Cochrane Training

Assessing risk of bias in included studies

Trusted evidence.
Informed decisions.
Better health.

Cochrane Training

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

Session outline

- **risk of bias in systematic reviews**
- assessing sources of bias : the RoB 2 tool
- putting it into practice
- incorporating risk of bias in a review

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

Bias is not the same as…

Low quality

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

Poor reporting

- good methods may have been used but not well reported
- inappropriate methods may have been used but not clearly described

Imprecision

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

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

Risk of bias

- 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 **M**issing **E**vidence
    - see presentation **Bias due to missing results in a synthesis (**incl. **ROB ME** tool)

Recommended tool for new Cochrane Reviews: 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**
  - see later
- funding and vested interests should be examined separately, and used to inform RoB 2 assessments
  - **TACIT** (Tool for Addressing Conflicts of Interest in Trials) will address this issue

RoB 2 process

For each outcome (each key synthesis in the review)

For each study

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

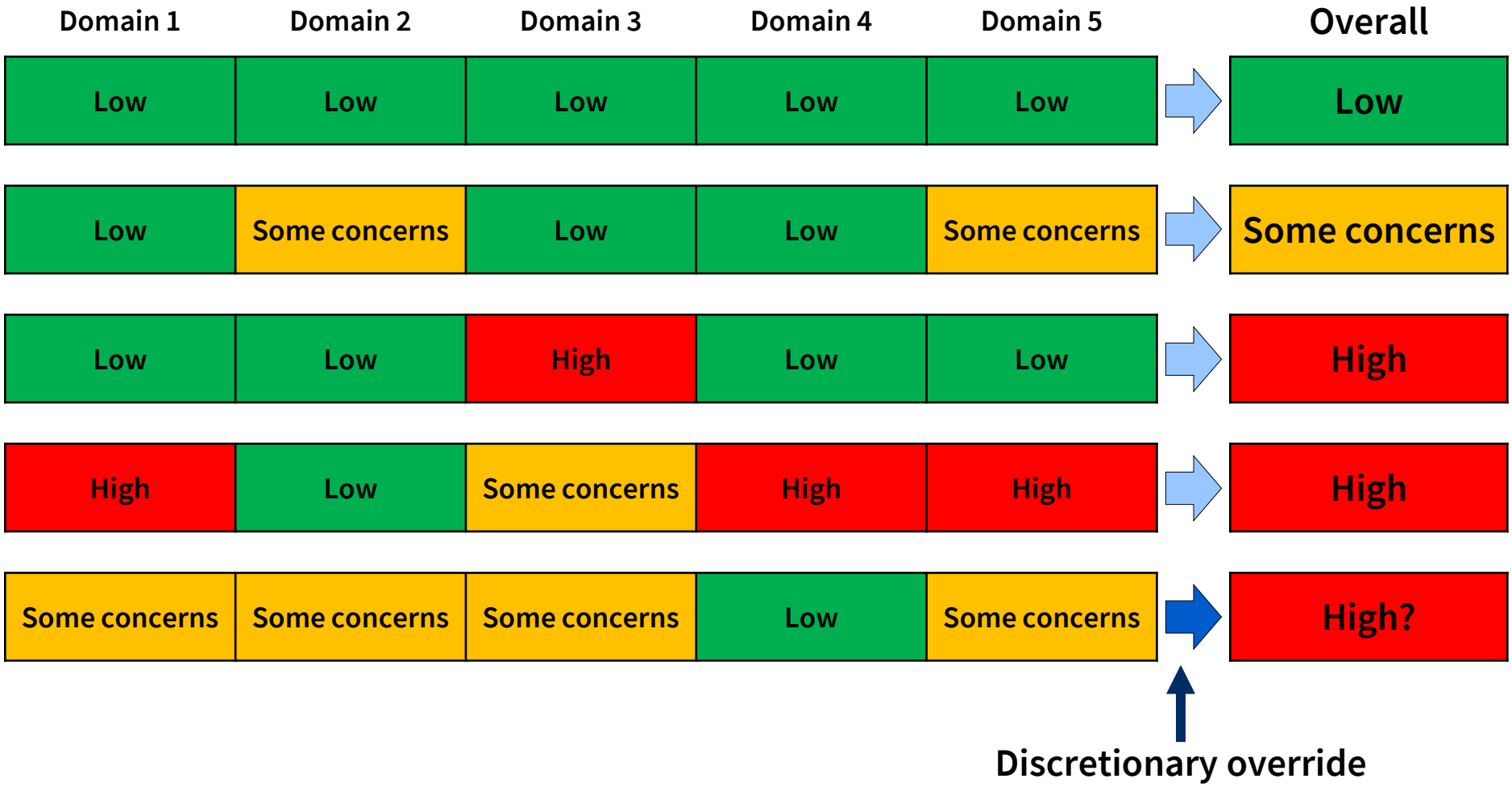
Signalling questions and judgements

- **signalling questions** increase transparency
  - 'Yes', 'Probably yes', 'Probably no', 'No', 'No information'
  - 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
  - see next slide

