A tool for evaluating risk of bias in non-randomized studies of interventions (ROBINS-I): development and applications

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Version 1.0.0 was posted at www.riskofbias.info in September 2014

Further modifications since then have been based on piloting, practical experience and feedback from workshops and training sesions

Change of name (from ACROBAT-NRSI) based on legal advice

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Scope

- ROBINS-I ("Risk Of Bias In Non-randomized Studies - of Interventions") is concerned with evaluating the risk of bias (RoB) in the results of NRSI that compare the health effects of two or more interventions.
  - quantitative studies estimating the effectiveness (harm or benefit) of an intervention, which did not use randomization to allocate units (individuals or clusters of individuals) to comparison groups

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Overview of ROBINS-I (1)

- At protocol stage:
  - Specify the research question by defining the “PICO”
  - Specify the nature of the target comparison (effect of interest)
  - List the confounding areas relevant to all or most studies
  - List the possible co-interventions that could differ between intervention groups and could have an impact on study outcomes

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Overview of ROBINS-I (2)

- For each study:
  - Specify a target trial specific to the study
  - Specify the outcome
  - Specify the effect of interest
  - Specify the specific result being assessed
  - Conduct a preliminary consideration of confounders and co-interventions
- Outcome level risk of bias assessments within bias domains:
  - Signalling questions (cf. QUADAS-2)
  - Free text descriptions
  - Risk of bias judgements
- Overall (outcome-level) risk of bias judgement
  - feed into GRADE

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Key features of ROBINS-I

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Assessing risk of bias in relation to a target trial

- Evaluations of RoB are facilitated by considering each NRSI as an attempt to emulate (mimic) a hypothetical randomized trial that compares the health effects of two or more interventions
  - We refer to this as a "target" randomized trial
  - A target trial need not be feasible or ethical
- At review level, define the PICO of interest
- At study level, define the design of the target trial that the NRSI aims to emulate
  - e.g. a review might evaluate the effect of a class of drugs but individual NRSI might evaluate specific drugs within that class
  - individual studies may have clustered designs
- The key idea is to explicitly identify the interventions that would be compared in the target trial that the NRS is trying to emulate

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RoB assessments should relate to a specified intervention effect

- The **specified intervention effect** is typically either:
  - the effect of **assignment** to the interventions at baseline (regardless of whether the interventions are received during follow-up), or
  - the effect of **receiving the interventions as intended**
  - e.g. to inform a health policy question we would estimate the effect of assignment to intervention, whereas to inform care decisions by individual patients we would estimate the effect of receiving the treatment according to a specified protocol
- Specification of the intervention effect is particularly important when we assess departures from intended intervention ("performance biases")
  - Note the difference between per-protocol *effect* (well-defined) and per-protocol *analysis* (often leading to a biased estimate of the per-protocol effect).

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Summary of issues addressed by the seven bias domains

Domain	Issues addressed
Bias due to confounding	Selection bias *as it is often used in relation to clinical trials* (and currently in widespread use within Cochrane); Allocation bias; Case-mix bias; Channelling bias.
Bias in selection of participants into the study	Selection bias *as it is usually used in relation to observational studies*; Inception bias; Lead-time bias; Immortal time bias
Bias in classification of interventions	Definition of intervention; Whether information on intervention status was recorded at the time of intervention; Awareness of outcome when measuring intervention
Bias due to departures from intended interventions	Co-interventions; Intervention switches; Fidelity; Statistical adjustment for co-interventions
Bias due to missing data	Completeness of outcome data; Imbalance and reasons for missing data; Completeness of intervention data; Other missing data; Statistical methods used to address missing data
Bias in measurement of outcomes	Whether outcome measure was objective; Awareness of intervention when measuring outcome; Systematic errors in measuring outcome
Bias in selection of the reported result	From multiple outcomes/time points; Multiple analyses; Reporting a subset of participants.

