Assessing risk of bias in included studies

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Steps of a Cochrane review

1. define the question
2. plan eligibility criteria
3. plan methods
4. search for studies
5. apply eligibility criteria
6. collect data
7. **assess studies for risk of bias**
8. analyse and present results
9. interpret results and draw conclusions
10. improve and update review

Outline

- **risk of bias in systematic reviews**
- assessing sources of bias
- putting it into practice: ‘Risk of bias’ tables
- incorporating findings into your review

See Chapter 8 of the Handbook

What is bias?

Systematic error or deviation from the truth

- systematic reviews depend on included studies
  - incorrect studies = misleading reviews
  - should I believe the results?
- assess each study for risk of bias
  - can’t measure the presence of bias
  - may overestimate or underestimate the effect
  - look for methods shown to minimise risk

Bias is not the same as

Imprecision

- random error due to sampling variation
- reflected in the confidence interval

Quality

- bias can occur in well-conducted studies
- not all methodological flaws introduce bias

Reporting

- good methods may have been used but not well reported

Quality scales and checklists

- > 30 scales available
- not supported by empirical evidence
- different scales, different conclusions
- may include criteria not related to bias
- numerical weighting not justified
- difficult for readers to interpret the score

Quality scales should not be used in Cochrane

Cochrane 'Risk of bias' assessment

- domain-based evaluation
  - 6 evidence-based domains
  - detailed description of what happened
  - review authors' judgement
    - was bias unlikely to be introduced through this item?
    - ✓ **Yes** = low risk of bias
    - ✗ **No** = high risk of bias
    - ? **Unclear** = not enough information to make a clear judgement

Domains to address

- sequence generation
- allocation concealment
- blinding
- incomplete outcome data
- selective outcome reporting
- other risk(s)

- Note: you will need to consider other factors if assessing
  non-randomised studies

Overview

- risk of bias in systematic reviews
- **assessing sources of bias**
- putting it into practice: ‘Risk of bias’ tables
- incorporating findings into your review

