Assessing Risk of Bias in Randomized Controlled Trials

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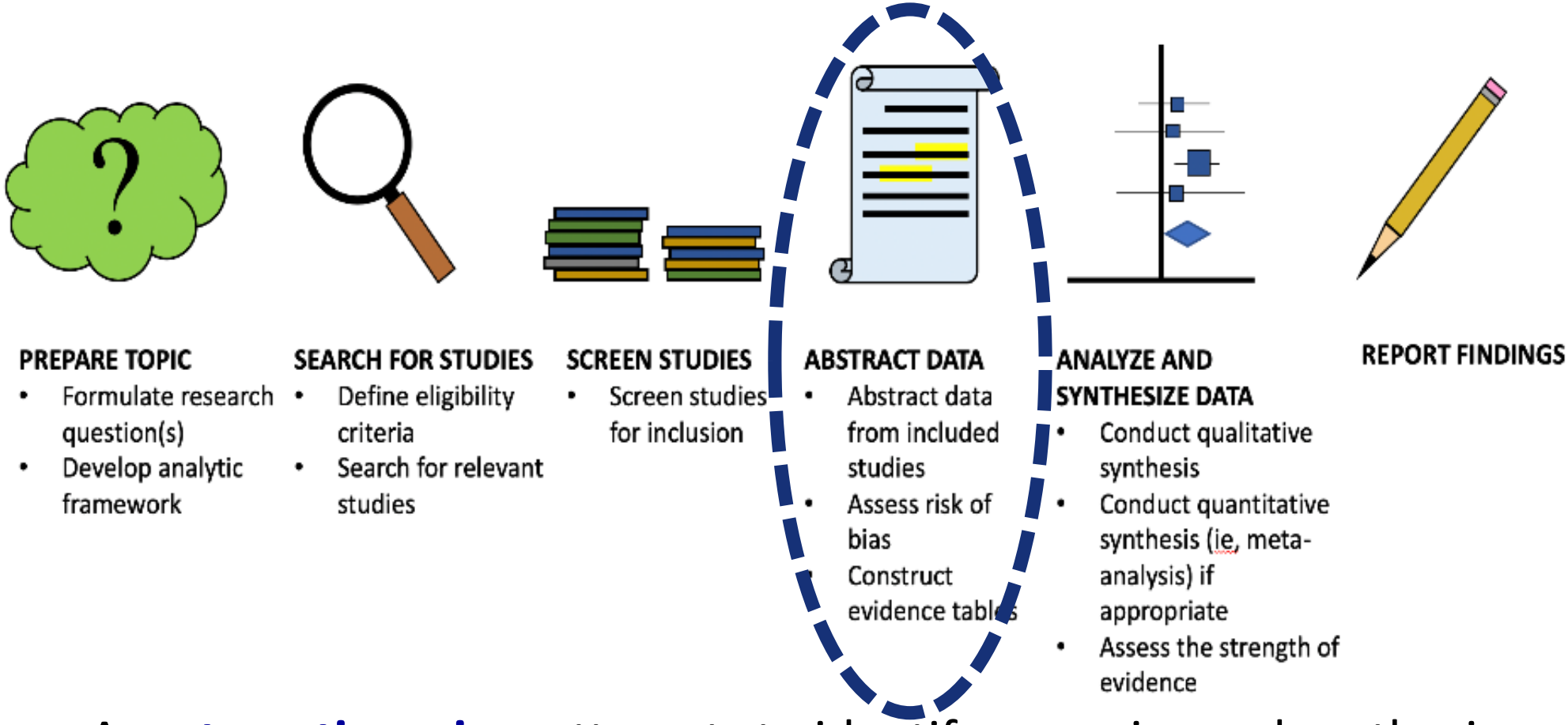
Steps in Completing a Systematic Review



PREPARE TOPIC
- Formulate research question(s)
- Develop analytic framework

SEARCH FOR STUDIES
- Define eligibility criteria
- Search for relevant studies

SCREEN STUDIES
- Screen studies for inclusion

ABSTRACT DATA
- Abstract data from included studies
- Assess risk of bias
- Construct evidence tables

ANALYZE AND SYNTHESIZE DATA
- Conduct qualitative synthesis
- Conduct quantitative synthesis (ie, meta-analysis) if appropriate
- Assess the strength of evidence

REPORT FINDINGS

A **systematic review** attempts to identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a specific research question.

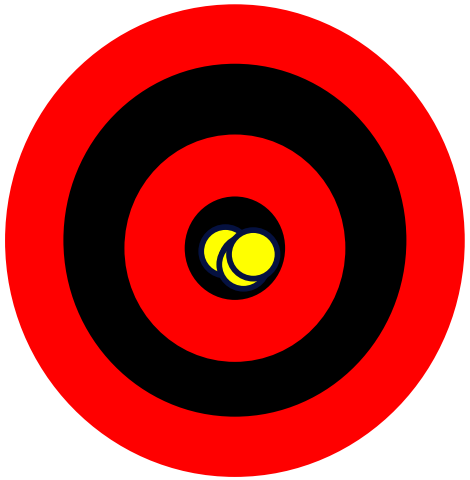
Adapted from Wallace C et al. J Compar Effect Res 2013; 2(3):273-282

Acknowledgement

- The latest version of the RoB 2 tool is available from https://www.riskofbias.info/welcome/rob-2-0-tool/

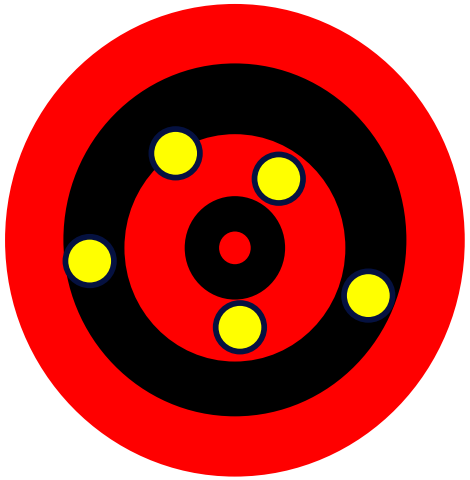
- Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ.* 2019 Aug 28;366:l4898. doi: 10.1136/bmj.l4898.

Systematic versus random error

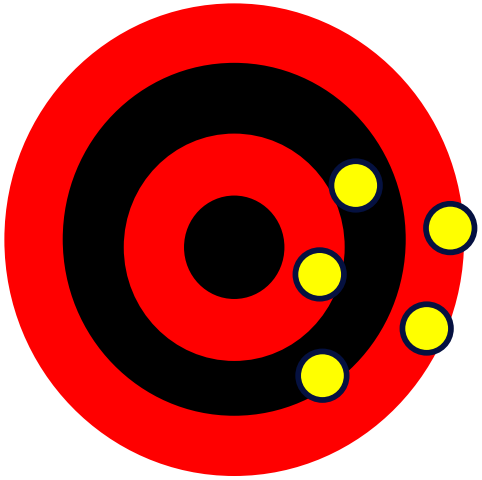


Neither systematic error nor random error

Systematic error, but no random error



Random error, but no systematic error



Random error AND systematic error

What is bias?

- Systematic error or deviation from the truth
  - 'Internal validity'
  - May overestimate or underestimate the effect

- We can't measure the presence of bias
  - Assess each study for **risk of bias**
  - Look for methods shown to minimize risk

Risk of bias *is not the same as...*

Bias

Actual deviations from the truth

Imprecision

Reflected in the confidence interval

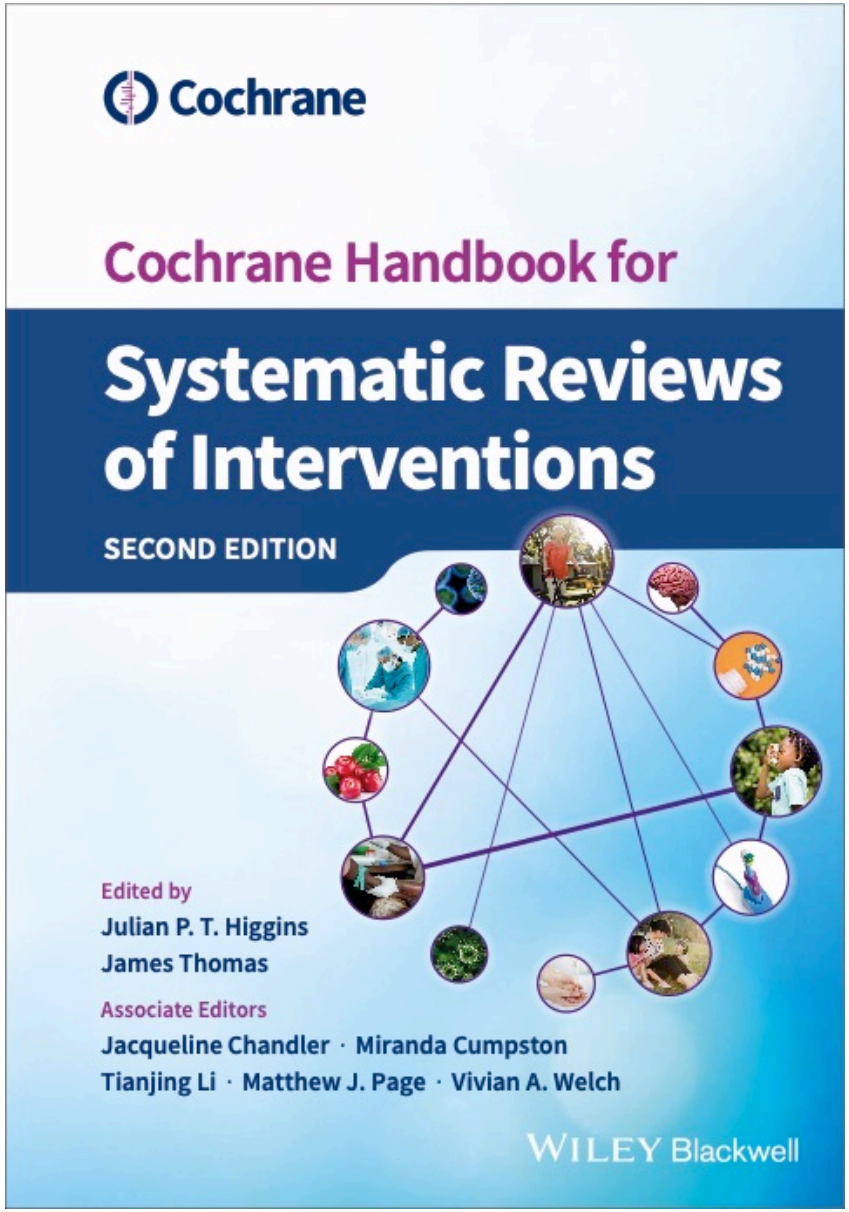
Quality

Bias can occur in well-conducted studies

Reporting

Good methods may have been used but not well reported

Version 2 of the Cochrane risk of bias tool (RoB 2)



