbiens et al., *Annals of Internal Medicine*, 2000
2) Fair, J et al., *Chronic Dis.*, 1987
3) Byington et al., *JAMA*, 1985
Performance bias
Low risk of bias

- **Blinding** of participants and key study personnel ensured, and unlikely that the blinding could have been broken.

- No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.
Performance bias
High risk of bias

• No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding

• Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
Example

- **Outcome:** cumulative survival without mechanical ventilation or oxygen dependency at 30 days

- No mention on blinding and blinding of patients and care providers not feasible

- “Patients were crossed over to the alternative ventilator in case of therapy failure”
  - Seven patients (19%) treated with HFOV crossed over to CV
  - In the CV group four patients (17%) were switched to HFOV.
  - Of the four patients that crossed over in the CV group, two patients died and one patient was on supplemental oxygen therapy at 30 days. In the HFOV group, five patients that crossed over died and two patients were still on ventilator or needed extra oxygen.

*Bollen, Critical Care, 2005*
No mention on blinding and blinding of patients and care providers not feasible

“Patients were crossed over to the alternative ventilator in case of therapy failure”

- Seven patients (19%) treated with HFOV crossed over to CV
- In the CV group four patients (17%) were switched to HFOV.
- Of the four patients that crossed over in the CV group, two patients died and one patient was on supplemental oxygen therapy at 30 days. In the HFOV group, five patients that crossed over died and two patients were still on ventilator or needed extra oxygen.

Blinding of participant and personnel: High risk of bias
Detection bias
Assessment

- Who is assessing the outcome?
  - Patients
  - Care providers
  - Other

- Is the outcome assessment blinded?

- Is the blinding procedure efficient?

- Is the outcome subjective/objective?
Detection bias
Low risk of bias

- **Blinding of outcome assessment** ensured, and unlikely that the blinding could have been broken

- **No blinding** of outcome assessment, but the review authors judge that the outcome measurement is **not likely** to be influenced by lack of blinding
Detection bias
High risk of bias

- **No blinding** of outcome assessment, and the outcome measurement **is likely** to be influenced by lack of blinding

- **Blinding** of outcome assessment, but likely that the blinding could have been **broken**, and the outcome measurement is **likely to be influenced** by lack of blinding
Photochemotherapy for severe psoriasis without or in combination with acitretin: A randomized, double-blind comparison study

A. Tanew, MD,¹ A. Guggenbichler, MD,² H. Hönigsmann, MD,¹ J. M. Geiger, MD,³ and P. Fritsch, MD² Vienna and Innsbruck, Austria, and Basle, Switzerland

Acitretin (1 mg/kg body weight/day) or placebo was given for 5 days as a monotherapy. Beginning on day 6, photochemotherapy (four PUVA exposures per week) was added to the drug treatment. The combined treat-

[...]

for a maximum of 11 weeks. All patients were seen twice weekly by the same investigator for assessment of treatment response and UVA dose adjustments.

PO: clearing of psoriasis
Double blind procedure: not credible because of high frequency of cheilitis

Outcome: subjective outcome

High risk of bias
Assessment of the principal outcomes and repeated measurements was not blinded.

Outcomes consisted of:
- Therapy failure
- Mortality
Assessment of the principal outcomes and repeated measurements was not blinded.

Outcomes consisted of:
- Therapy failure;
- Mortality

Blinding of outcome assessment:
- Mortality: low risk of bias
- Therapy failure: high risk of bias
Randomisation and masking

We randomised participants using an independent telephone randomisation system that included a minimisation algorithm balancing for sex (male, female), age (16–18 years, 19–34 years, and >34 years), educational level (to age ≤16 years, >16 years), and Fagerstrom score for nicotine addiction (≤5, >5). The system automatically generated intervention or control group texts according to the allocation. Researchers who gathered data and undertook laboratory analyses were masked to treatment allocation.

Outcomes

Self-reporting continuous abstinence at 6 months
Biochemically verified continuous abstinence at 6 months
Randomisation and masking

We randomised participants using an independent telephone randomisation system that included a minimisation algorithm balancing for sex (male, female), age (16–18 years, 19–34 years, and >34 years), educational level (to age ≤16 years, >16 years), and Fagerstrom score for nicotine addiction (≤5, >5). The system automatically generated intervention or control group texts according to the allocation. Researchers who gathered data and undertook laboratory analyses were masked to treatment allocation.

Blinding of outcome assessment

**Self-reporting continuous abstinence at 6 months**: high risk

**Biochemically verified continuous abstinence at 6 months**: low risk
Radiographic progression in early rheumatoid arthritis: a 12-month randomized controlled study comparing the combination of cyclosporin and methotrexate with methotrexate alone

A. Marchesoni, N. Battafarano, M. Arreghini, B. Panni, M. Gallazzi and S. Tosi

**Study design**

This was a 12-month, controlled, randomized single-blind (the clinical investigator was blinded to the treatment) trial designed to compare the efficacy of CsA plus MTX with that of MTX alone in terms of radiographic progression.