Sources of bias

Selection

Performance

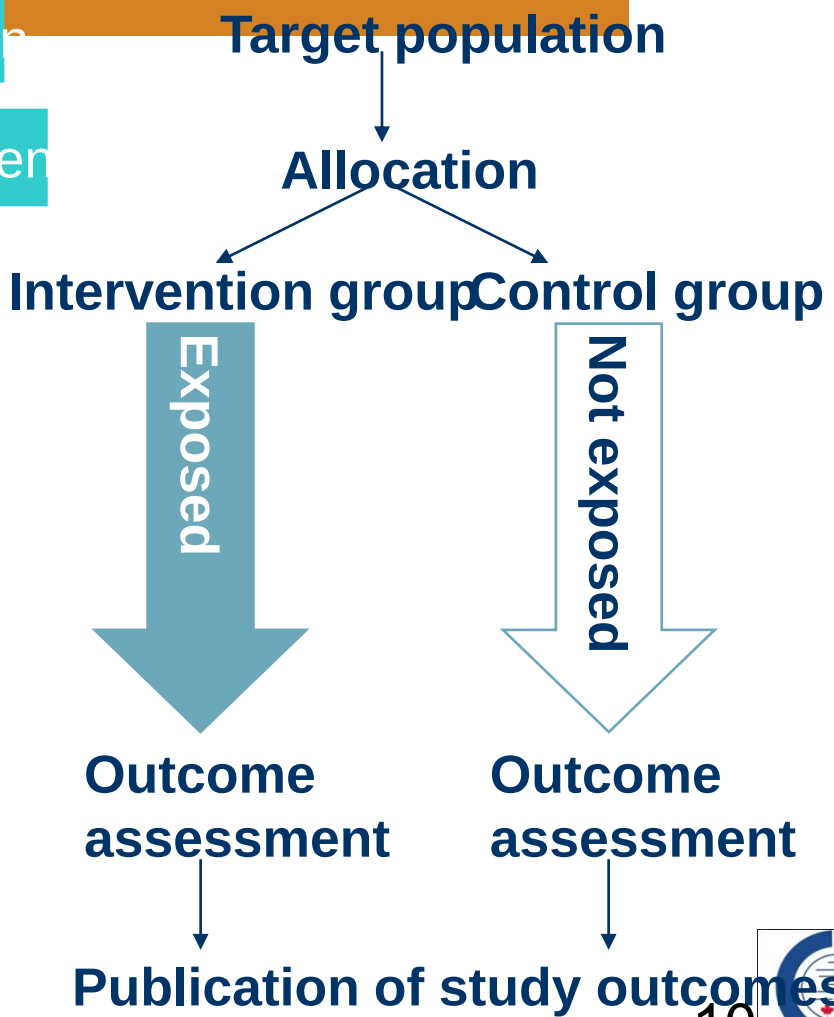
Detection

Attrition

Reporting

Sequence generation

Allocation concealmen



Random sequence generation

- occurs at the start of a trial before allocation of participants
- minimises **selection bias**
- determines a random order of assigning people into intervention and control groups
- avoids systematic differences between groups
- accounts for known and unknown confounders

Was the sequence adequately generated?

Yes - unpredictable

- random number table
- computer random number generator
- can include stratified or block randomisation
- minimisation
- low tech - coin toss, shuffling cards or envelopes, throwing dice, drawing lots

No - predictable

- quasi-random – date of birth, day of visit, ID or record number, alternate allocation
- non-random – choice of clinician or participant, test results, availability

Allocation concealment

- occurs at the start of the trial during allocation of participants
- minimises **selection bias**
- when a person is recruited to the study, no-one can predict which group they will be allocated to
- ensures the strict implementation of the random sequence
  - prevents changing the order
  - prevents selecting who to recruit

Was allocation adequately concealed?

Yes - unpredictable

- central allocation (phone, web)
- coding and packaging of drugs in hospital pharmacy
- sequentially numbered, sealed, opaque envelopes

No - predictable

- random sequence known to staff in advance
- envelopes without all three safeguards
- non-random, predictable sequence

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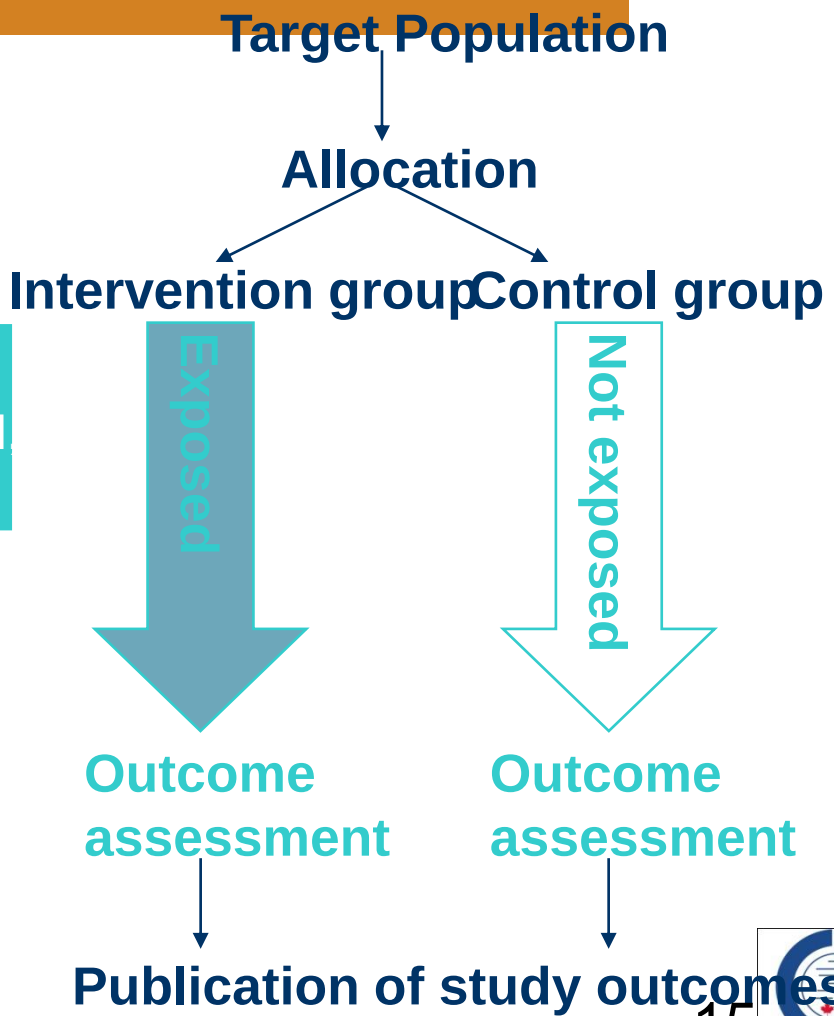
Blinding
(participants, personnel, outcome assessors)



