

RoB 2 Domain 3: Bias due to missing outcome data

Jonathan Sterne and Julian Higgins
University of Bristol, UK

Trusted evidence.
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- Missing outcome data
- When do missing outcome data lead to bias?
- *Questions*
- How do we know whether there is bias?
- *Questions*
- Assessing the risk of bias due to missing outcome data in RoB 2
- *Questions and discussion*

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

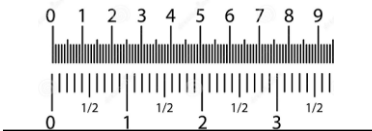
Bias due to missing outcome data

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:
 - 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 attend but do not provide outcome data
 - data or records lost or unavailable
 - 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?



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

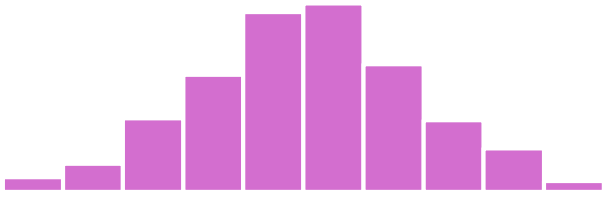
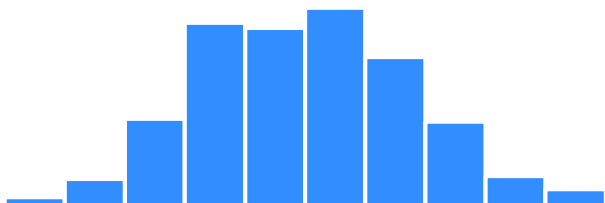


When do missing outcome data lead to bias?

- 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

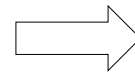
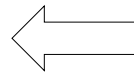


When do missing outcome data lead to bias?

Experimental intervention	Observed participants	
	Missing participants	?
Comparator intervention	Observed participants	
	Missing participants	?

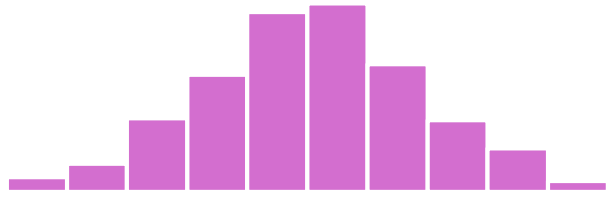
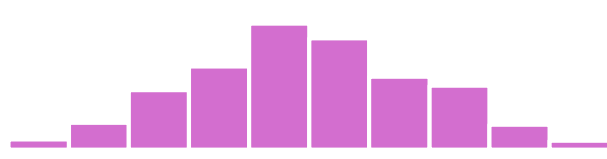
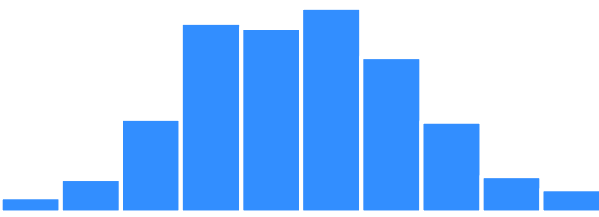
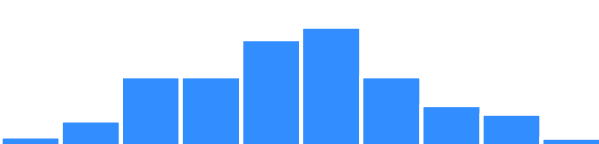
refer to this as
“missingness”
in the outcome
variable