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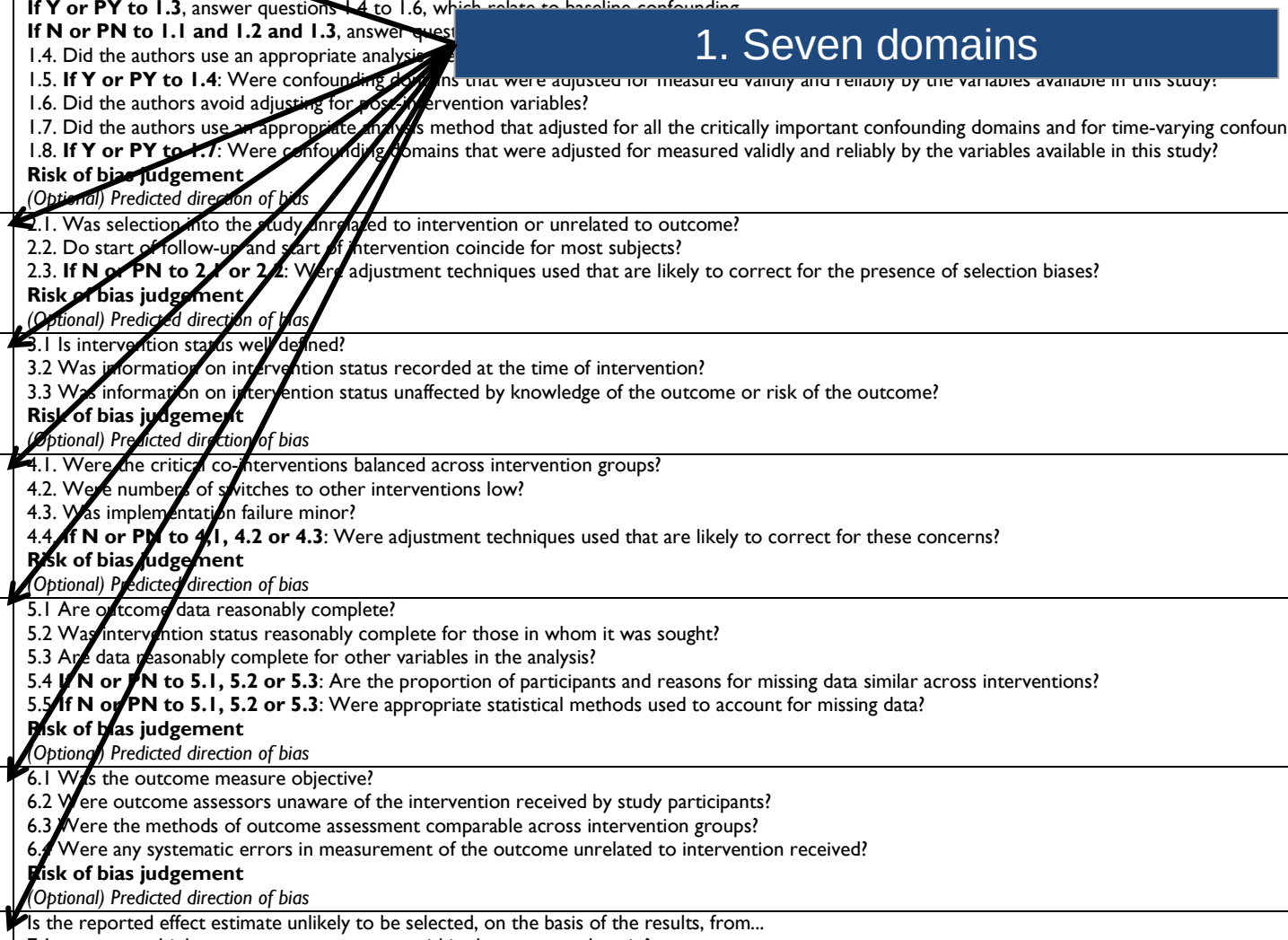
Summary of issues addressed by the seven bias domains