Suggested overall risk of bias judgement

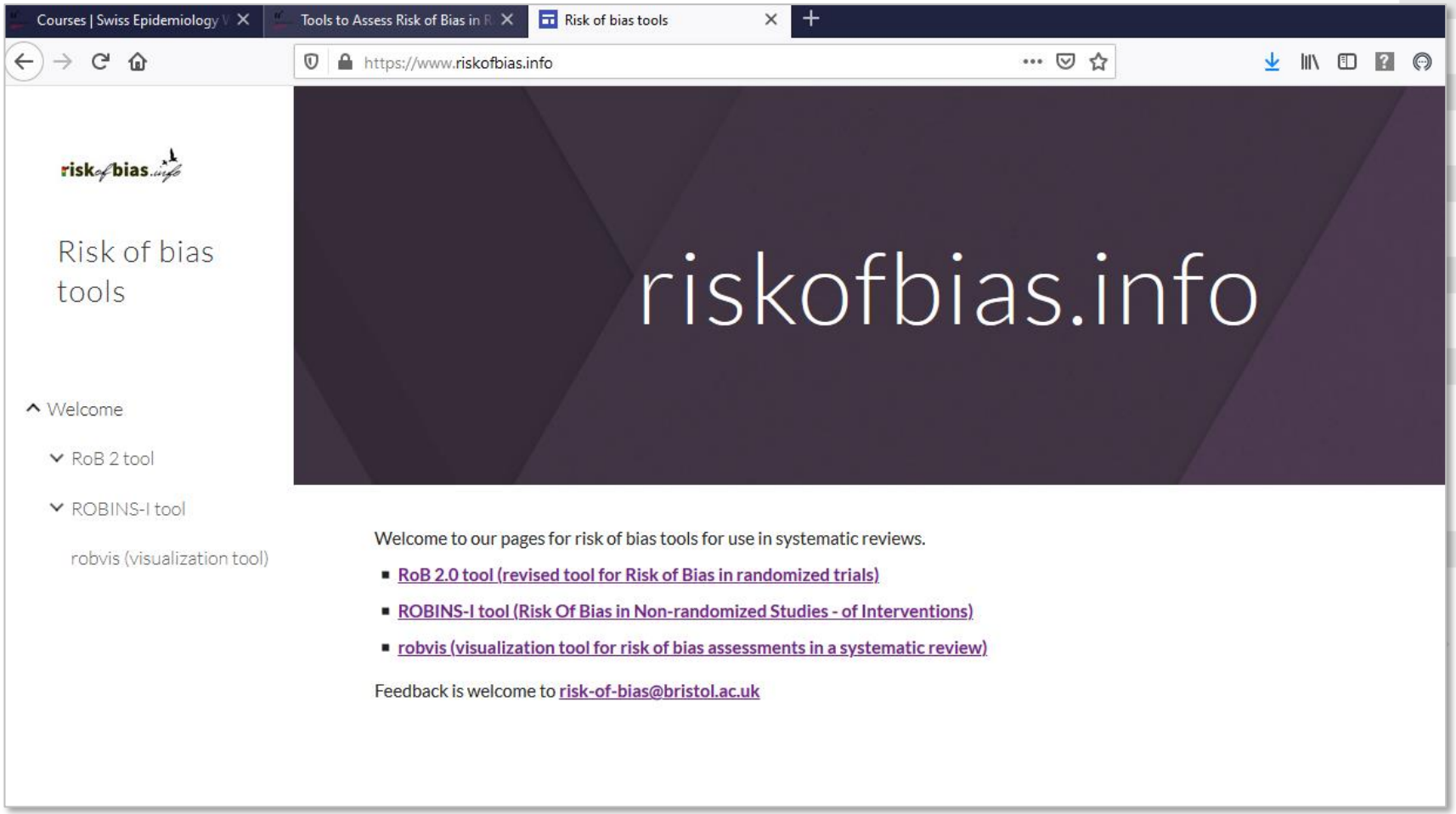
Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Overall
Low	Low	Low	Low	Low	?
Low	Some concerns	Low	Low	Some concerns	?
Low	Low	High	Low	Low	?
High	Low	Some concerns	High	High	?
Some concerns	Some concerns	Some concerns	Low	Some concerns	?

Suggested overall risk of bias judgement



Cochrane Training

riskofbias.info



Session outline

- risk of bias in systematic reviews
- **assessing sources of bias : the RoB 2 tool**
- putting it into practice
- incorporating risk of bias in a review

Risk of bias in randomized trials

Bias arising from the randomization process

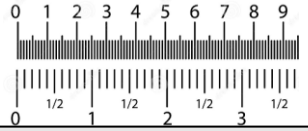
Bias due to deviations from intended intervention

Bias due to missing outcome data

Bias in measurement of the outcome

Experimental

Comparator



Outcome

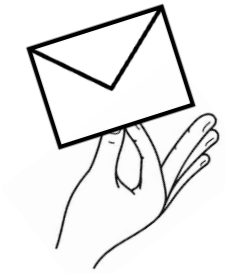
Outcome

1.02 3.87
2.20 4.32
1.38 5.44

Bias in selection of the reported result

Risk of bias in randomized trials

Bias arising from the randomization process



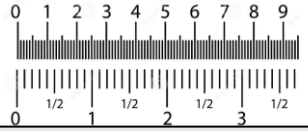
Bias due to deviations from intended intervention

Experimental

Comparator

Bias due to missing outcome data

Bias in measurement of the outcome



Outcome

Outcome

1.02	3.87
2.20	4.32
1.38	5.44

Bias in selection of the reported result

Random allocation sequence

- allocation of participants to interventions occurs at the start of a trial
  - based on random assignment of participants into experimental or comparator intervention groups
  - avoids systematic differences in known or unknown prognostic factors between groups

Random allocation sequence

Adequate - unpredictable sequence

- these days, almost always computer-generated
- low tech - coin toss, shuffling cards or envelopes, throwing dice, drawing lots, random number tables
- minimization

Inadequate – predictable sequence

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

Allocation sequence concealment

- occurs at the point of allocating participants to interventions
  - it is essential that when a person is recruited to the study, no-one can predict which group they will be allocated to
- ensures that the random sequence is implemented by preventing knowledge of the next allocation from:
  - changing the order of enrolment
  - affecting selection of who to enrol

Allocation sequence concealment

Adequate – cannot foresee

- central allocation (phone, web, pharmacy)
- sequentially numbered, sealed, opaque envelopes
- sequentially numbered, identical drug containers

Inadequate – can foresee

- random sequence known to staff in advance
- envelopes or packaging without all safeguards
- deducing last allocation(s) in fixed size blocks
- any non-random, predictable sequence

Evidence from baseline imbalance

- *Occasionally*, baseline imbalance provides evidence that randomization was not performed adequately
  - e.g. substantial differences between **intervention group sizes** (compared with intended allocation ratio)
  - e.g. **substantial excess in statistically significant differences** in baseline characteristics, clearly beyond that expected by chance
    - a few instances of "P <0.05" is not considered a substantial excess