Higher symptoms
of dementia



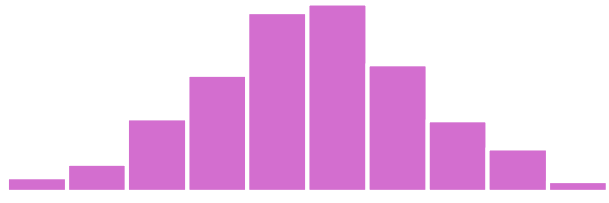

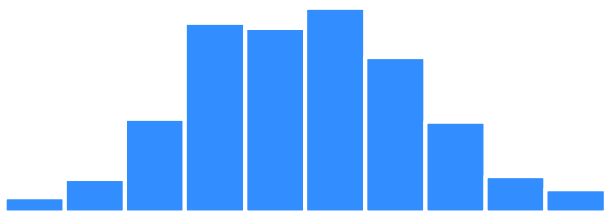

Higher cognitive
ability

No bias: missingness unrelated to true values

Experimental intervention	Observed participants	
	Missing participants	
Comparator intervention	Observed participants	
	Missing participants	

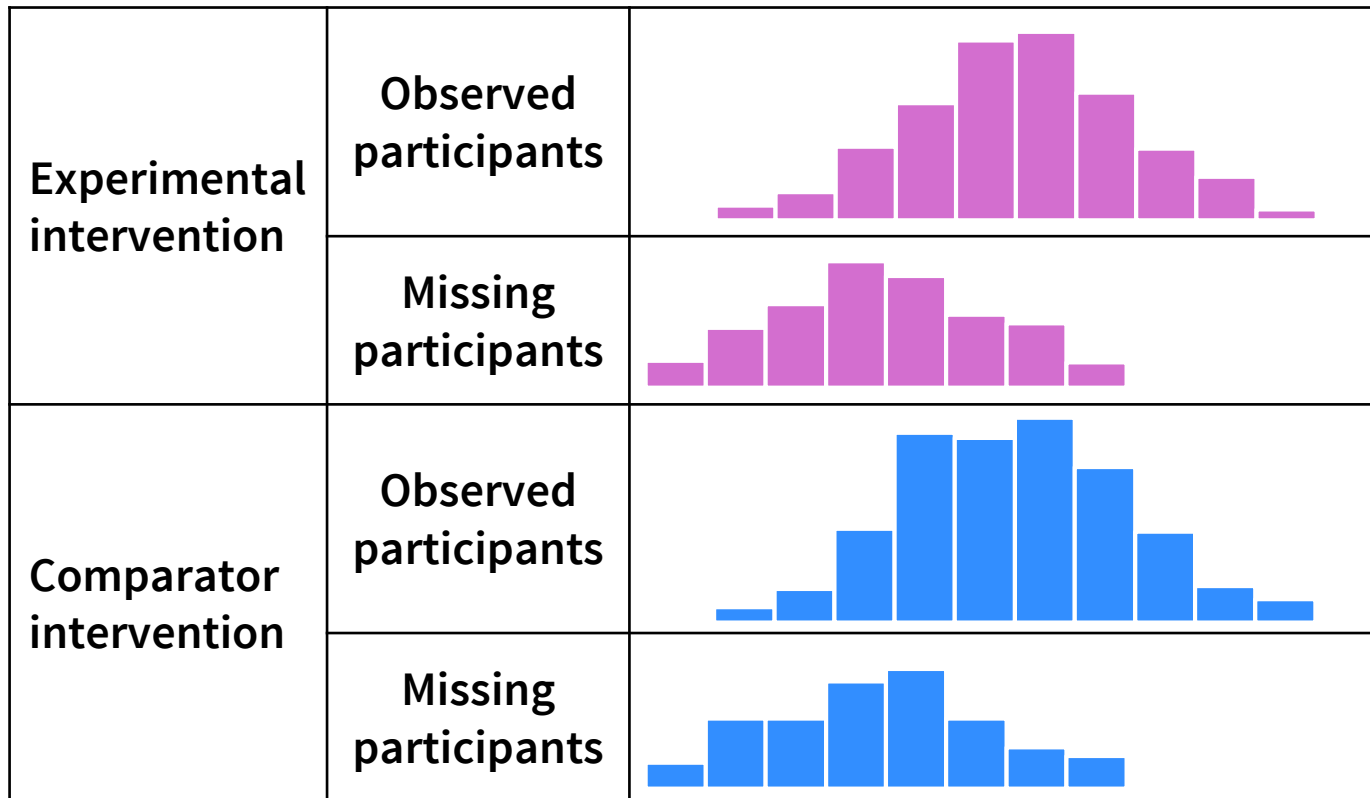
e.g. data missing because automatic measuring device failed for a subset of participants