Domain	Issues addressed
Bias due to confounding	*Pre- or at-intervention* features, for which considerations of bias in NRS are mainly distinct from those in RCTs
Bias in selection of participants into the study	
Bias in classification of interventions	
Bias due to departures from intended interventions	*Post-intervention* features, for which many considerations of bias in observational studies are similar to those in RCTs
Bias due to missing data	
Bias in measurement of outcomes	
Bias in selection of the reported result	

Bias due to confounding	1.1 Is confounding of the effect of intervention unlikely in this study? **If Y or PY to 1.1**, the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered 1.2. **If N or PN to 1.1**: Were participants analysed according to their initial intervention group throughout follow up? **If Y or PY to 1.2**, answer questions 1.4 to 1.6, which relate to baseline confounding 1.3. **If N or PN to 1.2**: Were intervention discontinuations or switches unlikely to be related to factors that are prognostic for the outcome? **If Y or PY to 1.3**, answer questions 1.4 to 1.6, which relate to baseline confounding **If N or PN to 1.1 and 1.2 and 1.3**, answer quest 1.4. Did the authors use an appropriate analysis 1.5. **If Y or PY to 1.4**: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study? 1.6. Did the authors avoid adjusting for post-intervention variables? 1.7. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains and for time-varying confounding? 1.8. **If Y or PY to 1.7**: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study? **Risk of bias judgement** *(Optional) Predicted direction of bias*
Bias in selection of participants into the study	2.1. Was selection into the study unrelated to intervention or unrelated to outcome? 2.2. Do start of follow-up and start of intervention coincide for most subjects? 2.3. **If N or PN to 2.1 or 2.2**: Were adjustment techniques used that are likely to correct for the presence of selection biases? **Risk of bias judgement** *(Optional) Predicted direction of bias*
Bias in measurement of interventions	3.1 Is intervention status well defined? 3.2 Was information on intervention status recorded at the time of intervention? 3.3 Was information on intervention status unaffected by knowledge of the outcome or risk of the outcome? **Risk of bias judgement** *(Optional) Predicted direction of bias*
Bias due to departures from intended interventions	4.1. Were the critical co-interventions balanced across intervention groups? 4.2. Were numbers of switches to other interventions low? 4.3. Was implementation failure minor? 4.4 **If N or PN to 4.1, 4.2 or 4.3**: Were adjustment techniques used that are likely to correct for these concerns? **Risk of bias judgement** *(Optional) Predicted direction of bias*
Bias due to missing data	5.1 Are outcome data reasonably complete? 5.2 Was intervention status reasonably complete for those in whom it was sought? 5.3 Are data reasonably complete for other variables in the analysis? 5.4 **If N or PN to 5.1, 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? 5.5 **If N or PN to 5.1, 5.2 or 5.3**: Were appropriate statistical methods used to account for missing data? **Risk of bias judgement** *(Optional) Predicted direction of bias*
Bias in measurement of outcomes	6.1 Was the outcome measure objective? 6.2 Were outcome assessors unaware of the intervention received by study participants? 6.3 Were the methods of outcome assessment comparable across intervention groups? 6.4 Were any systematic errors in measurement of the outcome unrelated to intervention received? **Risk of bias judgement** *(Optional) Predicted direction of bias*
Bias in selection of the reported result	Is the reported effect estimate unlikely to be selected, on the basis of the results, from... 7.1 ...among multiple outcome measurements within the outcome domain? 7.2 ...among multiple analyses of the intervention-outcome relationship? 7.3 ...among different subgroups? **Risk of bias judgement** *(Optional) Predicted direction of bias*
Overall risk of bias	**Risk of bias judgement** *(Optional)L Predicted direction of bias*