Chapter 8: Assessing risk of bias in a randomized trial

Julian PT Higgins, Jelena Savović, Matthew J Page, Roy G Elbers, Jonathan AC Sterne

Key Points:

- This chapter details version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2), the recommended tool for use in Cochrane Reviews.
- RoB 2 is structured into a fixed set of domains of bias, focusing on different aspects of trial design, conduct and reporting.
- Each assessment using the RoB 2 tool focuses on a specific result from a randomized trial.
- Within each domain, a series of questions ('signalling questions') aim to elicit information about features of the trial that are relevant to risk of bias.
- A judgement about the risk of bias arising from each domain is proposed by an algorithm, based on answers to the signalling questions. Judgements can be 'Low', or 'High' risk of bias, or can express 'Some concerns'.
- Answers to signalling questions and judgements about risk of bias should be supported by written justifications.
- The overall risk of bias for the result is the least favourable assessment across the domains of bias. Both the proposed domain-level and overall risk-of-bias judgements can be overridden by the review authors, with justification.

Cite this chapter as: 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.

8.1 Introduction

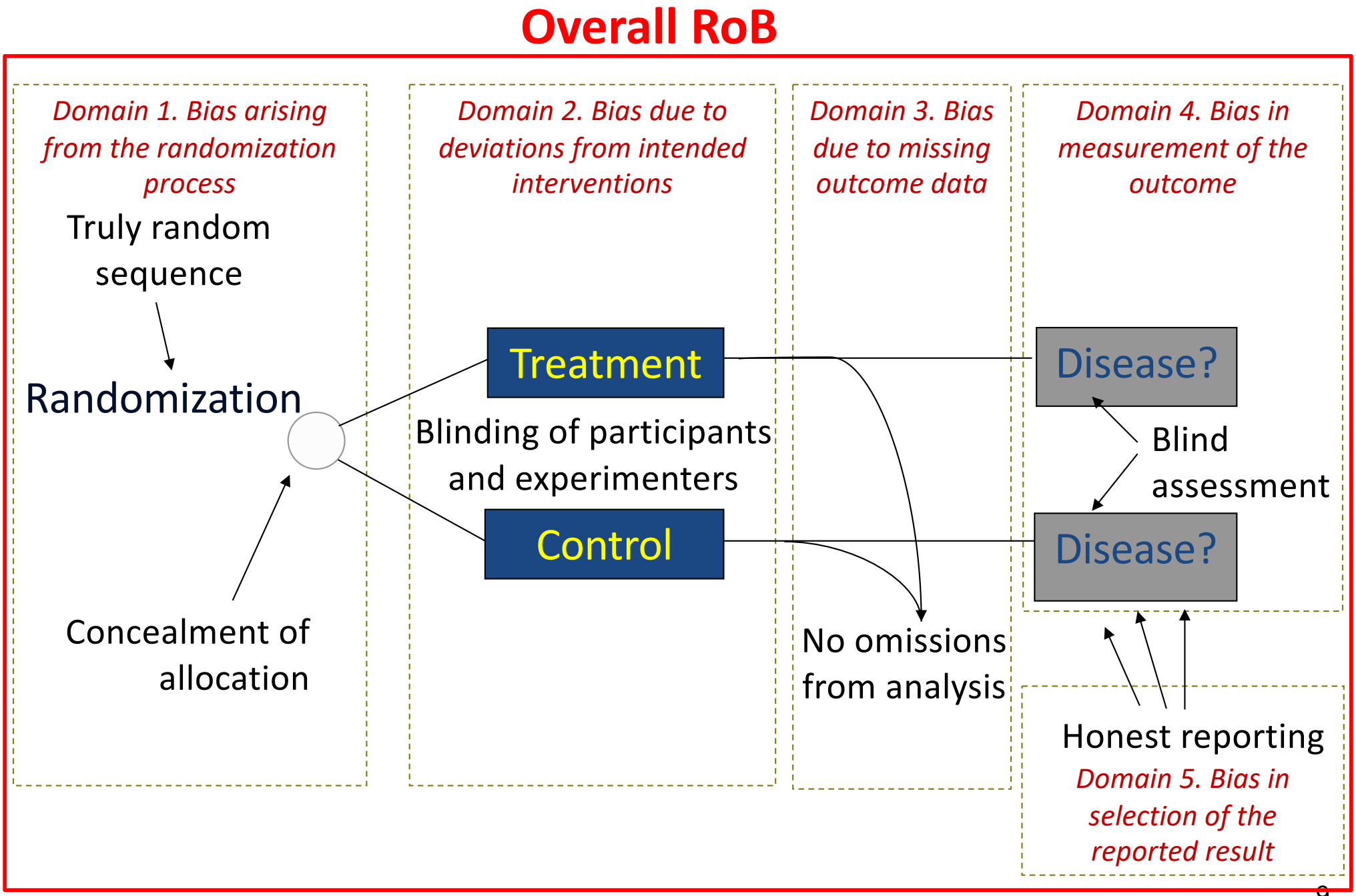
Cochrane Reviews include an assessment of the risk of bias in each included study (see Chapter 7 for a general discussion of this topic). When randomized trials are included, the recommended tool is the revised version of the Cochrane tool, known as RoB 2, described in this chapter. The RoB 2 tool provides a framework for assessing the risk of bias in a single result (an estimate of the effect of an experimental intervention compared with a comparator intervention on a particular outcome) from any type of randomized trial.

The RoB 2 tool is structured into domains through which bias might be introduced into the result. These domains were identified based on both empirical evidence and theoretical considerations. This chapter summarizes the main features of RoB 2 applied to individually randomized parallel-group trials. It describes the process of undertaking an assessment

RoB 2: Preliminary considerations before a RoB assessment

- What is the **study design**? (parallel group trial, cross-over trial, cluster-randomized trial)
  - Different RoB 2 templates for different trial variants
- Specify which **outcome and result** is being assessed for risk of bias
  - Typically from among outcomes earmarked for the 'Summary of findings' table, if planned
- Specify the **effect of interest**
  - Different RoB 2 templates for different effects of interest: the effect of assignment or adhering to the interventions
- Specify the **sources of information**

RoB 2 Domains



RoB 2: Signalling questions and judgements

Domain-specific judgements

- Signalling questions make the tool easier (and more transparent)
  - 'Yes', 'Probably yes', 'Probably no', 'No', 'No information'
- Risk of bias judgements follow from answers to signalling questions (can be over-ridden)
  - **'Low risk of bias', 'Some concerns', 'High risk of bias'**
- **Algorithms** to map answers to signalling questions onto risk of bias judgements

Overall risk of bias judgement

- Interpretation of the judgements is such that a 'High risk of bias' judgement in one domain puts the whole study at high risk of bias
- Can be completed automatically (can be over-ridden)

RoB 2: Overall risk of bias judgement

Low risk of bias	The study is judged to be at **low risk of bias for all domains** for this result.
Some concerns	The study is judged to have **some concerns** in at least one domain for this result.
High risk of bias	The study is judged to be at **high risk of bias** in at least one domain for this result. OR The study is judged to have **some concerns** for **multiple domains** in a way that substantially lowers confidence in the result.