Bias: missingness depends on true values and on intervention group

Experimental intervention	Observed participants	
	Missing participants	
Comparator intervention	Observed participants	
	Missing participants	

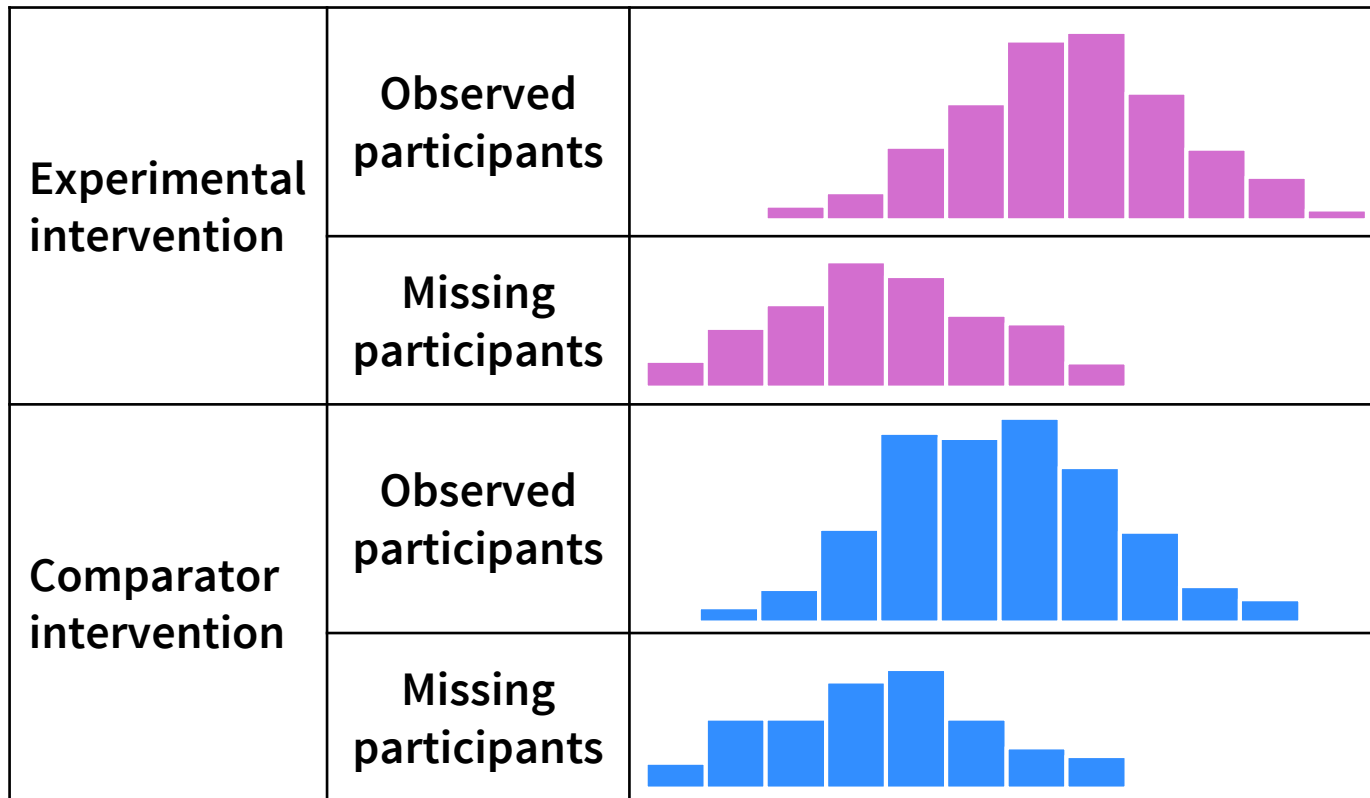
e.g. (1) more drop-outs in experimental group due to side effects and (2) those with continuing symptoms more likely to drop out

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



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



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

Scenario:

- Trial of physiotherapy vs none in patients with shoulder pain
- Outcome: shoulder pain
- 15% do not return for final assessment in control group due to loss of interest in the trial
- 29% do not return for final assessment in physiotherapy group because pain was resolved early in the trial



Questions



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
- 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



Single imputation

Imputation approaches replace missing values by one or more new values.