Bias due to confounding	1.1 Is confounding of the effect of intervention unlikely in this study? **If Y or PY to 1.1**, the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered 1.2. **If N or PN to 1.1**: Were participants analysed according to their initial intervention group throughout follow up? **If Y or PY to 1.2**, answer questions 1.4 to 1.6, which relate to baseline confounding 1.3. **If N or PN to 1.2**: Were intervention discontinuations or switches unlikely to be related to factors that are prognostic for the outcome? **If Y or PY to 1.3**, answer questions 1.4 to 1.6, which relate to baseline confounding **If N or PN to 1.1 and 1.2 and 1.3**, answer quest 1.4. Did the authors use an appropriate analysis me 1.5. **If Y or PY to 1.4**: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study? 1.6. Did the authors avoid adjusting for post-interv 1.7. Did the authors use an appropriate analysis me nding? 1.8. **If Y or PY to 1.7**: Were confounding domains **Risk of bias judgement** *(Optional) Predicted direction of bias*
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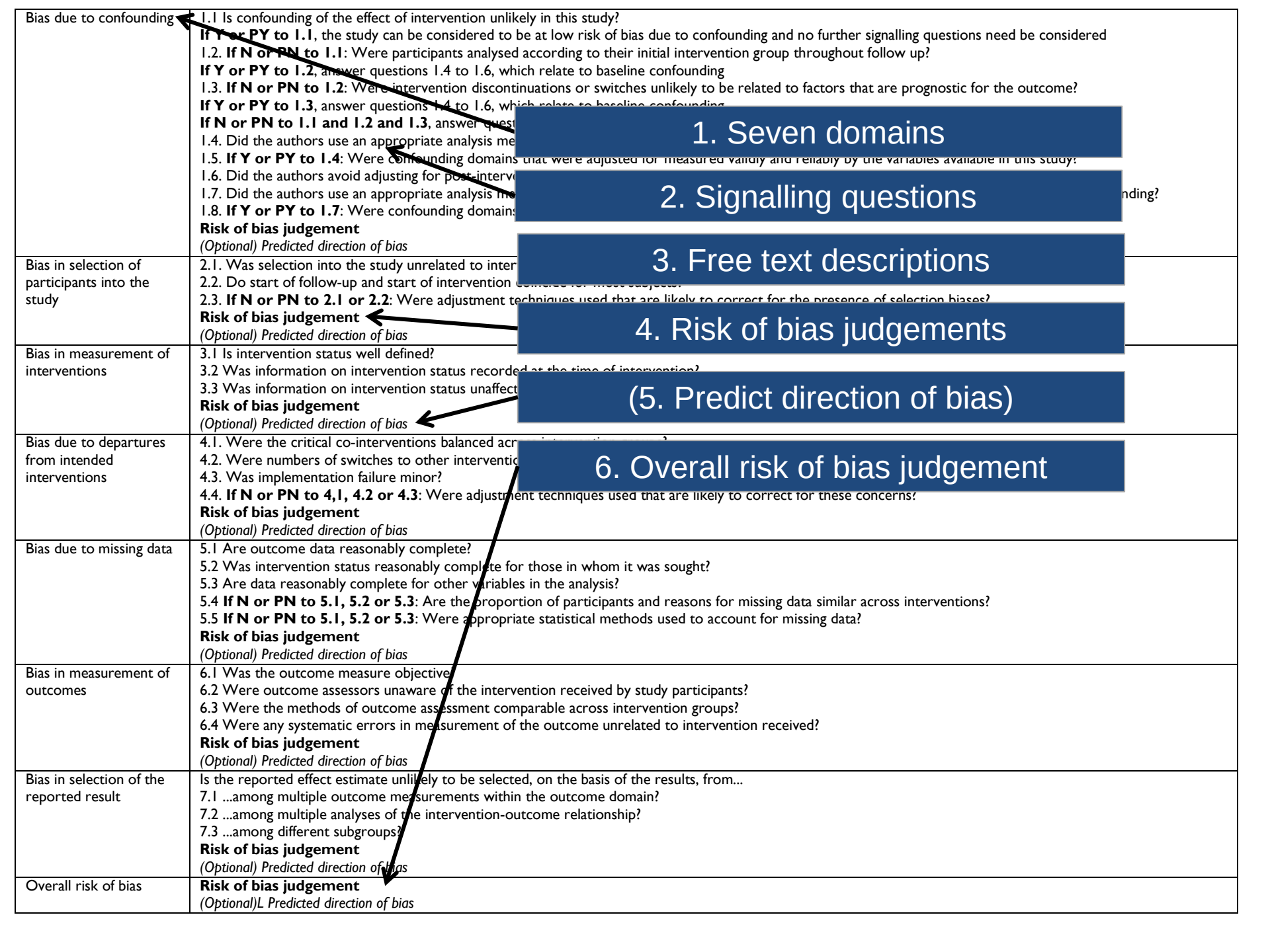
Bias in selection of the reported result	Is the reported effect estimate unlikely to be selected, on the basis of the results, from... 7.1 ...among multiple outcome measurements within the outcome domain? 7.2 ...among multiple analyses of the intervention-outcome relationship? 7.3 ...among different subgroups? **Risk of bias judgement** *(Optional) Predicted direction of bias*
Overall risk of bias	**Risk of bias judgement** *(Optional)L Predicted direction of bias*