Domain 1. Bias arising from the randomization process

Domain 1. Bias arising from the randomization process

- Two inter-related processes
  - Sequence generation
  - Allocation concealment

- Failure to implement either process adequately creates opportunities for either the enrolment into the study or the allocation of enrolled participants into groups to be influenced by both allocation and prognostic factors

- The end result is the same – unbalanced (biased) distribution of patients between groups (not a fair comparison, ***confounding***)

1.1 Random sequence generation

- Occurs at the start of a trial before allocation of participants
- Determines a random order of assigning people into intervention and comparison groups
- Accounts for known and unknown prognostic factors
- Prevents systematic differences between groups

1.1 Random sequence generation (cont'd)

Low risk of bias – unpredictable

- Random number table
- Computer random number generator
- Stratified or block randomisation
- Coin toss, shuffling cards or envelopes, throwing dice

High risk of bias – 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

1.2 Allocation concealment

- Occurs at the start of the trial during allocation of participants
- When a person is recruited to a study, no one is able to predict which group the person will be allocated to
- Ensures strict implementation of the randomly generated sequence
  - Prevents changing the order
  - Prevents selecting who to recruit
- Not to be confused with masking/blinding

ID	Assignment
1	A
2	A
3	B
4	A
5	B
6	B
7	B
8	A
9	A
10	B
…	…

1.3 Baseline imbalances

- Baseline imbalance can be related to the success of randomization
- Imbalances can occur by chance – this is not bias
- But baseline imbalances can provide clues to problems with randomization

1.3 Baseline imbalances (cont'd)

- Indicators from baseline imbalance that randomization was not performed adequately include the following:
  - Unusually large differences in intervention group sizes
  - Substantially more differences in baseline characteristics and key prognostic factors than would be expected by chance alone
  - Excessive similarity in baseline characteristics that is not compatible with chance

Baseline imbalance despite solid methods described

International Journal of Epidemiology, 2016, 223–231
doi: 10.1093/ije/dyv292
Advance Access Publication Date: 3 November 2015
Original article

Miscellaneous

The effect of u
incidence of di
scuba diving: a

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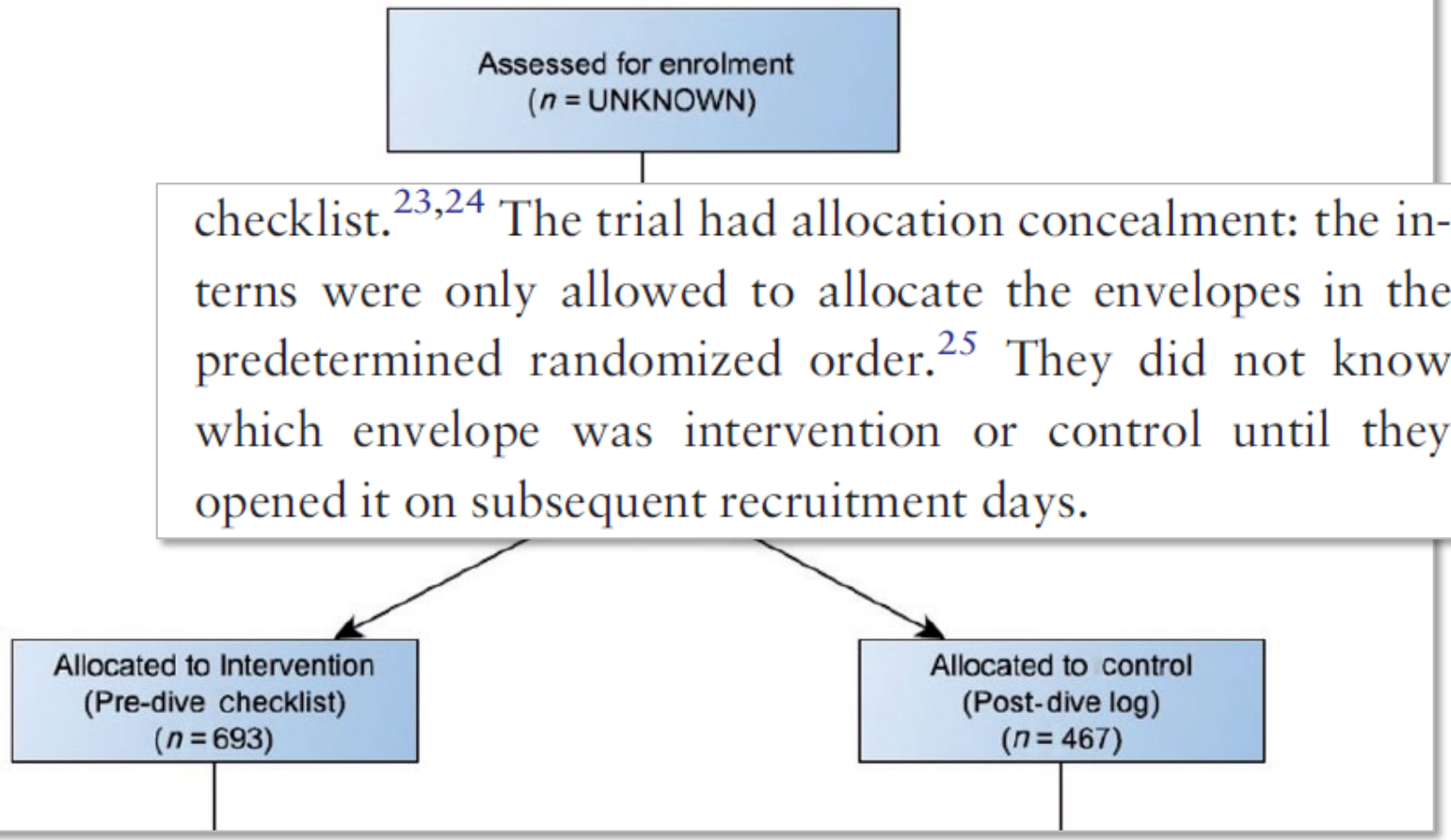
Accepted 5 October 2015

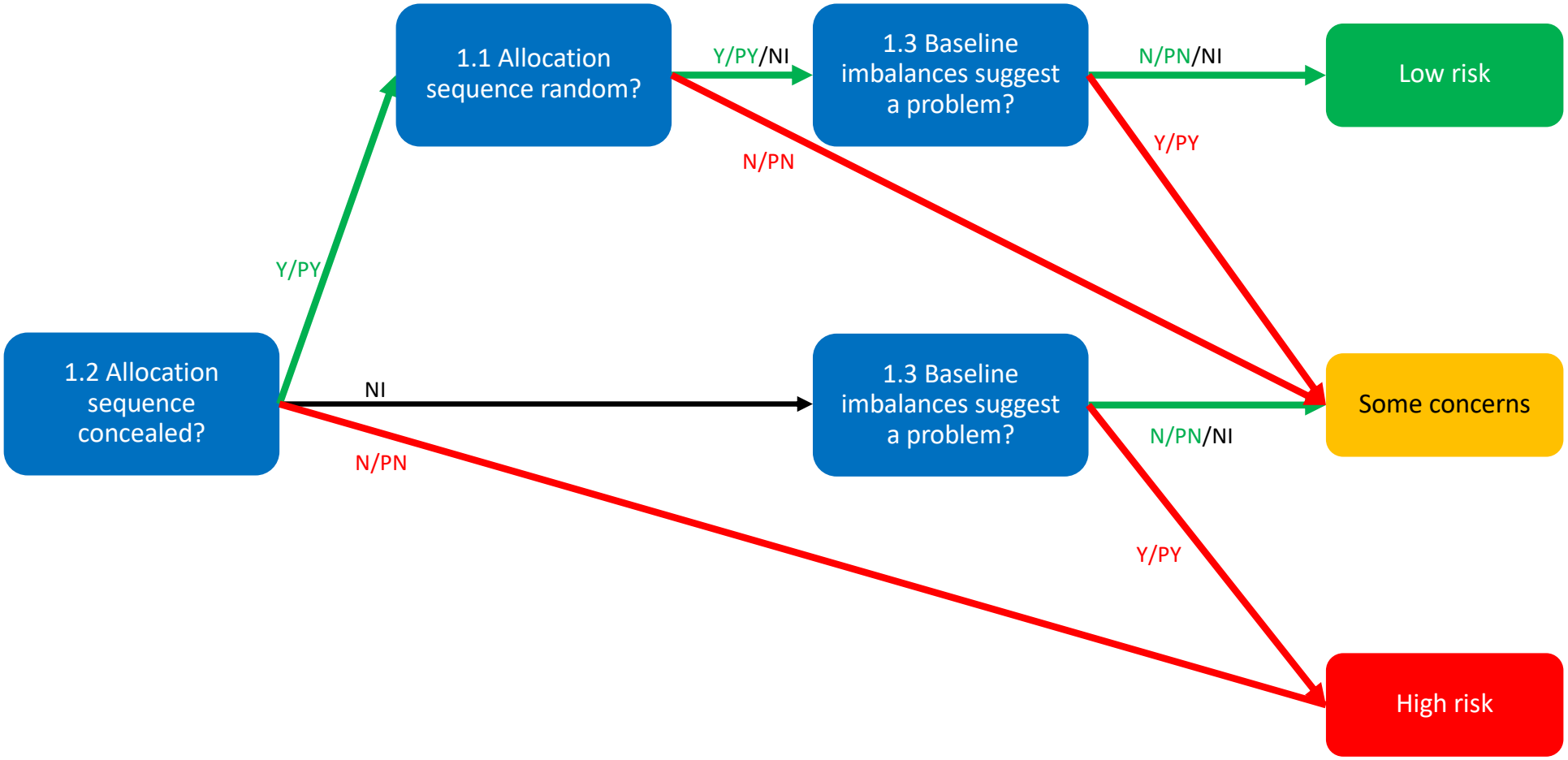
checklist.[23,24] The trial had allocation concealment: the interns were only allowed to allocate the envelopes in the predetermined randomized order.[25] They did not know which envelope was intervention or control until they opened it on subsequent recruitment days.



Domain 1. Bias arising from the randomization process

1.1 Was the allocation sequence random? 1.2 Was the allocation sequence concealed until participants were recruited and assigned to interventions?	**Randomization methods**
1.3 Were there baseline imbalances that suggest a problem with the randomization process?	**Additional evidence of problems**

Domain 1. Bias arising from the randomization process



Domain 2. Bias due to deviations from intended interventions

What is the effect of interest?

- Investigators conducted a large randomized trial of screening for colorectal cancer:
  - Patients registered with family doctors were individually randomized to receive an invitation to attend for screening
  - 55% of patients in the intervention arm attended screening
  - All patients were followed up for colorectal cancer 10 years after randomization, using routine data
- What can we learn from this trial? Who would be interested in the results?