Blinding

- occurs during the intervention and measurement of outcomes
- minimises **performance bias**
  - different treatment of the two groups
  - participant expectations
- minimises **detection bias**
  - different measurement of outcomes between the two groups
- can blind participant, care provider, outcome assessor, others
  - consider blinding of all these groups together
  - avoid terms like “single blinding” and “double blinding”
  - may not be feasible for some interventions
- check for intention and success of blinding

Assessing blinding by outcome

- may reach different conclusions for different outcomes
  - measurement of only some outcomes may be blinded
  - subjective outcomes may be more vulnerable to bias e.g. death vs quality of life
- option to design your table with two or more outcome groups for ‘blinding’
  - consider carefully – same groups will be applied to all included studies
  - if a particular study does not measure that outcome or type, assess as ‘unclear’

Was knowledge of the allocated intervention adequately prevented?

Yes

- participants and key personnel blinded, and blinding probably not broken
- a key group not blinded, but outcome assessment blinded and non-blinding of others unlikely to introduce bias
- no blinding, but outcomes unlikely to be influenced

No

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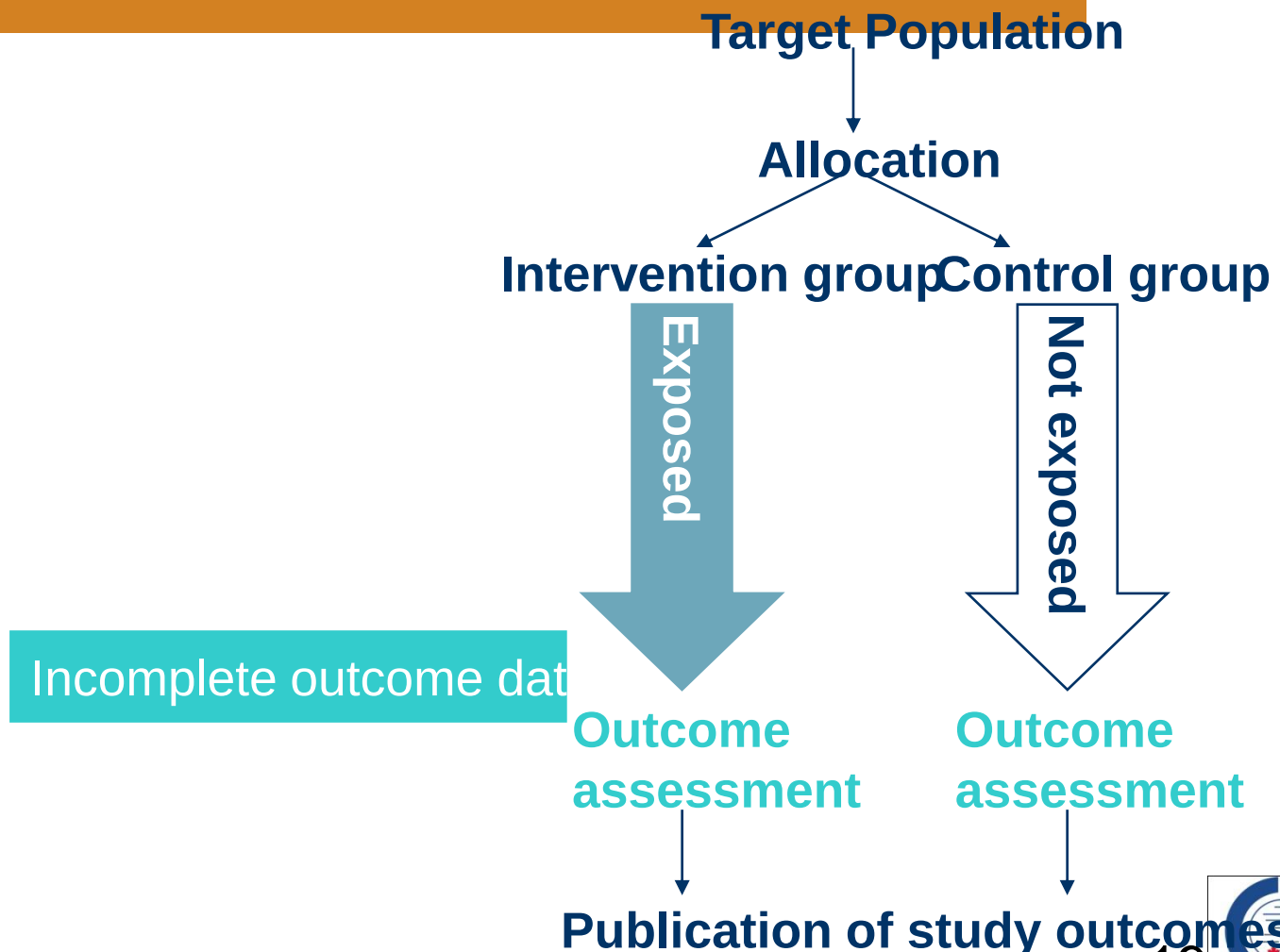