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Signalling questions

- Attempt to elicit **reasonably factual information** about how the study was done
- e.g.
  - "Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?"
  - "Are outcome data reasonably complete?"

Yes
Probably yes
Probably no
No
No information

- Some are conditional on previous answers

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Risk of bias judgements

- For each domain, there is guidance on how to judge risk of bias based on the answers to the signalling questions

Response option	Interpretation
Low risk of bias	The study is comparable to a well-performed randomized trial with regard to this domain.
Moderate risk of bias	The study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial.
Serious risk of bias	The study has some important problems in this domain.
Critical risk of bias	The study is too problematic in this domain to provide any useful evidence.
No information	No information on which to base a judgement about risk of bias for this domain.

It is usually impossible to exclude bias due to residual or unmeasured confounding of the results of an non-randomized study. **We expect few NRSI to be assessed as at low risk of bias du to confounding**

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Overall RoB judgement

Low risk of bias	The study is judged to be at **low risk of bias for all domains** (for the outcome).
Moderate risk of bias	The study is judged to be at **low or moderate risk of bias for all domains** (for the outcome).
Serious risk of bias	The study is judged to be at **low or moderate risk of bias for most domains but at serious risk of bias in at least one domain** (for the outcome)**.**
Critical risk of bias	The study is judged to be at **critical risk of bias in at least one domain** (for the outcome).
No information	There is a lack of information in one or more key domains of bias (for the outcome) (*a judgement is required for this*).

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Outcome-specific assessments

Domain	Mortality	Viral load	QoL
Bias due to confounding	Serious risk	Moderate risk	Serious risk
Bias in selection of participants into the study	Low risk	Low risk	Low risk
Bias in measurement of interventions	Low risk	Low risk	Low risk
Bias due to departures from intended interventions	Moderate risk	Moderate risk	Moderate risk
Bias due to missing data	Low risk	No info	No info
Bias in taking measurements	Low risk	Low risk	Serious risk
Bias in selection of the reported result	Moderate risk	Moderate risk	Serious risk
Overall	*Serious risk*	*Moderate risk*	*Serious risk*

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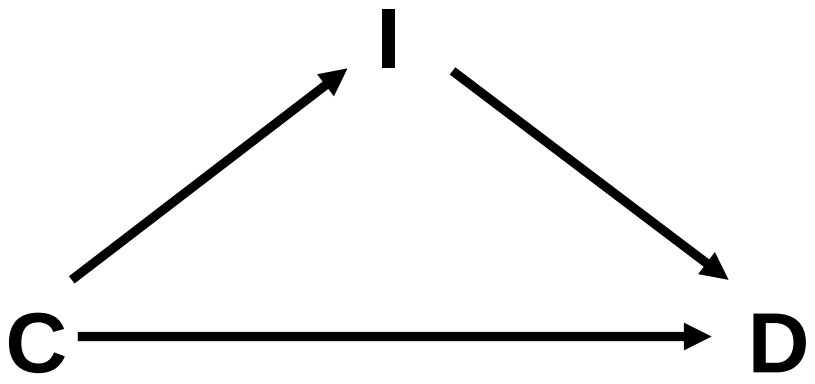
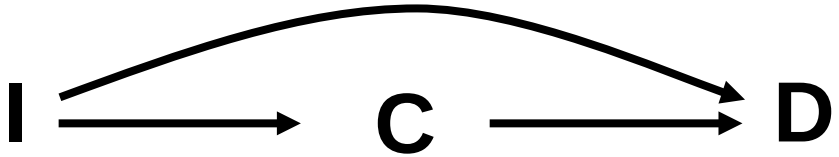
Detailed description: assessing risk of bias due to confounding