- In **single imputation**, only one estimate is filled in.
 - Commonly used approaches include ‘last observation carried forward’ (LOCF) and ‘baseline observation carried forward’ (BOCF).
 - Each of these is unlikely to remove the bias that occurs when missingness in the outcome depends on its true value, unless there is no change in the outcome after the last time it was measured.
 - They also improve precision artificially.

Multiple imputation

Imputation approaches replace missing values by one or more new values.

- In **multiple imputation**, multiple values of the missing outcomes are drawn at random from a predictive distribution, forming multiple distinct filled-in datasets.
 - Because these datasets do not have missing values they can be analysed using standard methods.
 - Results from the multiple datasets are analysed then combined to produce a single summary estimate and confidence interval that reflect the uncertainty associated with missing data.



Limitations of multiple imputation

Multiple imputation methods will not remove or reduce the bias that occurs when missingness in the outcome depends on its true value, unless such missingness can be explained by measured variables.

- Multiple imputation does not reduce or remove bias when outcome data are missing not at random ('MNAR').
- Imputing missing outcome data based only on intervention group will give results that are near-identical to those from a complete-case analysis
- If the imputation model is not correctly specified, multiple imputation will not remove, and can even increase, bias.



Limitations of multiple imputation

Multiple imputation methods will not remove or reduce the bias that occurs when missingness in the outcome depends on its true value, unless such missingness can be explained by measured variables.

- Multiple imputed estimates should be considered as at low risk of bias only when there is justification for the assumption that missingness in the outcome does not depend on its true value other than through measured variables included in the imputation model.



Potential of multiple imputation

It *may be* possible to reduce bias associated with missing outcome data when values of the outcome are measured repeatedly over time and these measurements are used to predict the missing outcome data

- Even when such an approach is used, review authors should consider carefully whether loss to follow up is plausibly related to the outcome trajectory after the last recorded measurement.