Incomplete outcome data

- when complete outcome data is not available for all participants
- can indicate **attrition bias**
- causes of incompleteness (assess together)
  - loss of participants to follow up
  - missing data
  - exclusion of participants from study or analysis
- considerations
  - how much data is missing from each group? (include numbers in your description)
  - why is it missing?

How much is too much missing data?

- **no simple rule**
- enough missing to meaningfully affect the results
  - overall proportion of missing data
  - event risk (dichotomous outcomes)
  - plausible effect size (continuous outcomes)
- reasons related to study outcomes
  - e.g. recovered, adverse event, refusal
  - reasons can have different meaning in each group
- missing data not balanced between groups
- trial authors may modify the analysis to address the problem
  - ‘as-treated’ analysis
  - inappropriate imputation of missing values

Assessing incomplete data by outcome

- may reach different conclusions for different outcomes
  - may be more missing data at different time points
  - some outcomes may have more missing data e.g. sensitive questions, invasive tests
- option to design your table with two or more outcome groups for 'incomplete data'
  - consider carefully – same groups will be applied to all included studies
  - if a particular study does not measure that outcome or time point, assess as 'unclear'

Were incomplete outcome data adequately addressed?

Yes

- no missing data
- reasons for missing data not related to outcome
- missing data balanced across groups, and reasons similar
- proportion missing or plausible effect size not enough to change effect to clinically important extent

No

- reasons for missing data related to outcome, and imbalance in numbers or reasons
- proportion missing or plausible effect size enough to change effect to clinically important extent
- ’as-treated’ analysis with substantial departure from allocation
- inappropriate use of imputation

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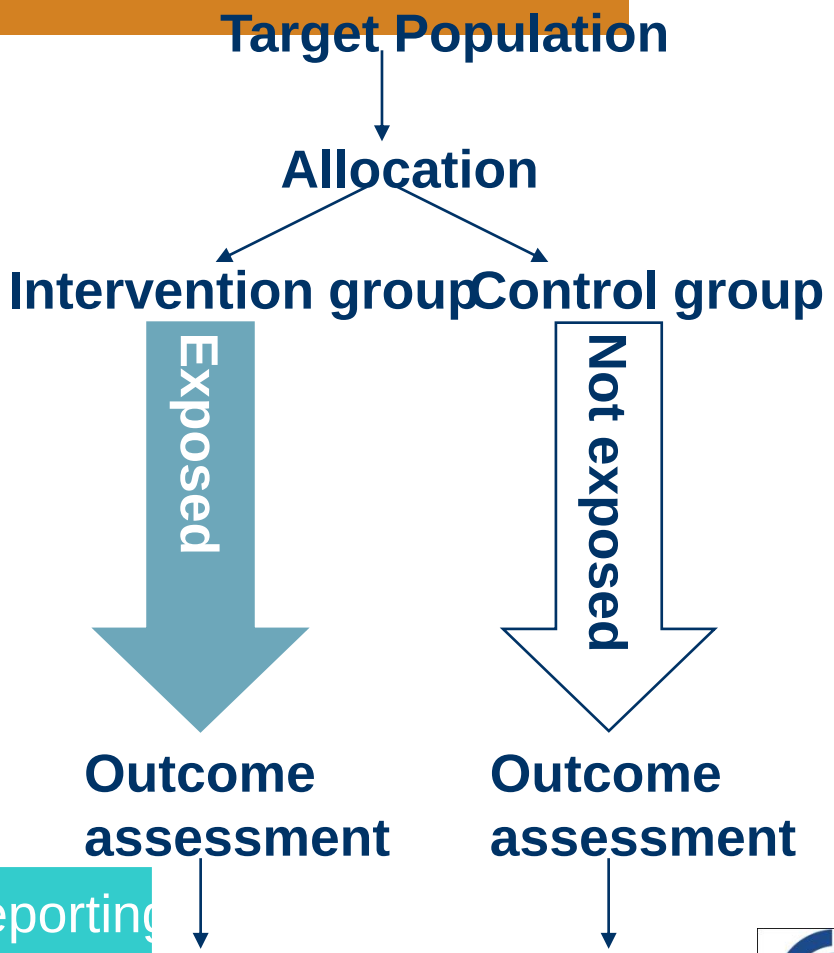