The effect of interest

- "Intention-to-treat (ITT) effect": **effect of assignment to intervention**
  - e.g., the question of interest to a policy maker about whether to introduce a screening program
- "Per protocol effect": **effect of adhering to intervention**
  - e.g., the question of interest to an individual about whether to attend screening

▽ Not to be confused with ITT or per protocol **analyses**

JAMA | Original Investigation

Effect of a Low-Intensity PSA-Based Screening Intervention on Prostate Cancer Mortality
The CAP Randomized Clinical Trial

Richard M. Martin, PhD; Jenny L. Donovan, PhD; Emma L. Turner, PhD; Chris Metcalfe, PhD; Grace J. Young, MSc; Eleanor I. Walsh, MSc; J. Athene Lane, PhD; Sian Noble, PhD; Steven E. Oliver, PhD; Simon Evans, MD; Jonathan A. C. Sterne, PhD; Peter Holding, MSc; Yoav Ben-Shlomo, PhD; Peter Brindle, MD; Naomi J. Williams, PhD; Elizabeth M. Hill, MSc; Siaw Yein Ng, PhD; Jessica Toole, MSc; Marta K. Tazewell, MSc; Laura J. Hughes, BA; Charlotte F. Davies, PhD; Joanna C. Thorn, PhD; Elizabeth Down, MSc; George Davey Smith, DSc; David E. Neal, MD; Freddie C. Hamdy, MD; for the CAP Trial Group

IMPORTANCE Prostate cancer screening remains controversial because potential mortality or quality-of-life benefits may be outweighed by harms from overdetection and overtreatment.

OBJECTIVE To evaluate the effect of a single prostate-specific antigen (PSA) screening intervention and standardized diagnostic pathway on prostate cancer–specific mortality.

DESIGN, SETTING, AND PARTICIPANTS The Cluster Randomized Trial of PSA Testing for Prostate Cancer (CAP) included 419 582 men aged 50 to 69 years and was conducted at 573 primary care practices across the United Kingdom. Randomization and recruitment of the practices occurred between 2001 and 2009; patient follow-up ended on March 31, 2016.