Sensitivity analyses

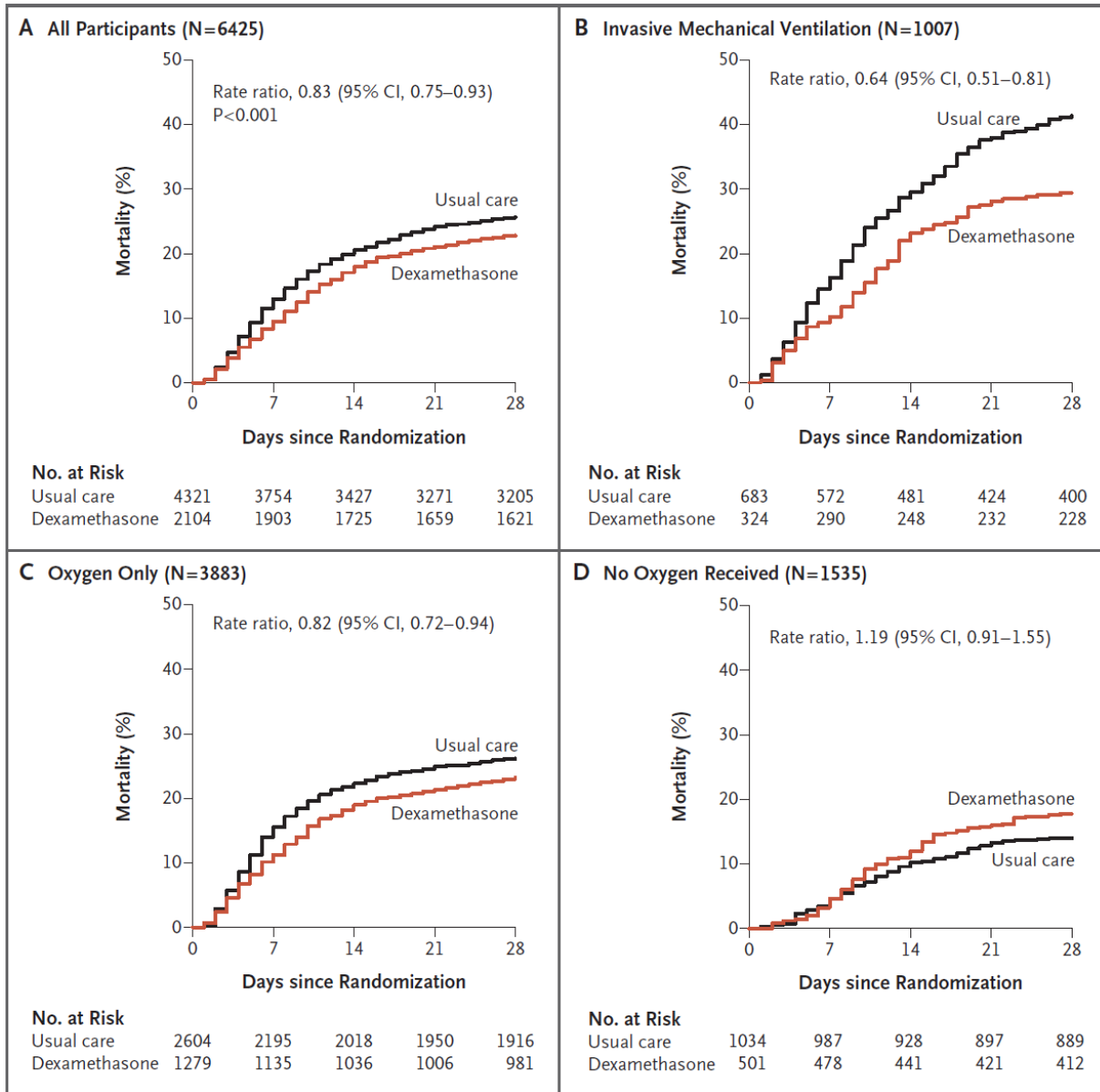
- In sensitivity analyses we make assumptions about the relationship between missingness in the outcome and its true value
 - Sensitivity analyses may be reported by trial authors, or can be done by the review authors to assist with risk of bias assessments
 - Multiple imputation can be adapted to conduct sensitivity analyses



Sensitivity analyses and risk of bias

- The important consideration is whether the **range of values for the missing outcome data** that have been considered in sensitivity analyses **is plausible**
 - this is usually more important than which *methods* have been used
 - If sensitivity analyses demonstrate that the trial results are robust to (not much altered by) plausible assumptions about the missing data then risk of bias will be low





Time to event data (1)

For ‘time-to-event’ data, the outcome is a combination of:

1. The length of time for which the participant was followed
2. A dichotomous variable that indicates whether the outcome event was observed in each participant.
 - Follow-up times for participants in whom the outcome event was not observed before observation stopped are ‘censored’.

Results of time-to-event analyses will be unbiased only if censoring is ‘non-informative’

- This means that censoring times are unrelated to the (subsequent) times at which outcome events occur.
 - For example, if all participants are followed until a specified date after which follow up ends, then censoring can be assumed to be non-informative.

Time to event data (2)

In the presence of informative censoring, a time-to-event analysis will be biased if:

1. the chance that the follow up is censored also depends on the intervention group
 - For example, if censoring is more likely because participants in the experimental intervention group are lost to follow up because of severe side effects); and
2. the effect of the experimental and comparator interventions on the outcome differs.

Either differences in rates of censoring or differing reasons for censoring may provide evidence that censoring was informative



Time to event data (3)

A particular risk of bias arises when participants' follow up is censored if they stop or change their assigned intervention

- Participants censored during trial follow-up should be regarded as having missing outcome data
- CONSORT flow diagrams may show such participants as included in analyses



Questions



Assessing the risk of bias due to missing outcome data



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



Bias due to missing outcome data

3.1. Were data for this outcome available for all, or nearly all, randomized participants?

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?