Selective outcome reporting

- positive results more likely to be reported
  - as planned
  - in detail
- can indicate **reporting bias**
- difficult to determine
  - compare methods to results – look for:
    - outcomes missing, added, statistics changed, subgroups only
    - commonly reported outcomes
    - reporting that cannot be used in a review
      (e.g. only noting significance without numerical results)
  - refer to study protocol or trial register
- focus on outcomes of interest to your review

e reports of the study free of lective outcome reporting?

Yes

- protocol is available and all pre-specified outcomes of interest to the review reported in the pre-specified way
- protocol not available but it is clear that all pre-specified and expected outcomes of interest to the review are reported
- **most studies will be judged 'unclear' in this category**

No

- outcomes not reported as pre-specified or expected
  - (missing, added, or unexpected methods used)
- outcomes reported incompletely so they cannot be entered in a meta-analysis

Other sources of bias

- must be a clear rationale why a factor may cause bias
- if possible, identify important issues in your protocol
  - e.g. issues relating to study designs you plan to include
- option to add rows to your table for items to be assessed
  - specify the item so that a “yes” answer indicates a low risk of bias
  - will be added to all studies

Was the study free of other problems that could put it at a high risk of bias?

Yes

- study appears to be free of other sources of risk

No

- issues specific to the study design
  - carryover in crossover trials
  - cluster-randomized trials e.g. differences in recruitment
- trial stopped early using data-dependent process (including a formal stopping rule)
- extreme baseline imbalance
- inappropriate influence of funders
- other problem

Overview

- risk of bias in systematic reviews
- assessing sources of bias
- **putting it into practice: 'Risk of bias' tables**
- incorporating findings into your review

Completing the assessments

- at least two assessors
  - ensure all understand the methodological issues
  - include content and methods experts
- pilot on 3-6 studies to check consistency of assessment
- look for missing information
  - study protocol
  - contact authors

‘Risk of bias’ tables

- one for each included study
- description
  - supporting information for your judgement
  - direct quotes where possible
  - additional comments
  - rationale for any assumptions (e.g. “probably done”)
  - state explicitly if no information available
- your judgement

Risk of bias table

Item	Authors' judgment	Description
Adequate sequence generation?	Unclear	"Patients were randomly allocated"
Allocation concealment?	Unclear	No information.
Blinding?	Yes	"double blind design". "Millet... resembles lecithin in appearance... When ground, each substance could be distinguished from the other by hue and taste but staff were not informed as too which was which."
Incomplete outcome data addressed?	No	Data unavailable for meta-analysis. Randomised: lecithin = Not stated, placebo = Not stated, Total = 33.Missing: lecithin = 7 (non-cooperation or diarrhoea = 2; moved to nursing home = 4, death = 2), placebo = 5 (non-cooperation or diarrhoea = 3, death = 2), total missing = 36%.
Free of selective reporting?	No	No quantitative results reported due to lack of effect.It is apparently clear which outcomes were measured.
Free of other bias?	Yes	No problems apparent

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- **incorporating findings into your review**

Prioritise domains for your review

- all reviews address all domains, but you can specify one or more as priorities for your review
  - specify in your protocol
  - may be all domains or only some
- give a rationale, considering:
  - empirical evidence of impact
  - likely direction of impact
    - bias most likely to exaggerate effect
    - if likely to underestimate and a significant effect observed, may be ok
  - likely magnitude of impact in relation to observed effect