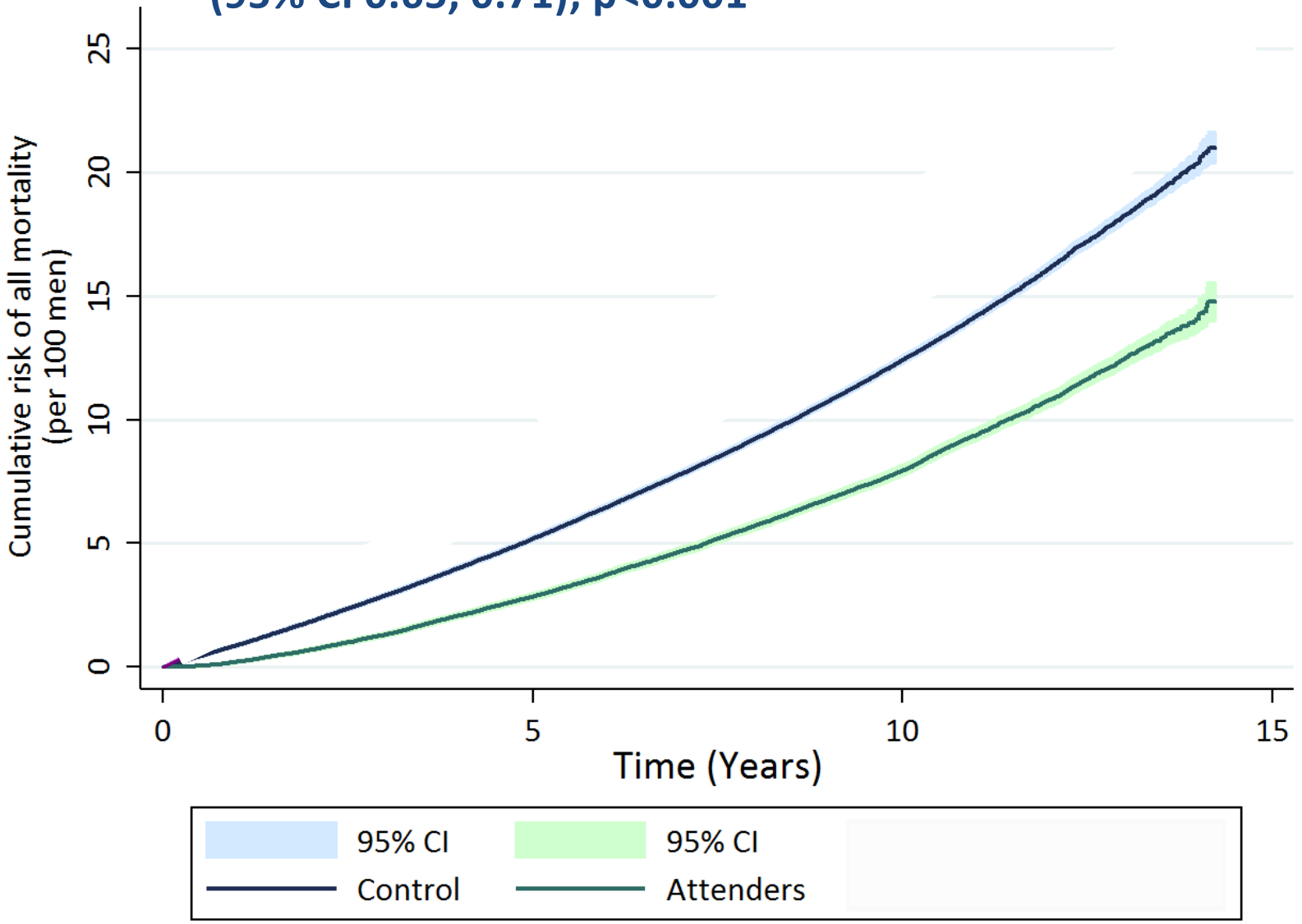
Editorial page 868

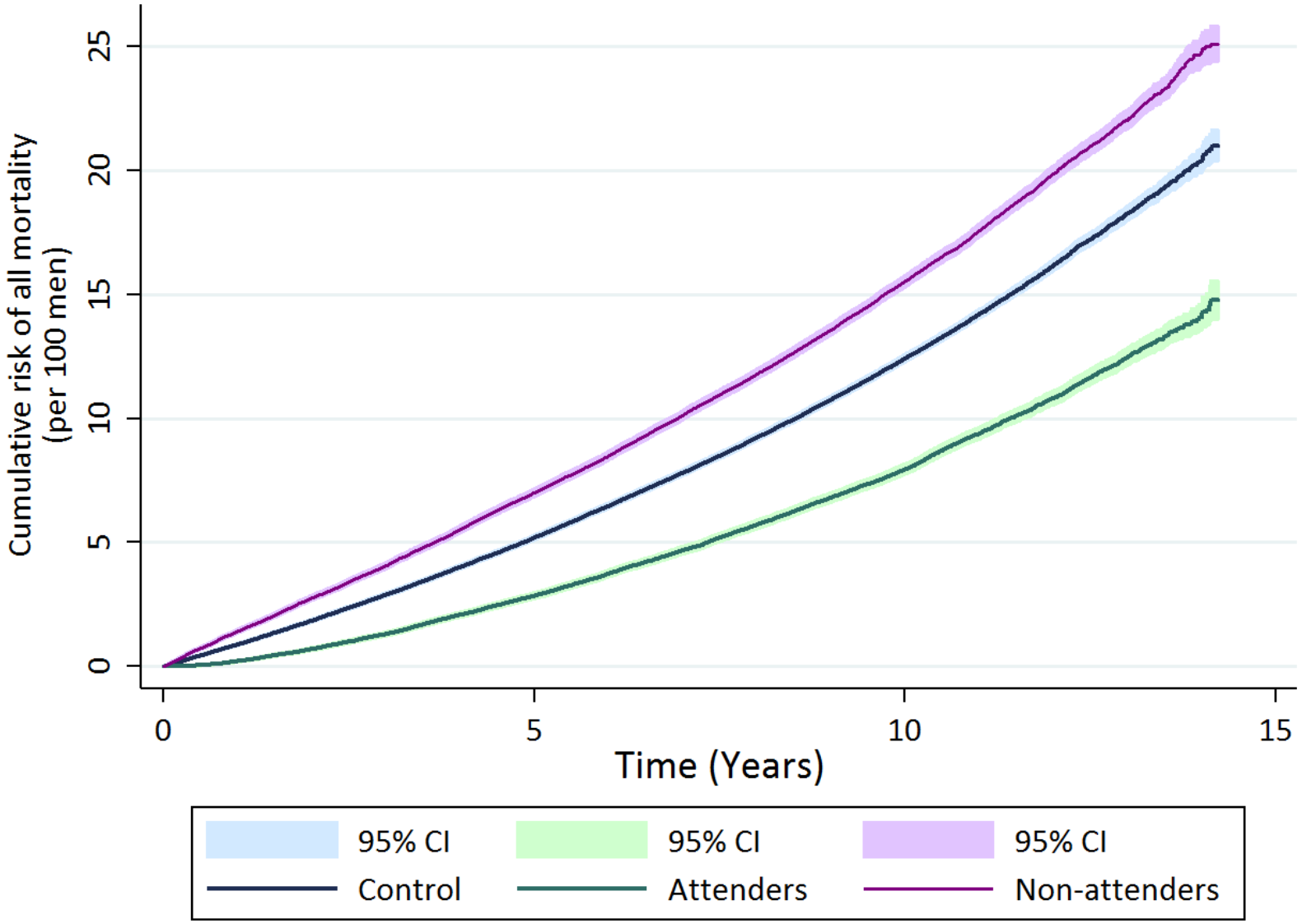
Related article page 896

Supplemental content

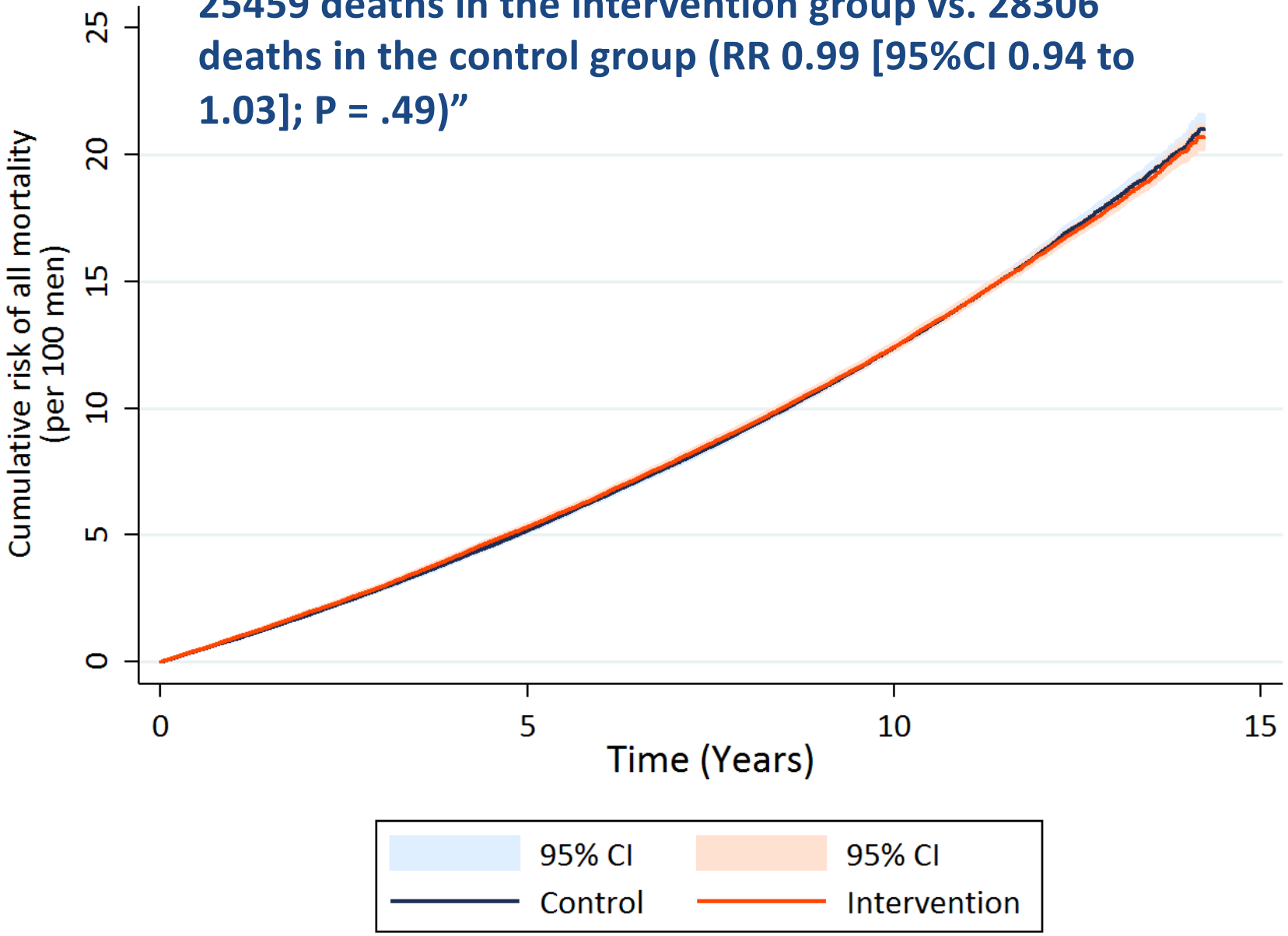
CME Quiz at jamanetwork.com/learning and CME Questions page 929

Rate ratio comparing attenders with control: 0.68 (95% CI 0.65, 0.71); p<0.001




Cumulative risk of all mortality
(per 100 men)
0
5
10
15
20
25
0
5
10
15
Time (Years)
95% CI
95% CI
95% CI
Control
Attenders
Non-attenders

“In the analysis of all-cause mortality, there were 25459 deaths in the intervention group vs. 28306 deaths in the control group (RR 0.99 [95%CI 0.94 to 1.03]; P = .49)”



Deviations from intended intervention

- Deviations from intended intervention **are not important** when interest is on the effect of **assignment to** intervention
  - E.g. some people don't respond to invitations to be screened
- But deviations such as poor adherence, poor implementation and co-interventions may lead to bias when interest is in the effect **adhering to** intervention
- This domain of RoB 2 differs according to the effects of interest

Deviations from intended intervention

- Is there a problem if:
  - In a trial of a new drug to control symptoms of rheumatoid arthritis, participants experiencing severe toxicities receive additional care and/or switch to an alternative drug?
  - In a trial of a specified cancer drug regimen, participants whose cancer progresses switch to a second-line intervention?
  - In a trial comparing surgical intervention with conservative management of stable angina, participants who progress to unstable angina receive surgical intervention?

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

Deviations from intended intervention

- Could be:
  - Administration of additional interventions that are inconsistent with the trial protocol (*non-protocol interventions*)
    - Non-protocol interventions that trial participants might receive during trial follow up and that are likely to affect the outcome of interest can lead to bias in estimated intervention effects.
    - If possible, review authors should specify potential non-protocol interventions at review protocol writing stage.
  - Failure to implement the protocol interventions as intended
  - Non-adherence to assigned intervention by trial participants
- The interventions that were intended should be fully specified in the trial protocol
  - However this is often not done, particularly when it is intended that interventions should change or evolve in response to the health of, or events experienced by, trial participants.

The role of blinding in RoB 2 assessments

- RoB 2 assumes that when participants and trial personnel were blinded during the trial, deviations from intended intervention **are not influenced by the trial context**.
  - Therefore, when interest is in the effect of assignment to intervention the signalling question addressing such deviations is asked only when these groups were not blinded.
- Blinding of outcome assessors is considered separately, in the 'Bias in measurement of outcomes' domain
- Blinding may not be successful in practice
  - For many blinded drug trials, the side effects of the drugs allow the possible detection of the intervention
  - Deducing the intervention received does not in itself lead to a risk of bias.

Intention-to-treat analysis

- **Principles underlying ITT analysis** are:
  1. All participants analysed in the groups randomized, regardless of the intervention they actually received
  2. Include all randomized participants in the analysis, which requires measuring outcome data on all participants
- Issues that may arise
  - **modified intention to treat (mITT)**
    - Follows the first principle of ITT, but exclude participants with missing outcome data
  - **per protocol** analysis (may be seriously biased)
    - Non-compliers excluded from analysis
  - **as-treated** analysis (may be seriously biased)
    - Non-compliers moved between groups

Analysis population as described by trial authors

"Primary and secondary efficacy analyses were performed on the intent-to-treat population, which included all randomly assigned patients **who took at least one dose of study medication** and had **at least one postbaseline efficacy assessment**."

Is this an ITT analysis?

Use judgement rather than relying on how trial authors described the analysis!

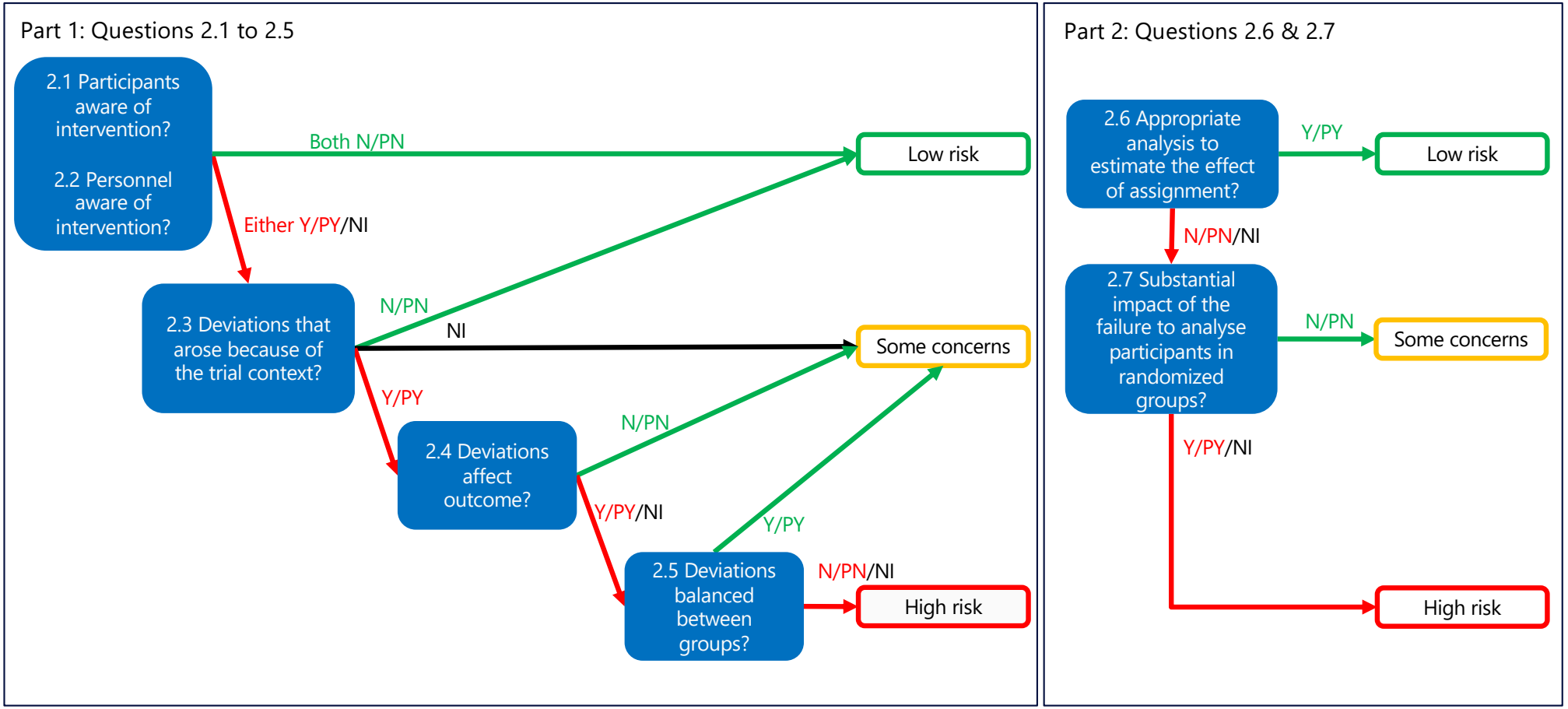
Domain 2. Bias due to deviations from intended interventions