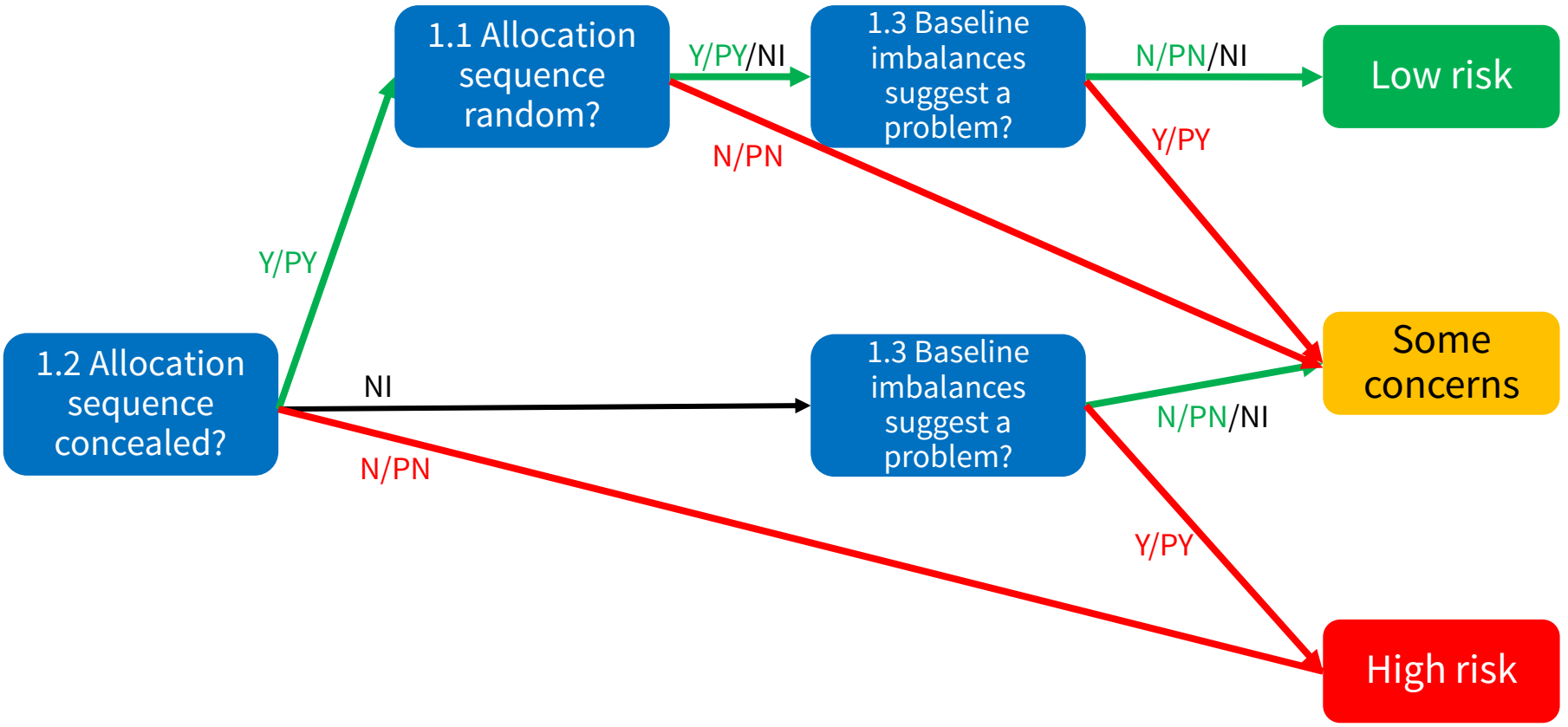
Imbalances in baseline variables that have arisen due to chance do not lead to bias

Illustration of signalling questions: Domain 1

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



Risk of bias in randomized trials

Bias arising from the randomization process

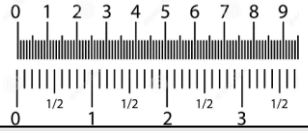
Bias due to deviations from intended intervention

Bias due to missing outcome data

Bias in measurement of the outcome

Experimental

Comparator



Outcome

Outcome

1.02	3.87
2.20	4.32
1.38	5.44

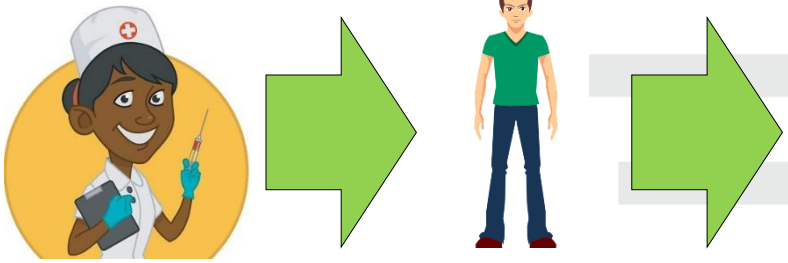
Bias in selection of the reported result

What are deviations from intended intervention?

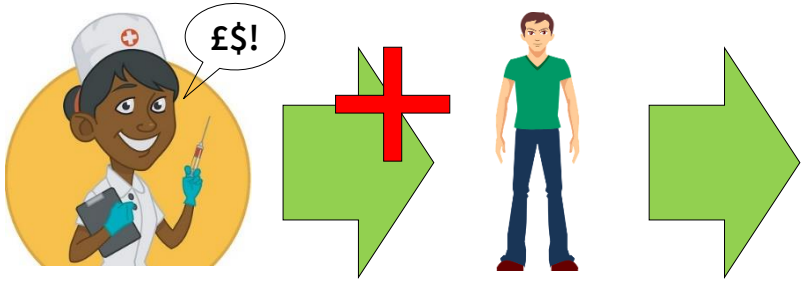
Intervention provider

Participant

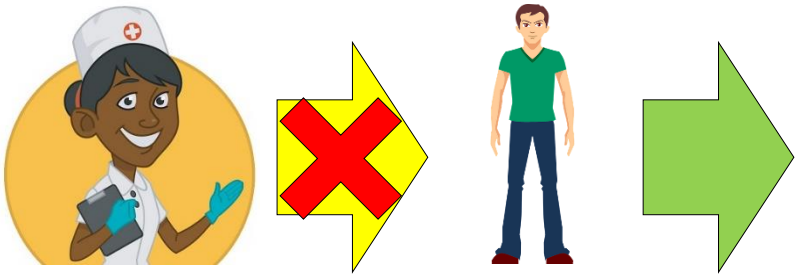
Intended intervention protocol:



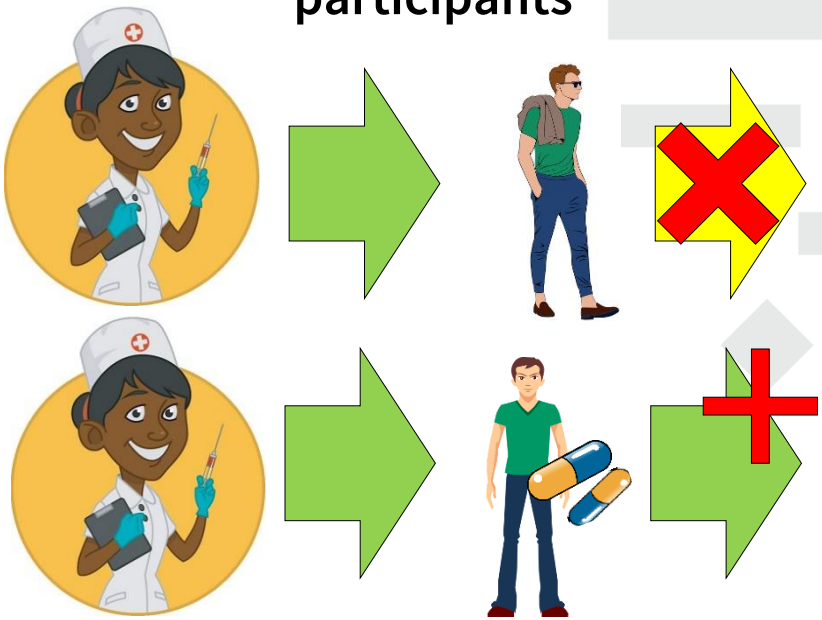
1. Additional interventions given



2. Failure to implement as intended



3. Non-adherence by trial participants



Images by iStock and OpenClipart-Vectors from Pixabay

Deviations from intended intervention

1. administration by trial staff of **additional interventions** that are inconsistent with the trial protocol (*non-protocol interventions)*
   - if possible, specify potential non-protocol interventions in the review protocol
2. **failure** by trial staff **to implement** the protocol interventions **as intended**
3. **non-adherence** to assigned intervention **by trial participants**

NB Trial protocols may not fully specify the interventions that are intended

Specify potential non-protocol interventions in the review protocol if possible

Changes to intervention

- It is often intended that the intervention will change over time
- For example, trial investigators may intend that:
  - participants experiencing severe toxicities should receive additional care and/or switch to an alternative therapy
  - participants whose disease progresses should switch to a second-line intervention

Such changes to intervention

- **are consistent with the trial protocol**
- **do not cause bias, and**
- **should not be considered to be deviations from intended intervention**

The role of blinding

Blinding of participants and trial personnel should prevent knowledge of intervention assignment from influencing:

- contamination (application of one of the interventions in participants intended to receive the other)
- switches to non-protocol interventions
- non-adherence by trial participants

The role of blinding

Blinding of participants and trial personnel:

- **essential** in trials that aim to eliminate placebo effects and isolate specific effects of protocol interventions
- **not appropriate** in pragmatic trials whose goal is to compare interventions in individuals who are aware of their care

Blinding of outcome assessors is considered separately in RoB 2 (see domain 4)

The effect of interest

Scenario: large RCT of screening for colorectal cancer

- patients individually randomized to receive an invitation to attend screening
- 55% of patients in the intervention arm attended screening
- all patients were followed up for 10 years after randomization

We could be interested in either or both of:

- the **effect of assignment to intervention**
  - the 'intention-to-treat' (ITT) effect
  - may be of most interest to a policymaker considering whether to introduce a screening programme
- the **effect of adhering to intervention** as specified in the trial protocol
  - the 'per-protocol' effect
  - may be of most interest to a patient deciding whether to be screened

Cochrane Reviews usually address the effect of assignment to intervention (the 'intention-to- treat' [ITT] effect)

Research

Original Investigation

Effect of Flexible Sigmoidoscopy Screening on Colorectal Cancer Incidence and Mortality
A Randomized Clinical Trial

Øyvind Holme, MD; Magnus Løberg, MD; Mette Kalager, MD, PhD; Michael Bretthauer, MD, PhD; Miguel A. Hernán, MD, DrPH; Eline Aas, PhD; Tor J. Eide, MD, PhD; Eva Skovlund, PhD; Jørn Schneede, MD, PhD; Kjell Magne Tveit, MD, PhD; Geir Hoff, MD, PhD

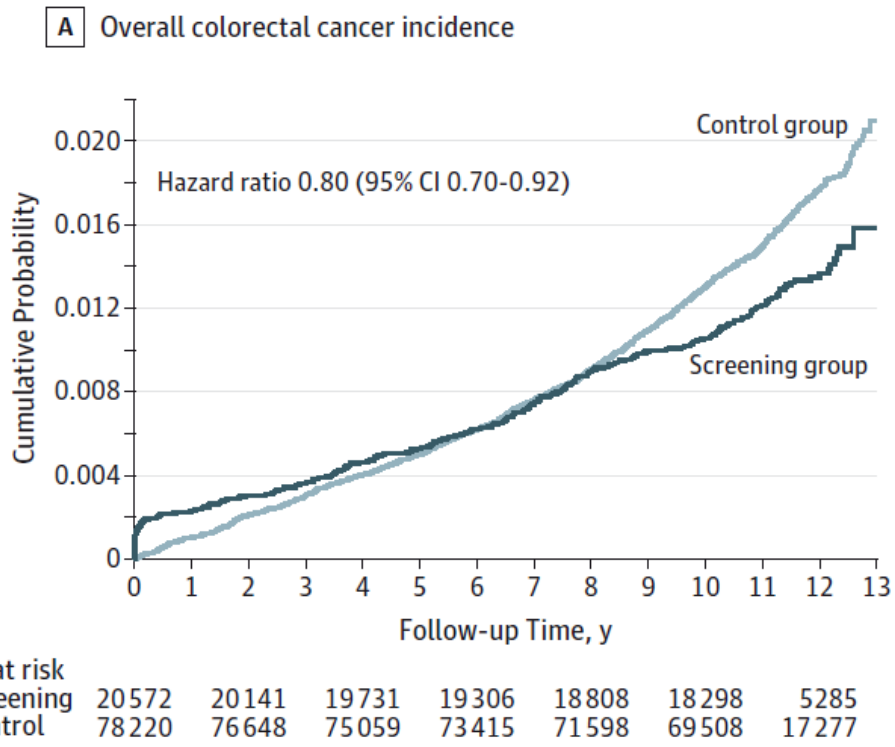
IMPORTANCE Colorectal cancer is a major health burden. Screening is recommended in many countries.

OBJECTIVE To estimate the effectiveness of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality in a population-based trial.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial of 100 210 individuals aged 50 to 64 years, identified from the population of Oslo city and Telemark County, Norway. Screening was performed in 1999-2000 (55-64-year age group) and in 2001 (50-54-year age group), with follow-up ending December 31, 2011. Of those selected, 1415 were excluded due to prior colorectal cancer, emigration, or death, and 3 could not be traced in the population registry.

INTERVENTIONS Participants randomized to the screening group were invited to undergo screening. Within the screening group, participants were randomized 1:1 to receive once-only flexible sigmoidoscopy or combination of once-only flexible sigmoidoscopy and fecal occult blood testing (FOBT). Participants with positive screening test results (cancer, adenoma, polyp ≥10 mm, or positive FOBT) were offered colonoscopy. The control group received no intervention.

MAIN OUTCOMES AND MEASURES Colorectal cancer incidence and mortality.