See Handbook Sections 8.5-8.14

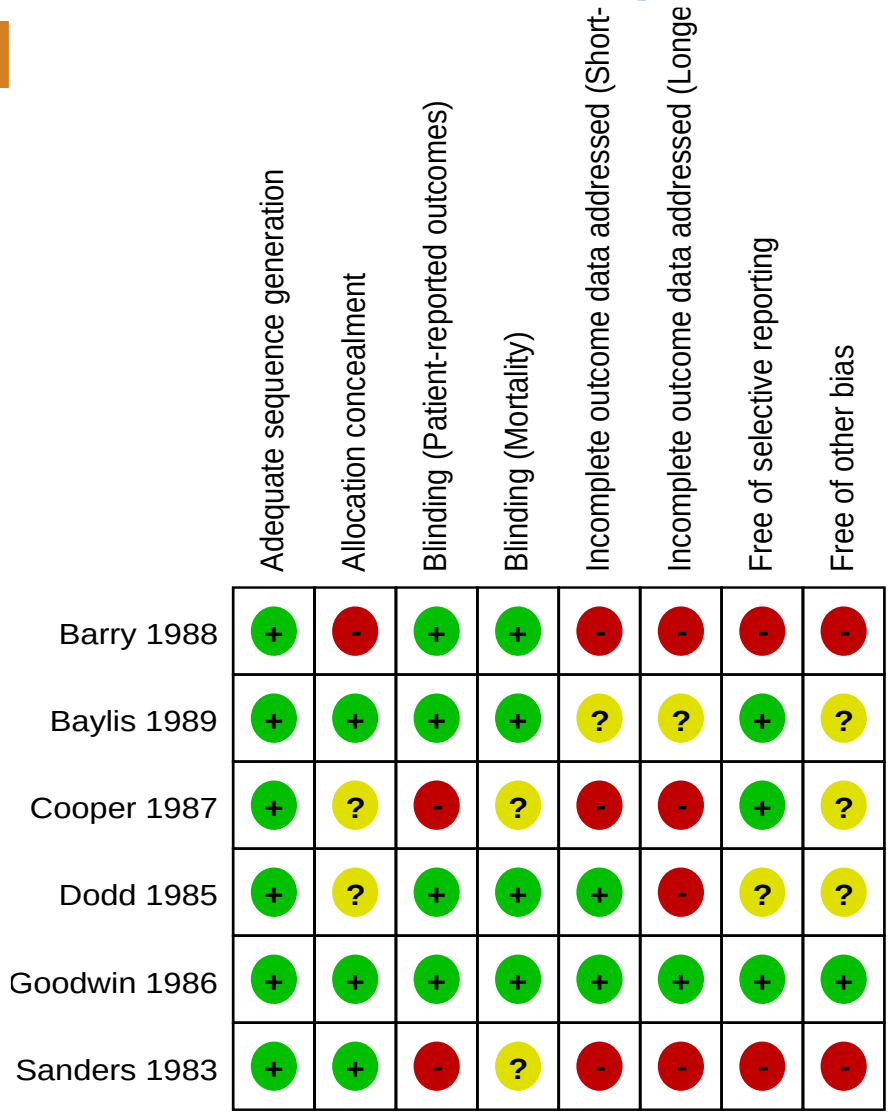
Incorporating findings into your review

- always give a narrative description
  - may be missed by readers
- may restrict primary analysis to studies at lower risk
  - may be inappropriate to combine high risk results
  - based on a reasoned (but arbitrary) threshold
  - always conduct sensitivity analysis
  - not possible if all studies have similar risk
- additional exploration
  - consider heterogeneity of results between studies
  - metaregression, comparison of subgroups - get statistical advice