Effect of assignment to intervention

2.1. Were participants aware of their assigned intervention during the trial? 2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	**Masking**
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context? 2.4. If Y/PY to 2.3: Were these deviations from intended intervention unbalanced between groups? 2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	**Deviations reflect usual practice?**
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention? 2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?	**First principle of ITT**

Domain 2. Bias due to deviations from intended interventions

- effect of assignment to intervention



Criteria for the domain

'Low risk' of bias in Part 1 AND 'Low risk' of bias in Part 2	Low risk
'Some concerns' in either Part 1 or in Part 2, AND Not 'High risk' in either Part	Some concerns
High risk in either Part 1 or in Part 2	High risk

Domain 3. Bias due to missing outcome data

Incomplete outcome data

- When complete outcome data for all participants are not available
  - Attrition - loss to follow up, withdrawals, other missing data
  - Inappropriate exclusions by trialists – some available data not included in the analysis (addressed in the domain 'bias due to deviations from intended interventions')
- Considerations
  - How many data are missing from each group? (include numbers in your description)
  - Why are the data missing?
  - How were the data analysed?

How many are too many missing data?

- No simple rule
- Enough missing data to affect the results meaningfully
  - Overall proportion of missing data
  - Event risk (dichotomous outcomes)
  - Plausible effect size (continuous outcomes)
- Reasons related to study outcomes
  - E.g., recovered, adverse event, lack of efficacy
  - Reasons can have different meaning in each group
- Missing data or reasons not balanced between groups

Intention-to-treat analysis

- Recall, **principles underlying ITT analysis** are:
  1. All participants analysed in the groups randomized, regardless of the intervention they actually received
  2. Include all randomized participants in the analysis, which requires measuring outcome data on all participants

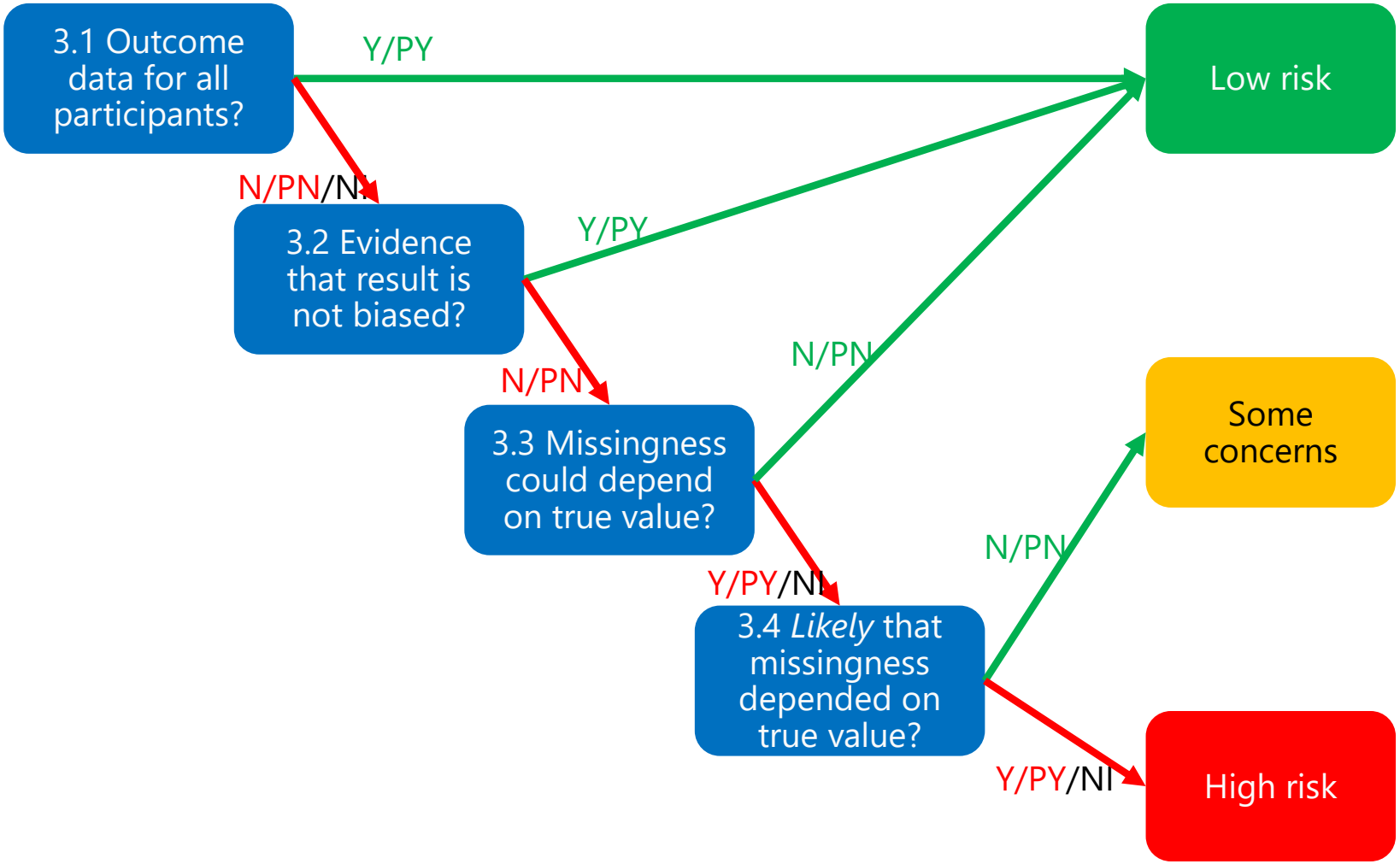
- **Imputation** of missing values
  - Assumptions may be inappropriate - consult a statistician
- It may be possible to re-include some excluded data

Domain 3. Bias due to missing outcome data

3.1 Were data for this outcome available for all, or nearly all, participants randomized?	**Any missing data?**
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	**Results robust?**
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value? 3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	**Missingness depends on results?**

3.3 is theoretical 'could' whereas 3.4 is actual 'did' (though often requires judgement rather than evidence to answer). This is used to distinguish between 'some concerns' and 'high risk of bias'.

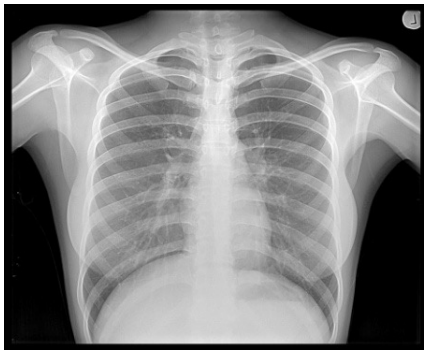
Domain 3. Bias due to missing outcome data



Domain 4. Bias in measurement of the outcome

Domain 4. Bias in measurement of the outcome

- Systematic differences between groups in how outcomes are assessed
- Some outcomes are **more** prone to bias than others
  - Patient-reported outcome (e.g., pain, quality of life)
  - Observer-reported involving judgement (e.g., clinical examination)
- Some outcomes are **less** prone to bias than others
  - Outcomes not involving judgement (e.g., all-cause mortality)



Minimizing bias in measurement of the outcome

- Masking outcome assessors
- Measure objective outcomes when possible
- Ensure outcome measured in the same way for all study groups