Adherence with screening was 63%

- 10-year risk absolute difference in colorectal cancer incidence:
  - Intention-to-screen effect: −0.22% (95% CI −0.38% to -0.06%)
  - Per-protocol effect (adherence-adjusted analysis using an instrumental variable approach): −0.42% (95% CI −0.69% to -0.15%)

Estimating the effect of assignment to intervention

Cochrane Reviews usually assess the effect of assignment to intervention (the ITT effect)

- we should use an 'intention-to-treat' (ITT) analysis:
  - analyse participants in the intervention groups to which they were randomized, regardless of the intervention received
  - include all randomized participants in the analysis
  - measure outcome data on all participants

- providing that the analysis is appropriate:
  - in blinded trials, risk of bias due to deviations from intended intervention **will be low**
  - in unblinded trials, risk of bias due to deviations from intended intervention **will usually be low**

Bias due to deviations from intended intervention
(effect of assignment to intervention)

In RoB 2 we assess only deviations that arose because of the trial context:

- whether the process of **recruiting and engaging with participants** affected their behaviour
  - e.g. participants assigned to the comparator group may feel unlucky and therefore seek the experimental intervention
- whether **trial personnel undermined trial comparisons** by implementing non-protocol interventions or failing to implement the protocol interventions
  - unconscious processes (e.g. lack of equipoise leading to administration of non-protocol interventions in one group
  - conscious processes (e.g. arising from a conflict of interest)

Bias due to deviations from intended intervention (effect of adhering to intervention)

- For details of assessing risk of bias in the **effect of adhering to intervention**, refer to the RoB 2 guidance

Risk of bias in randomized trials

Bias arising from the randomization process

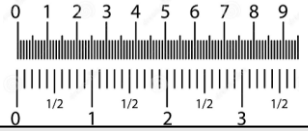
Bias due to deviations from intended intervention

Bias due to missing outcome data

Bias in measurement of the outcome

Experimental

Comparator



Outcome

Outcome

1.02 3.87
2.20 4.32
1.38 5.44

Bias in selection of the reported result

Missing outcome data

When outcome data are not available for all participants

- possible reasons:
  - ?
  - ?
  - ?

Missing outcome data

When outcome data are not available for all participants

- possible reasons include:
  - participants withdraw from the study or cannot be located
  - participants do not attend a study visit at which the outcome should have been measured
  - participants can no longer experience the outcome (e.g. died)

- exclusions from analysis for reasons other than missing data are not addressed in this domain
  - see domain 2 (deviations from intended intervention)

How much is too much missing outcome data?

There is no sensible threshold for 'small enough' in relation to the proportion of missing outcome data

- in situations where missing outcome data lead to bias, the extent of bias will increase as the amount of missing outcome data increases

- the potential impact of missing data on estimated intervention effects depends on:
  - the number of participants with missing data
  - the type of outcome
    - e.g. continuous, dichotomous, time-to-event
  - (for dichotomous outcomes) the risk of the event

When do missing outcome data lead to bias?

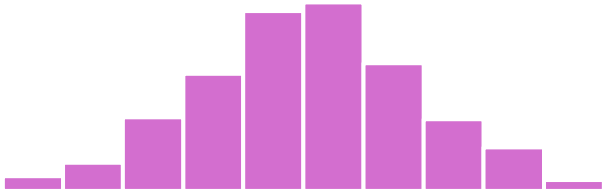
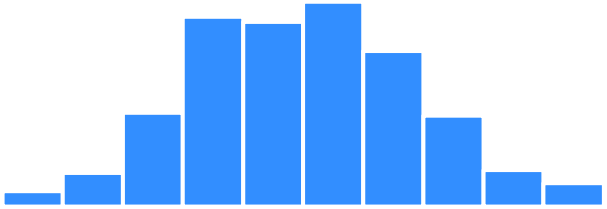
- we need to consider the **true value of the outcome** in participants with missing outcome data
  - this is the value of the outcome that should have been measured but was not
- **example**: trial of cognitive behavioural therapy compared with usual care for depression
  - if participants who are more depressed (true value of the outcome) are less likely to return for follow-up, then whether the depression outcome is missing depends on its true value
  - this implies that the measured depression outcomes will differ systematically from the true values of the missing depression outcomes

When do missing outcome data lead to bias?

refer to this as "missingness" in the outcome variable

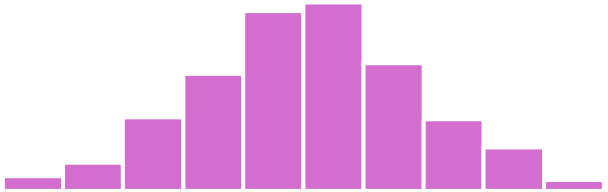
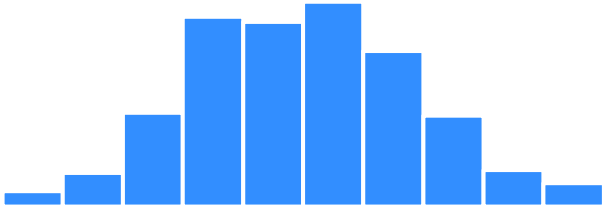
More depression symptoms ⟵ ⟶ Less depression symptoms

No bias: missingness unrelated to true values

Experimental intervention	Participants with measured outcomes	
	Participants with missing outcomes	
Comparator intervention	Participants with measured outcomes	
	Participants with missing outcomes	

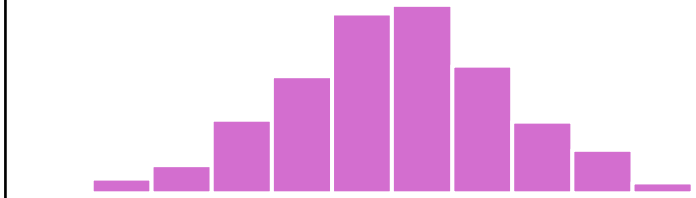
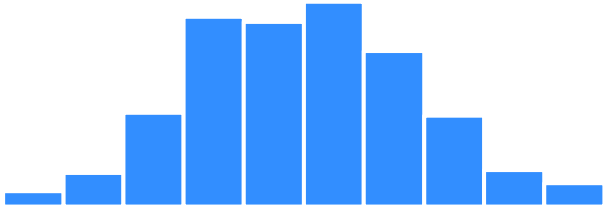
e.g. data missing because automatic measuring device failed for a subset of participants

Bias: missingness depends on true values and on intervention group

Experimental intervention	Participants with measured outcomes	
	Participants with missing outcomes	
Comparator intervention	Participants with measured outcomes	
	Participants with missing outcomes	