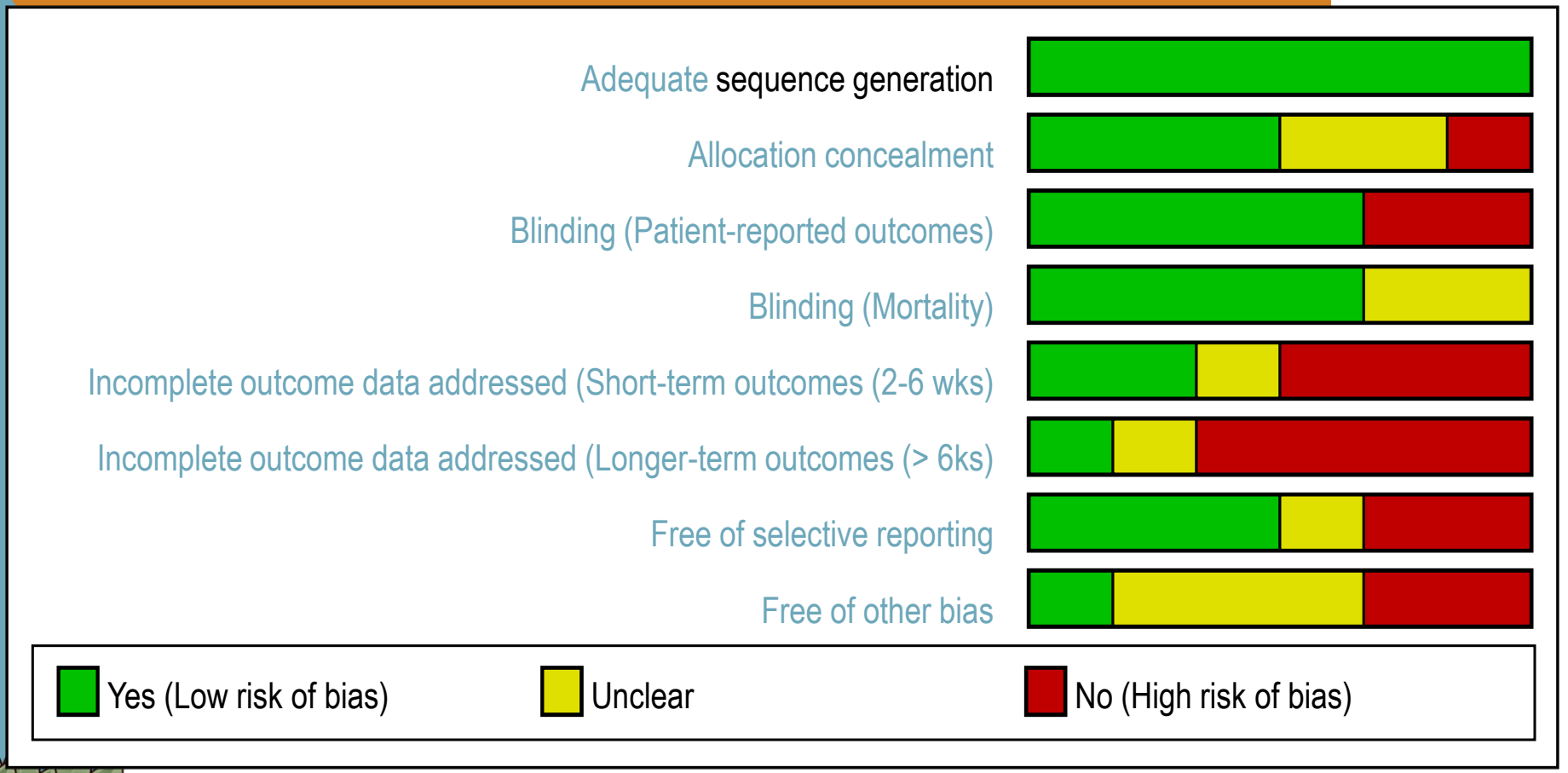
Reaching an overall interpretation

- don’t try to summarise all outcomes and all studies at once
- summarise by **outcome**
  - outcome may have different risks (e.g. blinding, incomplete data)
  - not all studies contribute to each outcome
  - start by summarising **within a study**, then **across studies**