Confounding

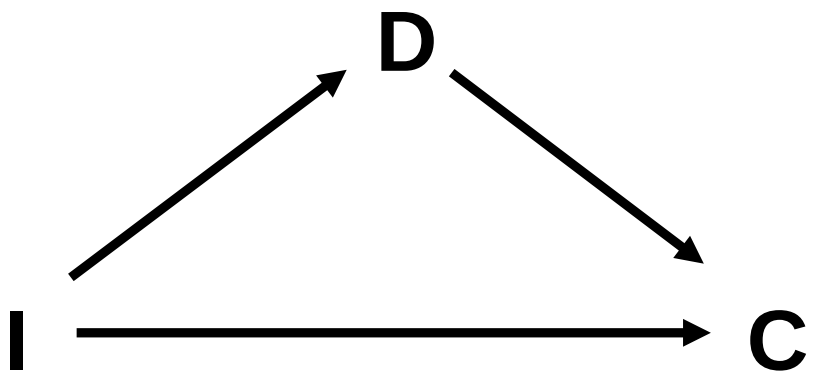
- A confounding domain C is a pre-intervention prognostic factor that predicts whether an individual receives one or the other intervention (I) of interest



- We should avoid controlling for (conditioning on) *factors on the causal pathway* from I to the outcome D



- We should also avoid conditioning on *common effects* of I and D



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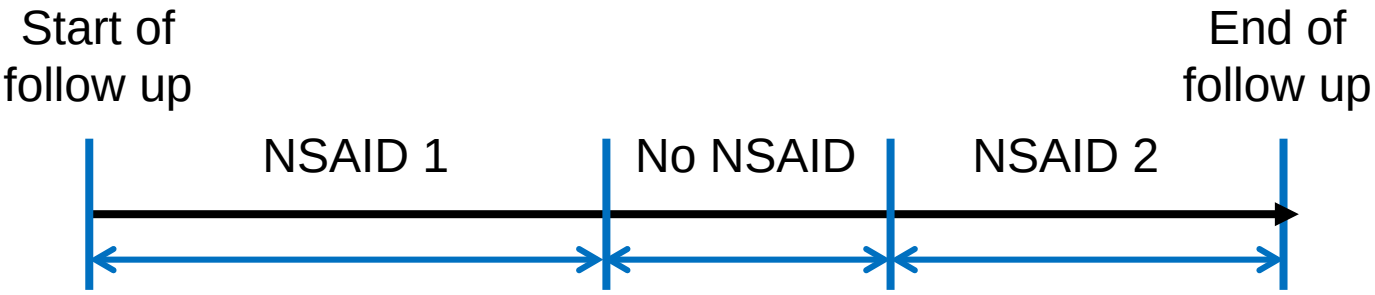
Principles for assessing risk of bias due to confounding

- Identification of potential confounding requires subject matter knowledge. **Subject-matter experts should be included** in the team writing the review protocol;
- Confounding domains should be listed in the review protocol but may also be **specific to the context of a particular study** or identified on reading a particular paper;
- We need to consider **inappropriate control** (of variables on the causal pathway, or for common effects);
- Appropriate analyses to adjust for measured confounders include stratification, regression, propensity score matching (or stratification on the propensity score), standardization, and inverse probability weighting;
  - **All these methods depends on an assumption of no unmeasured or residual confounding**