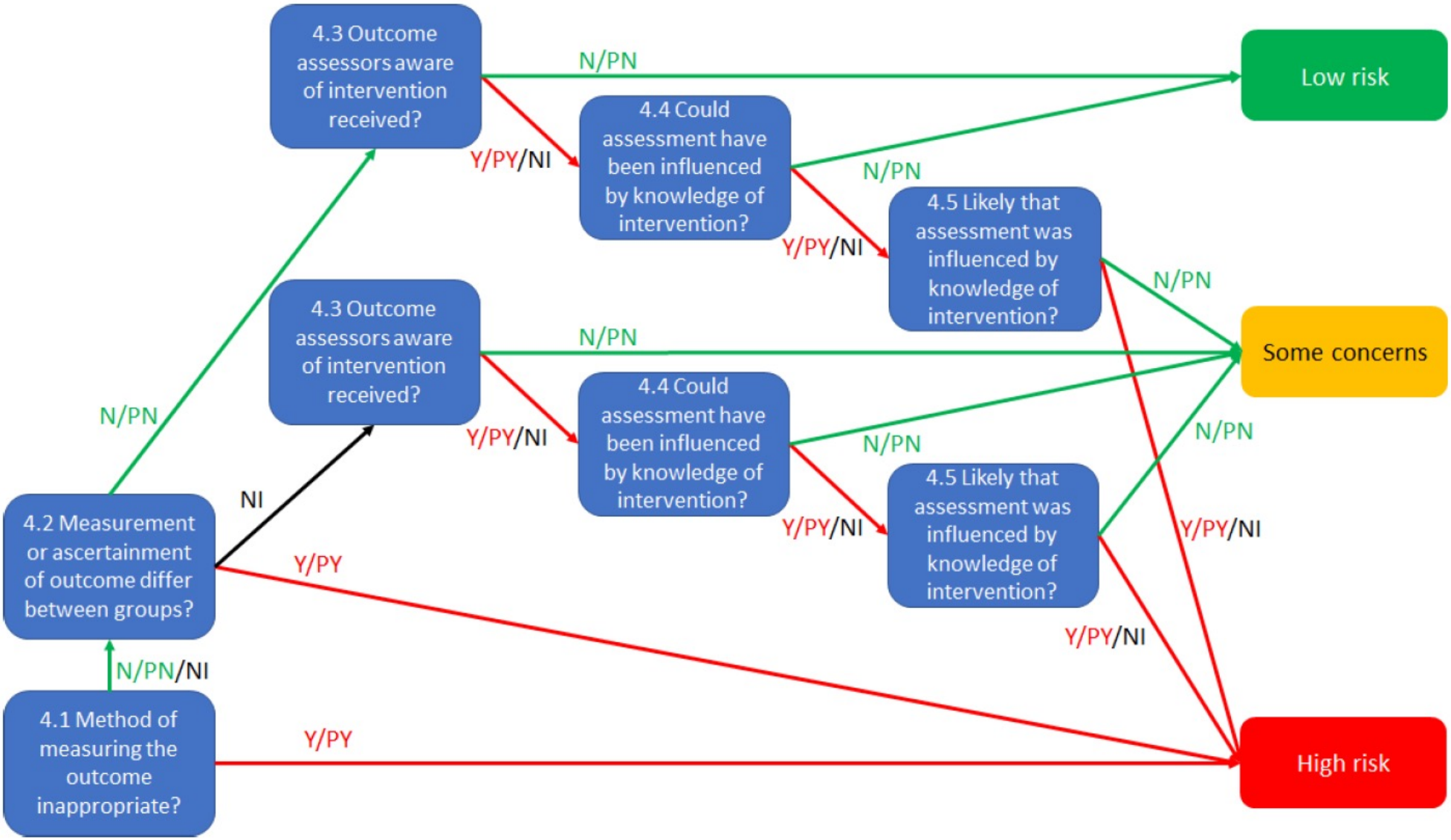
- Assess carefully
  - Avoid terms like “single blind” and “double blind”
  - Is it likely that blinding was broken?
  - Masking of outcome assessors may be feasible even when masking of participants and care providers is not
  - Remember that participants and personnel may also be outcome assessors

Source: Cochrane Training http://training.cochrane.org/resource/assessing-risk-bias-included-studies

Domain 4. Bias in measurement of the outcome

4.1 Was the method of measuring the outcome inappropriate?	**Assessment appropriate?**
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	**Assessment differed?**
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	**Masking?**
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received? 4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	**Assessment influenced?**

Domain 4. Bias in measurement of the outcome



Domain 5. Bias in selection of the reported result

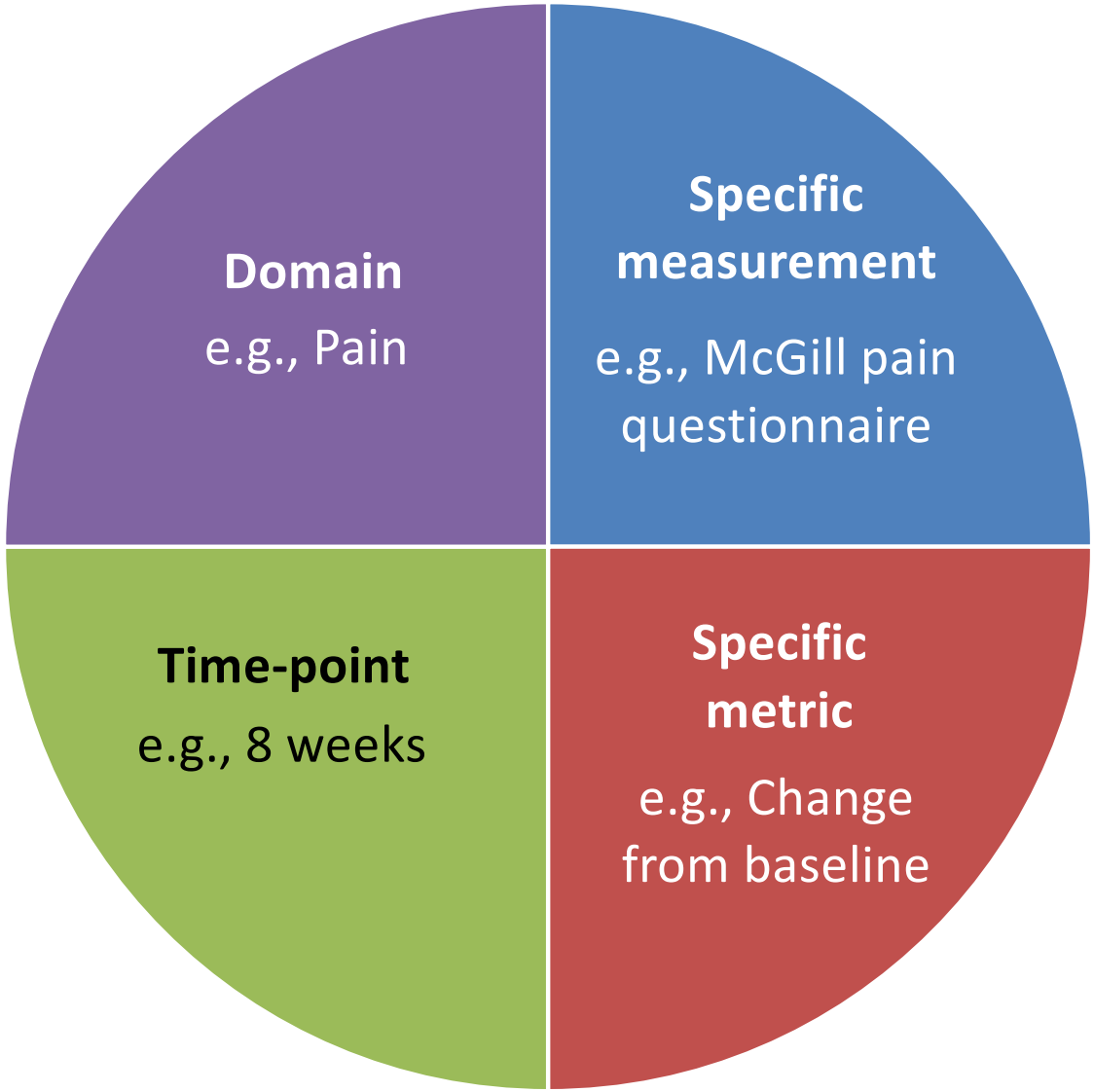
Domain 5. Bias in selection of the reported result

Trial result is biased because it has been selected on the basis of the results from multiple:

- Outcome measurements
  - Scales
  - Definitions of/criteria for an event
  - Time points

- Analyses
  - 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

Four elements of a completely defined outcome



Modified from: Zarin *NEJM* 2011. DOI: 10.1056/NEJMsa1012065
Saldanha *PLoS One* 2014. https://doi.org/10.1371/journal.pone.0109400

Domain 5. Bias in selection of the reported result

5.1 Were the data underlying this result analyzed in accordance with a pre-specified plan that was finalized before outcome data were available for analysis?

Pre-specified analysis plan?

Are the reported outcome data likely to have been selected, on the basis of the results, from...