Risk of bias summary

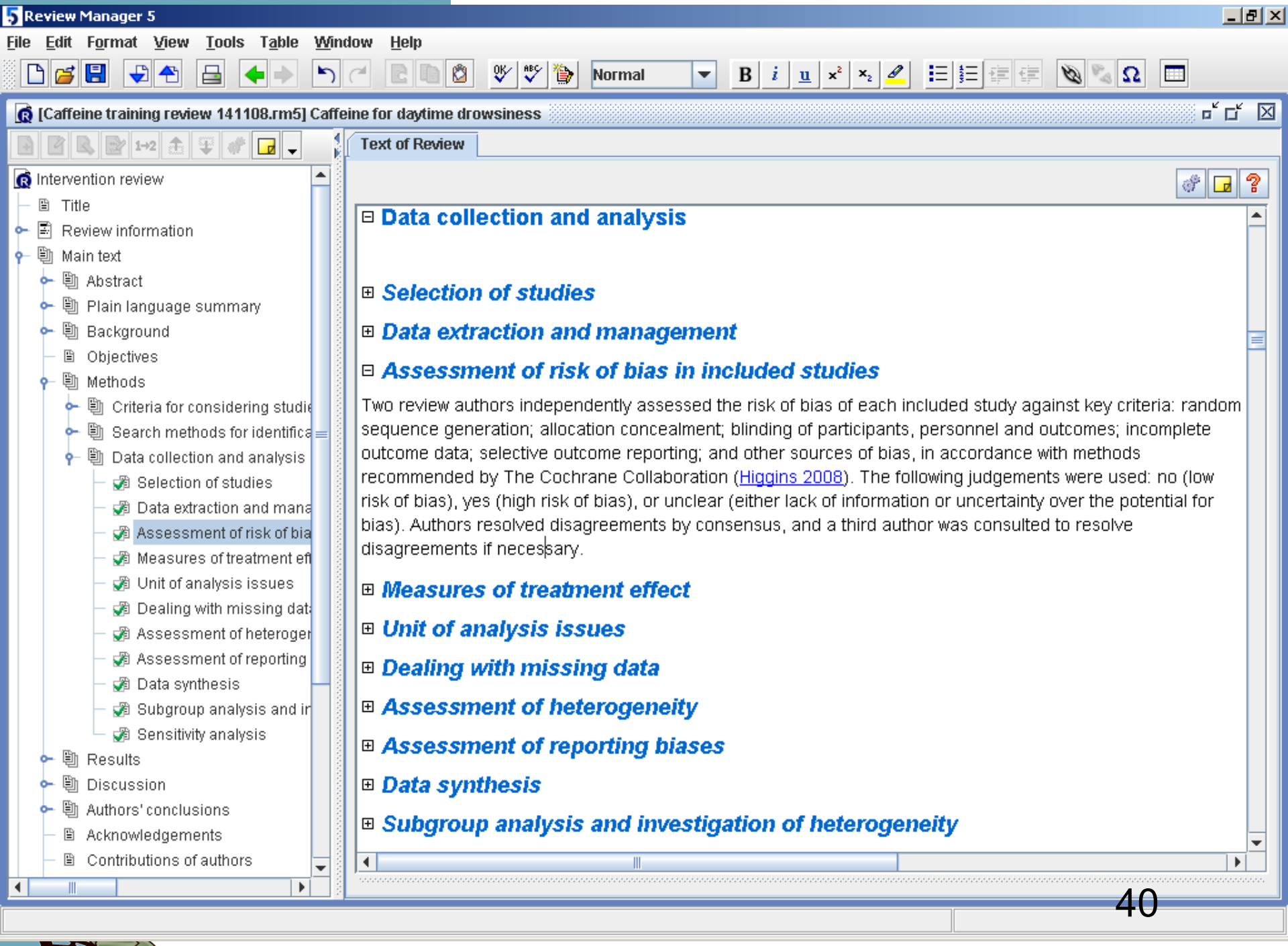


Risk of bias graph



What to include in your protocol

- check with your CRG for standard text
- brief description of risk of bias assessment tool
  - list domains
  - refer to Handbook Chapter 8
- more than one author will assess risk of bias
- how will disagreements will be resolved?
- are there specific domains you consider to be important for the review?
- how will you incorporate findings into your analysis?


Review Manager 5
File Edit Format View Tools Table Window Help
Normal
[Caffeine training review 141108.rm5] Caffeine for daytime drowsiness
Text of Review
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Title
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Main text
Abstract
Plain language summary
Background
Objectives
Methods
Criteria for considering studie
Search methods for identifica
Data collection and analysis
Selection of studies
Data extraction and mana
Assessment of risk of bia
Measures of treatment eff
Unit of analysis issues
Dealing with missing data
Assessment of heteroger
Assessment of reporting
Data synthesis
Subgroup analysis and ir
Sensitivity analysis
Results
Discussion
Authors' conclusions
Acknowledgements
Contributions of authors
Data collection and analysis
Selection of studies
Data extraction and management
Assessment of risk of bias in included studies
Two review authors independently assessed the risk of bias of each included study against key criteria: random sequence generation; allocation concealment; blinding of participants, personnel and outcomes; incomplete outcome data; selective outcome reporting; and other sources of bias, in accordance with methods recommended by The Cochrane Collaboration (Higgins 2008). The following judgements were used: no (low risk of bias), yes (high risk of bias), or unclear (either lack of information or uncertainty over the potential for bias). Authors resolved disagreements by consensus, and a third author was consulted to resolve disagreements if necessary.
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

Take home message

- biased studies may lead to misleading reviews
- six domains of bias to be assessed
- describe what happened in detail and give your judgement
- consider the possible effects and use appropriate caution in interpreting your results