**Concomitant medication**

Corticosteroids were allowed but their dose could not exceed 10 mg/day of prednisone or equivalent. Local corticosteroid injections were not allowed in the joints of the hands or feet used to score the radiographic changes.
Radiographic progression in early rheumatoid arthritis: a 12-month randomized controlled study comparing the combination of cyclosporin and methotrexate with methotrexate alone

A. Marchesoni, N. Battafarano, M. Arreghini, B. Panni, M. Gallazzi and S. Tosi

Primary outcome: radiographic damage score assessed by blinded outcome assessors

Blinding of patients and personnel: low risk of bias
Blinding of outcome assessment: low risk of bias
Experimental treatment: Home-based exercise

Comparator: attention control intervention on Nutrition
  - Believable treatment
  - Behavior change similar to exercise.
  - Booklet
  - Home visits
  - Food logs

Patients blinded to the active treatment
  - Information: comparison of the effects of both exercise and nutrition.
Outcome: WOMAC (patient reported outcome measuring pain and function)

- Adherence
  - Exercise group: Mean (SD) = 84+/-27%
  - Nutrition group: Mean (SD) = 65+/-32%
The “Risk of Bias tool” (RoB)

Attrition bias

- How much data is missing from each group?
- Why are data missing in each group?
- How were data analysed?
  - Handling of incomplete outcome data
Attrition bias
Low risk of bias

• No missing outcome data

• Reasons for missing data not related to outcome

• Missing data balanced across groups, with similar reasons

• Missing data not enough to have a clinically relevant impact on the intervention effect estimate

• Missing data have been imputed using appropriate methods.
Attrition bias

High risk of bias

- Reason for missing data related to outcome, with either imbalance in numbers or reasons

- Missing data enough to induce clinically relevant bias in intervention effect estimate

- ‘As-treated’ analysis with substantial departure of the intervention received from that assigned at randomization

- Inappropriate use of imputation
Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial

Michael Rud Lassen, Gary E Raskob, Alexander Gallus, Graham Pineo, Dalei Chen, Philip Hornick, and the ADVANCE-2 investigators

Outcome measures
The primary outcome measure of efficacy was the composite of adjudicated asymptomatic or symptomatic deep vein thrombosis, non-fatal pulmonary embolism, and all-cause death (all venous thromboembolism and all-cause death), with onset during the intended treatment period of 12 days (within 2 days) or within 2 days of last dose of study drug, whichever was longer. The main secondary outcome measure (major venous thromboembolism) was the composite of and venous thromboembolism-related death during this period. The presence or absence of asymptomatic deep vein thrombosis at the end of the intended treatment period was assessed with bilateral venography done between day 10 and day 14 (day 1 was the day of surgery). Clinically suspected deep vein thrombosis was confirmed or excluded with surgery.

Primary efficacy analysis included data for all patients randomly allocated to treatment who had an assessable efficacy outcome (patients who, during the intended treatment period, had a venogram adjudicated as assessable, who developed confirmed deep vein thrombosis or pulmonary embolism, or who died from any cause); patients who had important protocol violations were excluded from the per-protocol analysis.
Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial

Michael Rud Lassen, Gary E Raskob, Alexander Gailus
Incomplete outcome data
PO: High risk of bias: Missing outcome: 35\%
Impact of the Fit and Strong Intervention on Older Adults With Osteoarthritis

Susan L. Hughes, DSW,1 Rachel B. Seymour, MS,1 Richard Campbell, PhD,1 Naomi Pollak, MS, PT,1 Gail Huber, MHPE, PT,2 and Leena Sharma, MD3

Figure 1. Flow diagram: Iterations 1–7 (OA = osteoarthritis).
Individuals Screened (n = 495)

Enrolled (n = 150)
- Requested Deferment (n = 49)
- Patient Refused (n = 79)
- Did not meet inclusion criteria (n = 217)
  - Schedule conflict (n=64)
  - Age under 60 yrs (n=48)
  - Lower extremity OA (n=40)
  - Participating in aerobic exercise program (n=25)
  - Conflicting medical condition (n=25)
  - Language barrier (n=9)
  - Rheumatoid arthritis (n=6)

Treatment (n = 80)
Followed at 8 weeks (n = 68) 85%

Control (n = 70)
Followed at 8 weeks (n = 43) 61%

Incomplete outcome data
High risk of bias

Figure 1. Flow diagram: Iterations 1–7 (OA = osteoarthritis).
## Risk of bias summary

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>Quote: &quot;...participants born on even days were assigned to the experimental group and participants born on odd days were assigned to the control group.&quot;</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Comment: allocation by date of birth would allow prediction of the allocation sequence.</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Unclear risk</td>
<td>Quote: &quot;Caffeinated and decaffeinated coffee... was identical in appearance, colour and taste.&quot;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comment: it is likely that participants were blinded. Blinding of study personnel was not described.</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Comment: Blinding of outcome assessors was not described.</td>
</tr>
<tr>
<td>Self-reported outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Comment: Blinding of outcome assessors was not described, but is unlikely to affect measurement of this outcome.</td>
</tr>
<tr>
<td>Reaction time</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Comment: outcome data for adverse events were only reported for 53 of 58 participants in the caffeine group. Reasons for loss to follow-up were not described.</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Comment: alertness was the primary outcome of the study, but data were not reported. Study protocol was not available to identify any other unreported outcomes. Outcome data were presented for drowsiness although this was not listed as an outcome of interest in the study methods.</td>
</tr>
<tr>
<td>Other bias</td>
<td>Low risk</td>
<td>Comment: none were identified.</td>
</tr>
</tbody>
</table>
Figure 8.6.c: Example of a ‘Risk of bias summary’ figure
Risk of bias summary

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias) (patient-reported outcomes)
- Blinding of outcome assessment (detection bias) (all-cause mortality)
- Incomplete outcome data (attrition bias) (short-term [2-6 weeks])
- Incomplete outcome data (attrition bias) (long-term [> 6 weeks])
- Selective reporting (reporting bias)

Legend:
- Low risk of bias
- Unclear risk of bias
- High risk of bias
Assessing risk of bias in included studies
CHOC-ATT Trial

Does CHOColate improve ATTention during workshops and reduce sleepiness?
Conclusions

- Assessing the risk of bias is an essential step for an appropriate interpretation of systematic reviews and meta-analysis

- 7 items to be evaluated

- Training and use of the handbook recommendations

- Need for transparency