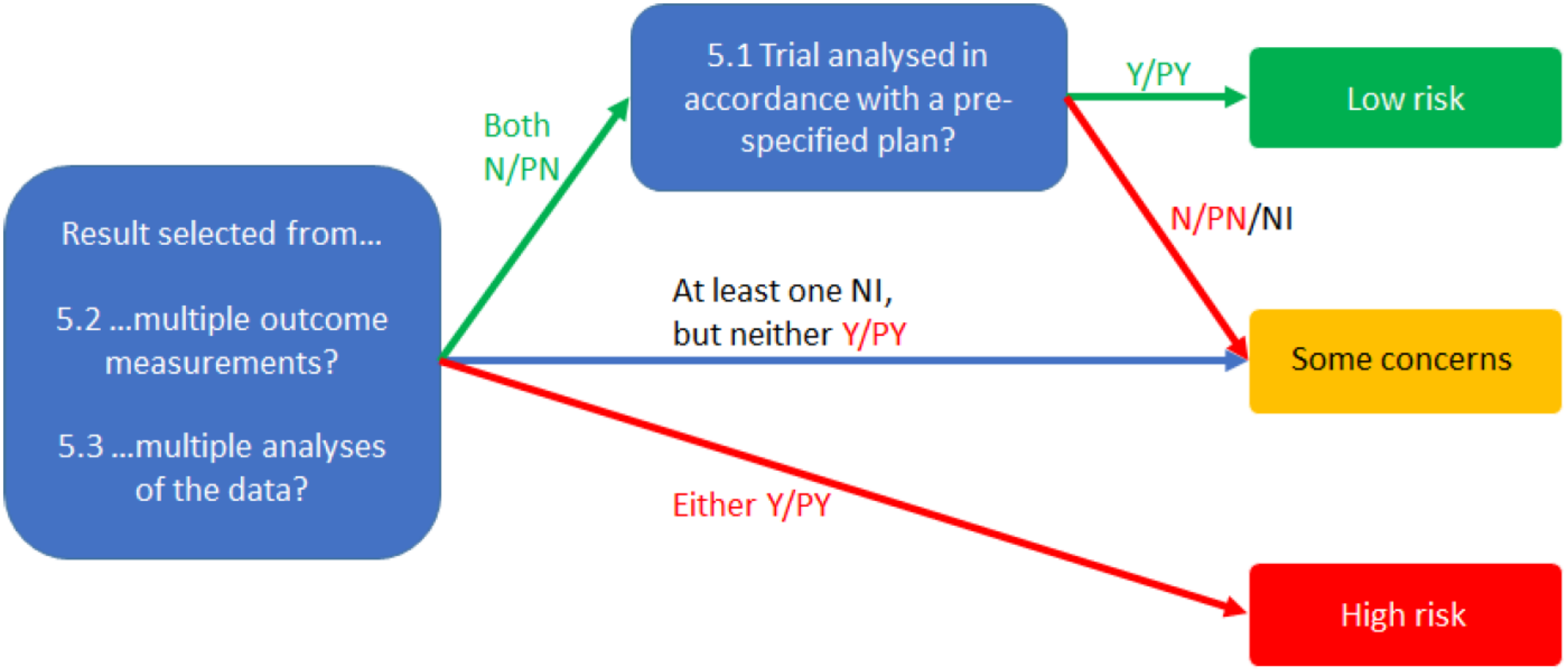
5.2 ... multiple outcome measurements (e.g., scales, definitions, time points) within the outcome domain?

Selective outcome reporting

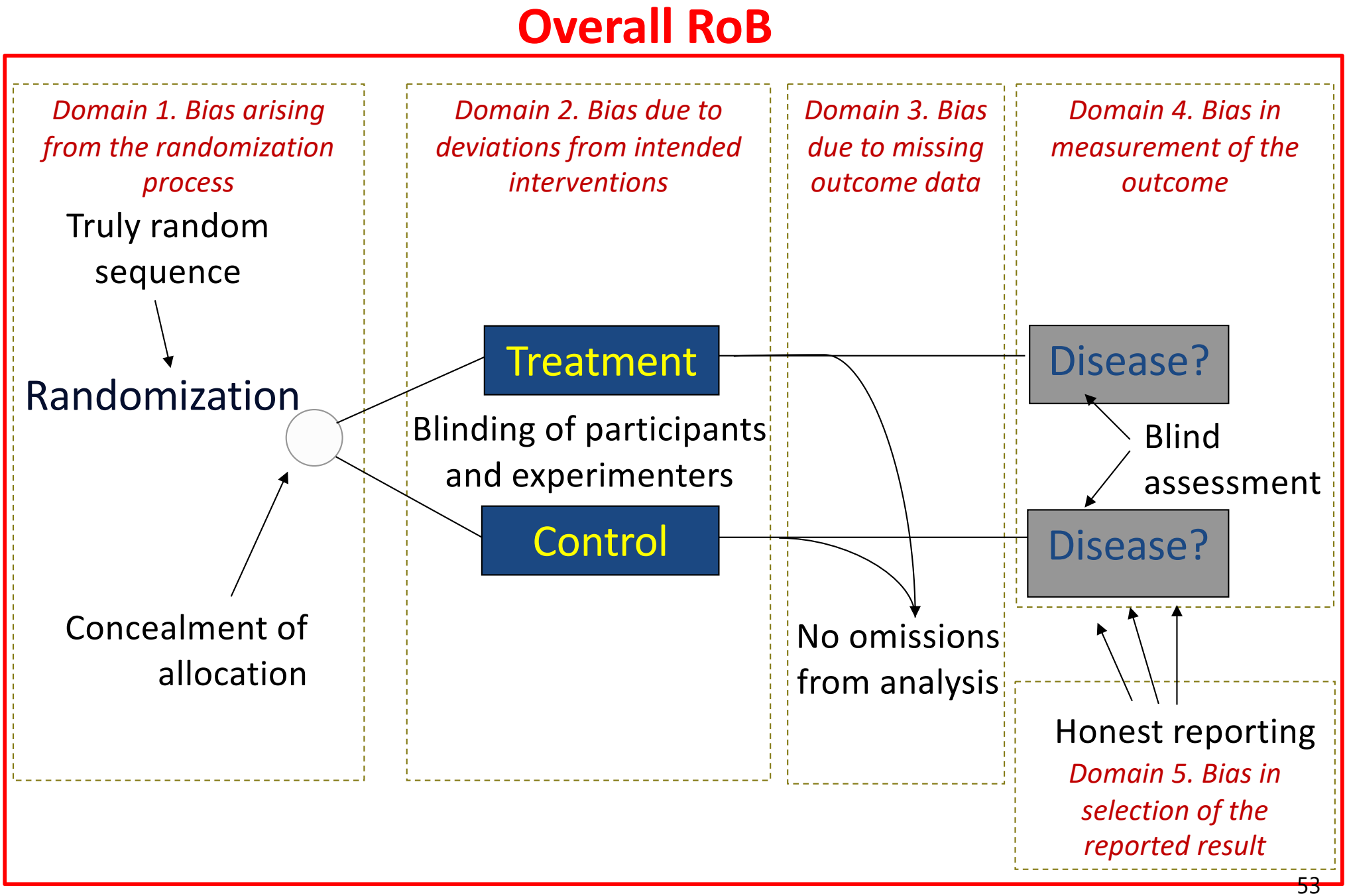
5.3 ... multiple analyses of the data?

Selective analysis reporting

Domain 5. Bias in selection of the reported result



RoB 2 Domains



Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y / PY / PN / N / NI	[Description]
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Y / PY / PN / N / NI	[Description]
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias arising from the randomization process?		[Rationale]
Bias due to deviations from intended interventions	2.1 Were participants aware of their assigned intervention during the trial?	Y / PY / PN / N / NI	[Description]
	2.2 Were carers and people delivering the interventions aware of participants' allocated intervention during the trial?	Y / PY / PN / N / NI	[Description]
	2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	NA / Y / PY / PN / N / NI	[Description]
	2.4 If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?	NA / Y / PY / PN / N / NI	[Description]
	2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?	NA / Y / PY / PN / N / NI	[Description]
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Y / PY / PN / N / NI	[Description]
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias due to deviations from intended interventions?		[Rationale]
Bias due to missing outcome data	3.1 Were outcome data available for all, or nearly all, participants randomized?	Y / PY / PN / N / NI	[Description]
	3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	NA / Y / PY / PN / N	[Description]
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA / Y / PY / PN / N / NI	[Description]
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias due to missing outcome data?		[Rationale]
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	Y / PY / PN / N / NI	[Description]
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Y / PY / PN / N / NI	[Description]
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Y / PY / PN / N / NI	[Description]
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA / Y / PY / PN / N / NI	[Description]
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias in measurement of the outcome?		[Rationale]
Bias in selection of the reported result	5.1 Was the trial analysed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?	Y / PY / PN / N / NI	[Description]
	Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
	5.2 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Y / PY / PN / N / NI	[Description]
	5.3 ... multiple analyses of the data?	Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction bias due to selection of the reported results?		[Rationale]
Overall bias	**Risk of bias judgement**	Low / High / Some concerns	[Support]
	Optional: What is the overall predicted direction of bias for this outcome?		[Rationale]

Overall risk of bias

Low risk of bias	The study is judged to be at **low risk of bias for all domains** for this result.
Some concerns	The study is judged to be at **some concerns** in at least one domain for this result.
High risk of bias	The study is judged to be at **high risk of bias** in at least one domain for this result. OR The study is judged to have **some concerns** for **multiple domains** in a way that substantially lowers confidence in the result.

Links to free Cochrane Trainings on the RoB 2 domains

Domain 1: Bias arising from the randomization process
https://training.cochrane.org/resource/rob-2-domain-1-bias-arising-randomisation-process

Domain 2: Bias due to deviations from the intended interventions
https://training.cochrane.org/resource/rob-2-domain-2-bias-due-deviations-intended-interventions

Domain 3: Bias due to missing outcome data
https://training.cochrane.org/resource/rob-2-domain-3-bias-due-missing-outcome-data

Domain 4: Bias in measurement of the outcome
https://training.cochrane.org/resource/rob-2-domain-4-bias-measurement-outcome

Domain 5: Bias in selection of the reported result
https://training.cochrane.org/resource/rob-2-domain-5-bias-selection-reported-result

Arriving at an overall assessment of risk of bias for the trial (after completing Domains 1-5)
https://training.cochrane.org/resource/reaching-overall-rob-judgement-and-incorporating-rob-assessment-analysis-and-interpretation

Bias in other types of studies: cluster-randomized and cross-over trials
https://training.cochrane.org/resource/rob-2-bias-other-types-studies-cluster-randomised-and-cross-over