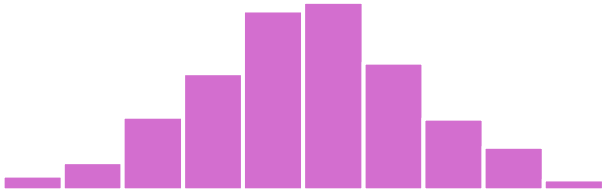
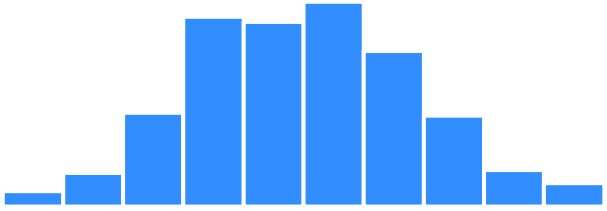
e.g. (1) more withdrawals in experimental group due to side effects and (2) those with continuing symptoms more likely to withdraw

No bias: missingness depends on true values, but things are identical in both intervention groups

Experimental intervention	Participants with measured outcomes	
	Participants with missing outcomes	
Comparator intervention	Participants with measured outcomes	
	Participants with missing outcomes	

e.g. (1) those with continuing symptoms more likely to drop out and (2) the experimental intervention has no effect

Bias likely: missingness depends on true values, and effects of experimental and comparator intervention differ

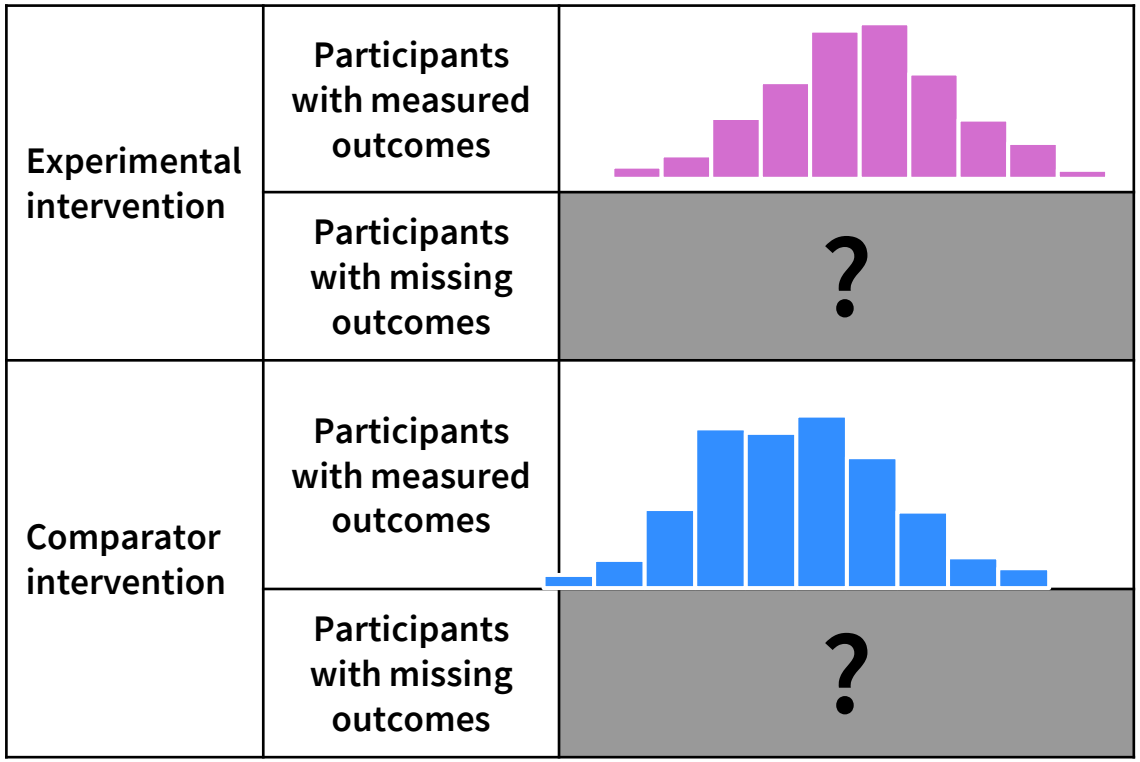
Experimental intervention	Participants with measured outcomes	
	Participants with missing outcomes	
Comparator intervention	Participants with measured outcomes	
	Participants with missing outcomes	

e.g. (1) those with continuing symptoms more likely to drop out and (2) the experimental intervention has an effect

It's a bit more complex than this (more details in the RoB 2 guidance)…

How do we know whether there is bias?

- unfortunately it is not possible to examine directly whether missingness in the outcome depends on its true value
- but, we can infer that missingness may depend on the true value if:
  - there were differences between intervention groups in the proportions of missing outcome data
  - reported reasons for missing outcome data provide evidence that missingness in the outcome depends on its true value
  - reported reasons for missing outcome data differ between the intervention groups



Looking at sensitivity analyses

- The important consideration is whether a **sufficiently wide range of plausible values for the missing outcome data** have been considered in the sensitivity analyses
  - this is usually more important than which *methods* have been used

- **multiple imputation** is commonly used to address bias and other problems caused by missing data
  - but in trials, multiple imputation will usually not remove or reduce the bias that occurs when missingness in the outcome depends on its true value
  - see RoB 2 guidance

Bias due to missing outcome data

Low risk of bias

- outcome data are available for all or nearly all participants
- there is evidence (e.g. from sensitivity analyses) that the result is not biased by missing outcome data
- missingness in the outcome does not depend on its true value

High risk of bias

- it is likely that missingness in the outcome depended on its true value

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

Bias in measurement of the outcome

Experimental

Comparator

Outcome

Outcome

1.02 3.87
2.20 4.32
1.38 5.44

Bias in selection of the reported result

Bias in measurement of the outcome

Need to consider:

- whether method of measuring the outcome is appropriate
- whether measurement or ascertainment of outcome differs between intervention groups
- who is assessing the outcome
- whether outcome assessor is blinded to intervention assignment
- whether assessment of outcome is likely to be influenced by knowledge of intervention assignment

Blinding of outcome assessment

- avoids knowledge of intervention received affecting measurement of the outcome
- assess carefully
  - blinding of outcome assessors may be feasible even where blinding of participants and care providers is not
  - remember that participants and carers may also be outcome assessors
  - is it likely that blinding was broken?
  - the terms “single-blind” and “double-blind” do not tell us who was blinded

Blinding of outcome assessment

Low risk of bias

- blinding implemented, and unlikely that the blinding could have been broken
- no blinding, but measurement unlikely to be influenced by knowledge of the intervention assignment