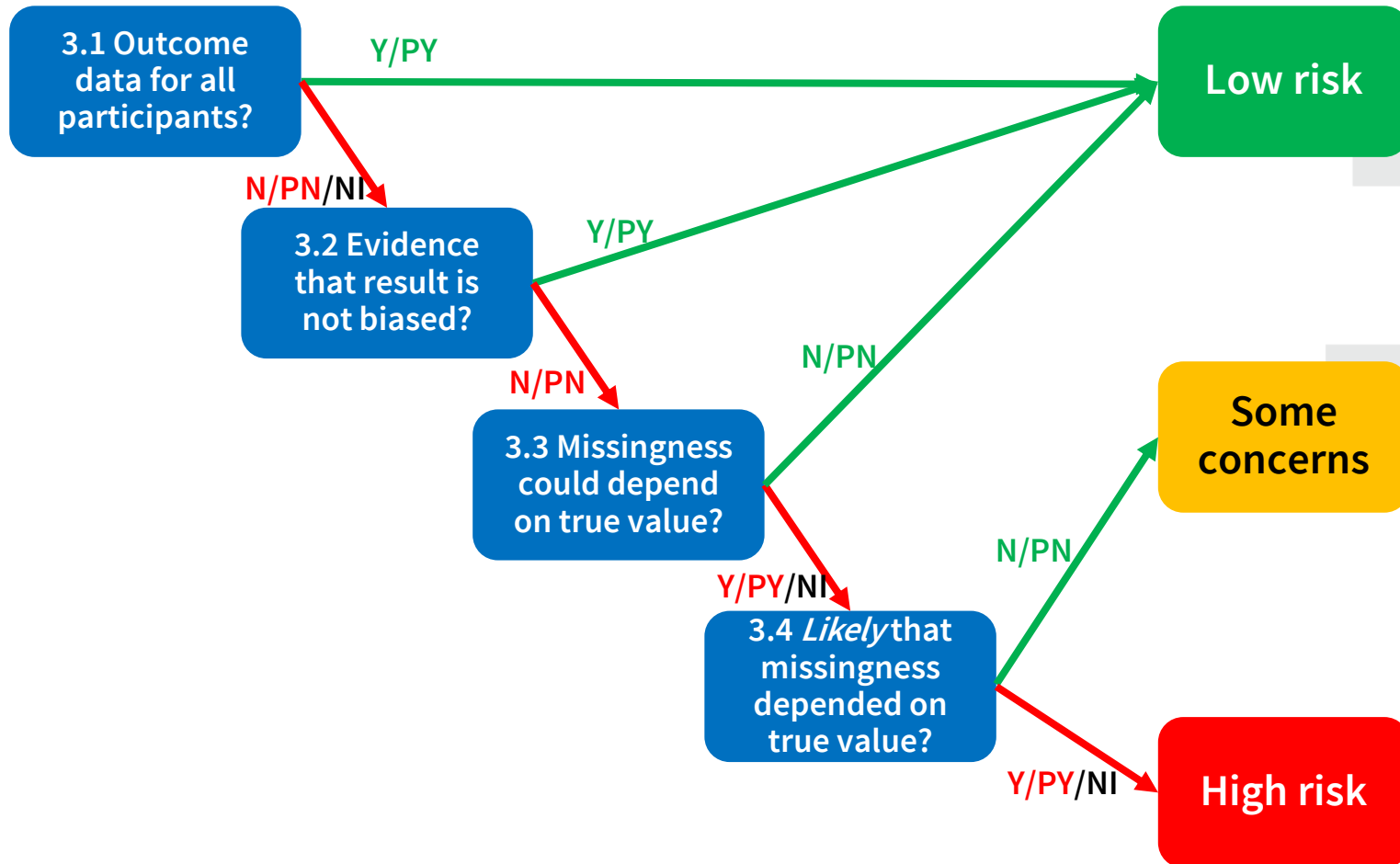
Results robust?

3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?

Missingness depends on result?

3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?

Bias due to missing outcome data



Questions and discussion