Studies that split follow up time for individual participants

- It is increasingly common (e.g. in pharmacoepidemiological studies) to split follow up time according to intervention received



- If prognostic factors predict switches between interventions of interest, then there is a risk of *time-varying confounding*.
  - e.g. an NRS compared cardiovascular events in patients taking a new diabetes medication with older therapies. Because of concerns that the new medication increased the risk of vascular events, patients whose blood pressure or lipid levels deteriorated after study entry were switched away from the new drug
- Specialist statistical methods are required to adjust for time-varying confounding

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- **Preliminary·consideration·of·confounders¶**

Complete·a·row·for·each·confounding·area·(i)·listed·in·the·review·protocol;·and·(ii)·relevant·to·the·setting·of·this·particular·study,·or·which·the·study·authors·identified·as·potentially·important.¶

- *In·the·table·below,·"critically·important"·confounding·areas·are·those·for·which,·in·the·context·of·this·study,·adjustment·is·expected·to·lead·to·a·clinically·important·change·in·the·estimated·effect·of·the·intervention.·"Validity"·refers·to·whether·the·confounding·variable·or·variables·fully·measure·the·area,·while·"reliability"·refers·to·the·precision·of·the·measurement·(more·measurement·error·means·less·reliability).¶*

(i)·Confounding·areas·listed·in·the·review·protocol¤					
Confounding·area¤	Is·the·confounding·area·critically·important?*¤	Measured·variable(s)·¤	Is·there·evidence·that·controlling·for·this·variable·was·unnecessary?*¤	Is·the·confounding·area·measured·validly·and·reliably·by·this·variable·(or·these·variables)?¤	OPTIONAL:·Is·adjusting·for·this·variable·(alone)·expected·to·favour·the·experimental·or·the·control·group?¤
¤	Yes·/·No¤	¤	¤	Yes·/·No·/·No·information¤	Favour·intervention·/·Favour·control·/·No·information¤
		¤	¤		¤
¤	¤	¤	¤	¤	¤
		¤	¤		¤

¶

(ii)·Additional·confounding·areas·relevant·to·the·setting·of·this·particular·study,·or·which·the·study·authors·identified·as·potentially·important¤					
Confounding·area¤	Is·the·confounding·area·critically·important?*¤	Measured·variable(s)·¤	Is·there·evidence·that·controlling·for·this·variable·was·unnecessary?*¤	Is·the·confounding·area·measured·validly·and·reliably·by·this·variable·(or·these·variables)?¤	OPTIONAL:·Is·adjusting·for·this·variable·(alone)·expected·to·favour·the·experimental·or·the·control·group?¤
¤	Yes·/·No¤	¤	¤	Yes·/·No·/·No·information¤	Favour·intervention·/·Favour·control·/·No·information¤
		¤	¤		¤
¤	¤	¤	¤	¤	¤
		¤	¤		¤

*·In·the·context·of·a·particular·study,·variables·can·be·demonstrated·not·to·be·confounders·and·so·not·included·in·the·analysis:·(a)·if·they·are·not·predictive·of·the·outcome;·(b)·if·they·are·not·predictive·of·intervention;·or·(c)·because·adjustment·makes·no·or·minimal·difference·to·the·estimated·effect·of·the·primary·parameter.·Note·that·"no·statistically·significant·association"·is·not·the·same·as·"not·predictive".¶

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Signalling questions: risk of bias due to confounding

Signalling question	Rationale/Remark
1.4. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	Appropriate methods to adjust for measured confounders include stratification, regression, matching, standardization, and inverse probability weighting. They may adjust for individual variables or for the estimated propensity score. Inverse probability weighting is based on a function of the propensity score. Each method depends on the assumption that there is no unmeasured or residual confounding.
1.5. If Y or PY to 1.4: **Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?**	Appropriate control of confounding requires that the variables adjusted for are valid and reliable measures of the confounding domains. For some topics, a list of valid and reliable measures of confounding domains will be specified in the review protocol but for others such a list may not be available. Study authors may cite references to support the use of a particular measure. If authors control for confounding variables with no indication of their validity or reliability pay attention to the subjectivity of the measure. Subjective measures (e.g. based on self-report) may have lower validity and reliability than objective measures such as lab findings.
1.6. Did the authors avoid adjusting for post-intervention variables?	Adjusting for post-intervention variables is not appropriate. Adjusting for mediating variables to the direct effect of intervention and may introduce confounding. Adjusting for common effects of intervention and outcome causes bias.