High risk of bias

- no blinding or broken blinding, and measurement likely to be influenced

Risk of bias in randomized trials

Bias arising from the randomization process

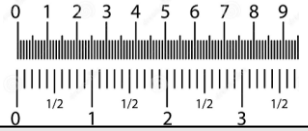
Bias due to deviations from intended intervention

Bias due to missing outcome data

Bias in measurement of the outcome

Experimental

Comparator



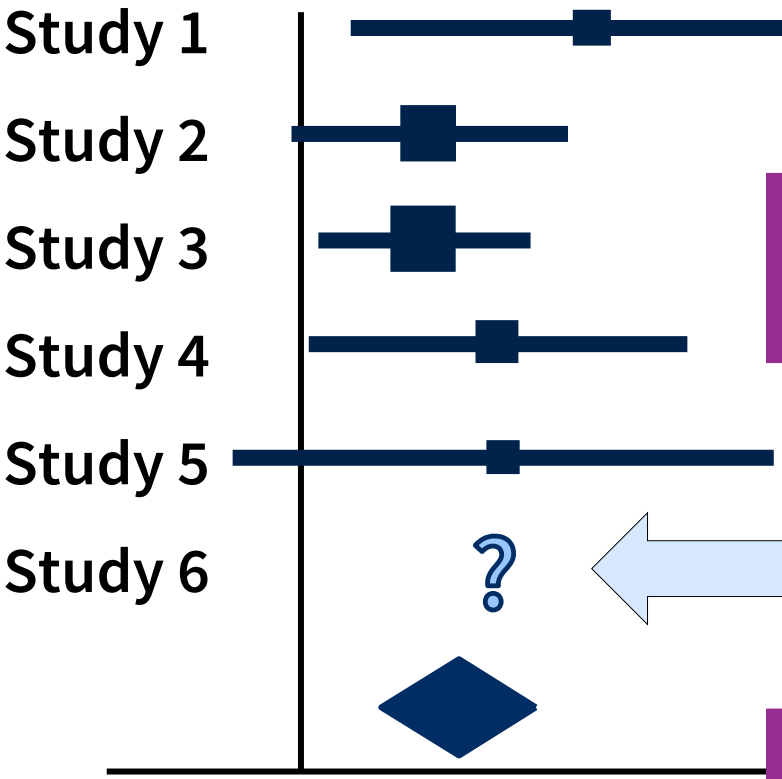
Outcome

Outcome

1.02	3.87
2.20	4.32
1.38	5.44

Bias in selection of the reported result

Selective reporting vs selective non-reporting



1 result reported from among 3 scales used for the same clinical outcome

Potential bias in selection of the reported result: Domain 5 in RoB 2

Not reported, because “P > 0.05”

Potential bias in the meta-analysis: ROB ME tool

Bias in selection of the reported result

May arise when results are selected based on their magnitude, direction or P value, from:

- multiple outcome measurements within the outcome domain, e.g.
  - multiple scales
  - multiple definitions of/criteria for an event
  - multiple time points
- multiple analyses of the outcome measurement, e.g.
  - unadjusted *vs* adjusted models
  - different sets of covariates in adjusted models
  - final values *vs* change from baseline *vs* analysis of covariance
  - continuous scale converted to categorical data with different cut-points

How to spot bias in selection of the reported result

- ideally, we have a pre-specified analysis plan
  - a trial protocol (even a registry record) may be sufficient
  - date stamped before (unblinded) data set available
  - outcome measures changed? statistics changed?
- what if there is no pre-specified analysis plan?
  - compare ‘Methods’ with ‘Results’ – look for:
    - outcomes measured (or likely to be measured) but not reported
    - reporting that cannot be used in a review (e.g. stating non-significance without numerical results)

Bias in selection of the reported result

Low risk of bias

- prespecified trial analysis plan is available
- review authors' preferred outcome measures (and analyses) reported according to trial analysis plan, irrespective of the results

Some concerns

- many trials will be judged in this category

High risk of bias

- evidence (or strong hint) that the reported outcome measure (or analysis) was selected on the basis of the results

Session outline

- risk of bias in systematic reviews
- assessing sources of bias : the RoB 2 tool
- **putting it into practice**
- incorporating risk of bias in a review

Completing the assessments

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

Implementation of RoB 2

- options for performing the assessment
  - Excel tool is available
  - Word template
  - online tool (forthcoming)
- in RevMan Web
  - RoB 2 assessments are attached to results within studies
  - input risk of bias judgements (for each domain and overall), plus support for each judgement, to create a table
  - answers to signalling questions (consensus version) can be included as a supplement
- The information in this slide is subject to change as tools are developed. Check **riskofbias.info** for the latest implementation tools

Cochrane Training

Cochrane RevMan

[Practice] Caffeine for daytime drowsiness

DS My reviews Practice reviews

Default view Full text

Dashboard
Review information
Text
Studies
Other references
Analyses
Tables
Figures
Appendices
Comments

Back to Analyses 1.1 Headache

Risk of bias: Amore-Coffea 2000

Results being assessed

1.1 Headache

Caffeine Events	Caffeine Total	Decaf Events	Decaf Total	Risk ratio M-H, Fixed, 95% CI
2	31	10	34	0.22 [0.05 , 0.92]

Bias arising from the randomization process

This is a study-level judgement, changes made here apply to all results within the study

Judgement Low risk of bias | **Some concerns** | High risk of bias

Support for judgement Allocation concealment was not described.

Bias due to deviations from intended interventions

Judgement Low risk of bias | **Some concerns** | High risk of bias

Support for judgement Unclear whether blinding of participants have been done.

All changes saved

Bias due to missing outcome data

Judgement **Low risk of bias** | Some concerns | High risk of bias

Support for judgement No concerns

https://documentation.cochrane.org/revman-kb/risk-of-bias/risk-of-bias-2-in-revman-web

Cochrane Training

Cochrane RevMan | [Template] Caffeine for daytime drowsiness | TM | My reviews | Practice reviews

Default view | Full text

- Dashboard
- Review information
- Text
- Studies
- Other references
- Analyses
- Tables
- Figures
- Appendices
- Comments

Risk of bias for analysis 1.1 Headache

Study	Bias							
	Randomisation process		Deviations from intended interventions		Missing outcome data		Measurement of the outcome	
	Authors' judgement	Support for judgement	Authors' judgement	Support for judgement	Authors' judgement	Support for judgement	Authors' judgement	Support for judgement
Subgroup 1.1.1 New Subgroup								
Amore-Coffea 2000	Some concerns	Neither the method of generating the randomisation sequence, or allocation concealment were described	Low risk of bias	It is likely that participants were blinded because steps were taken to ensure taste was similar. There were no deviations from the intended intervention.	Low risk of bias	Most data were available. n=78 participants recruited. Data for the majority of these (n=75, 96%)	Low risk of bias	Headache diaries is the usual way to record and report the number of headaches and were used for both groups. Outcome was assessed by the participants who were unaware of the intervention.
		Quote: "80 participants were randomized... using a computer-generated		Blinding of participants and personnel were not described. A		Comment: number of participants		Headache was assessed using "reaction time test" in both

Session outline

- risk of bias in systematic reviews
- assessing sources of bias : the RoB 2 tool
- putting it into practice
- **incorporating risk of bias in a review**

Incorporating findings into a review

Options include

- give a brief narrative summary
  - but it may be missed by readers
  - and it does not address impact on results
- present a stratified analysis
- restrict primary analysis to studies at low risk (or 'low risk' and 'some concerns')
  - conduct sensitivity analysis
- explore the impact further if sufficient studies are available
  - subgroup analysis
  - meta-regression - get statistical advice

Address risk of bias outcome by outcome

Cochrane Training

Risk of bias summary

Risk of bias

Click on one or more cells to see and compare the Support for judgement for that bias, or click on a bias header to open all bias in that column.

Legend: Low risk of bias | High risk of bias | Some concerns

Table Risk of bias for analysis 1.1 ADL Outcomes - Immediately after intervention

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Ada 2013	+	+	+	+	+	+
	Blinded outcome assessment using a validated measure, in which assessors were trained					
Burgar 2011	~	x	+	+	~	x
	Some data					
Dromerick 2009	+	~	+	x	+	~
	Some data					
English 2015	+	+	x	~	+	~
	Some data					
GAPS 2004	+	+	+	+	~	~
	Blinded outcome assessment, using a reliable and valid measure					
Lincoln 1999	~	~	x	+	+	~
	Some data					
Wang 2004	+	~	x	+	~	x
	Some data					

Table Risk of bias for analysis 1.1 ADL Outcomes - Medium term outcomes

Cite this Review
Request Permissions
Comment on Review
Read comments on this Review(0)

Print | Share | Follow

Abstract
Plain language summary
Authors' conclusions
Background
Objectives
Methods
Results
Discussion

Appendices

Information
Authors
History

References
Characteristics of studies
Risk Of Bias
Data and analyses

Figures and tables
Related content

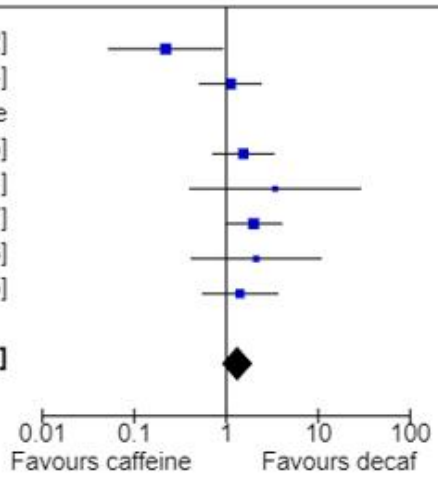
Risk of bias in a forest plot

Investigate sensitivity - 1.1 Headache

Odds ratio | **Risk ratio** | Risk difference | **Fixed effect** | Random effects | Scale 100 | Save image

Study or Subgroup	Caffeine Events	Caffeine Total	Decaf Events	Decaf Total	Weight	Risk ratio M-H, Fixed, 95% CI
✓ Amore-Coffea 2000	2	31	10	34	21.2%	0.22 [0.05 , 0.92]
✓ Deliciozza 2004	10	40	9	40	20.0%	1.11 [0.51 , 2.44]
✓ Kahve-Paradiso 2002	0	0	0	0		Not estimable
✓ Mama-Kaffa 1999	12	53	9	61	18.6%	1.53 [0.70 , 3.35]
✓ Morrocona 1998	3	15	1	17	2.1%	3.40 [0.39 , 29.31]
✓ Norscafe 1998	19	68	9	64	20.7%	1.99 [0.97 , 4.07]
✓ Oohlahlazza 1998	4	35	2	37	4.3%	2.11 [0.41 , 10.83]
✓ Piazza-Allerta 2003	8	35	6	37	13.0%	1.41 [0.54 , 3.65]
Total (95% CI)		**277**		**290**	**100.0%**	**1.31 [0.92 , 1.87]**
Total events:	58		46			

Heterogeneity: Chi² = 8.66, df = 6 (P = 0.19); I² = 31%
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

GRADEing the evidence

- 'Risk of bias' assessment is also incorporated into a GRADE assessment of the certainty of evidence
- for studies that contribute data for each outcome:
  - what is the overall risk of bias of these studies?
  - does the risk of bias reduce our confidence in the effect?

to be continued...

www.gradeworkinggroup.org

What to include in a protocol

- check with Cochrane group for standard text
- state risk of bias assessment tool(s) to be used
  - new Cochrane intervention reviews should use RoB 2
  - state the effect of interest (*effect of assignment to intervention* or of *adhering to intervention*) - usually the former
  - refer to Handbook Chapter 8 or another source
- which results will be assessed for risk of bias?
- how many people will assess risk of bias?
  - how will disagreements be handled
- how will findings be incorporated into the analysis?

Take-home message

- biased studies may lead to misleading reviews
- RoB 2 examines five domains of bias
- leads to a judgement about risk of bias in a result, with supporting evidence to justify it
- consider the possible impact of risk of bias on syntheses and use appropriate caution in drawing conclusions

References

- Higgins JPT, Savović J, Page MJ, Elbers RG, Sterne JAC. Chapter 8: Assessing risk of bias in a randomized trial. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). *Cochrane Handbook for Systematic Reviews of Interventions* version 6.0 (updated July 2019). Cochrane, 2019. Available from **www.training.cochrane.org/handbook**.
- Sterne JAC et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**: l4898; doi: 10.1136/bmj.l4898.
- Cochrane RoB 2 webinar series **training.cochrane.org/rob-2-learning-live-webinar-series**
- Full guidance available at **www.riskofbias.info**
- **Risk of Bias 2 Cochrane Review Starter Pack** (and other resources) – available at **https://methods.cochrane.org/risk-bias-2**

Acknowledgements

- Slides by Julian Higgins and Jonathan Sterne
- Using material from a previous version of the presentation by Miranda Cumpston, Cochrane Bias Methods Group and the Cochrane Australia