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From SQs to risk of bias judgements: bias due to confounding

- For each domain, there is guidance on how to judge risk of bias based on the answers to the signalling questions

Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain)	No confounding expected.
Moderate risk of bias (the study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial):	Confounding expected, all known critically important confounding domains appropriately measured and adjusted for; and Reliability and validity of measurement of critically important domains were sufficient that we do not expect serious residual confounding.
Serious risk of bias (the study has some important problems);	At least one known critically important domain not appropriately measured, or not adjusted for; or Reliability or validity of measurement of a critically important domain was low enough that we expect serious residual confounding.
Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention);	Confounding inherently not controllable, or use of negative controls strongly suggests unmeasured confounding.
No information on which to base a judgement about risk of bias for this domain.	No information on whether confounding might be present.

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Detailed description: assessing risk of selection bias

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Selection bias

- Selection bias occurs when exclusion of some eligible participants, or initial follow up time of some participants, leads to the association between intervention and outcome differing what would have been observed in the target trial
  - **This phenomenon is distinct from confounding**
  - We use “selection bias” to refer only to biases that are internal to the study, and not to issues of generalizability
- Issues of biased selection of controls in case-control studies are also addressed

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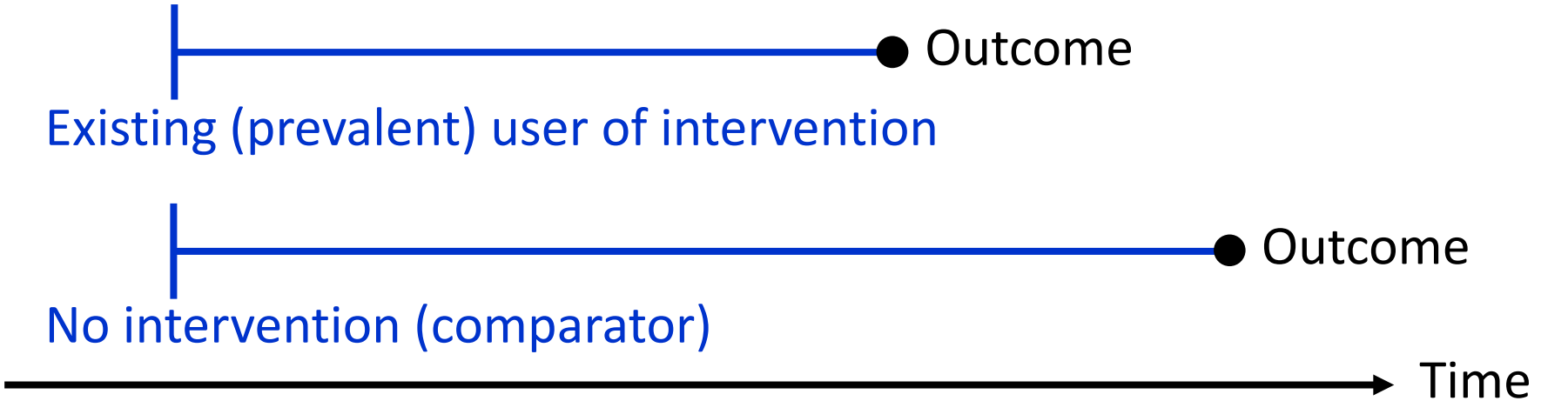
Bias due to selection of participants

- This can occur when selection of participants is **based on variables measured after intervention** that are **related to both intervention and outcome**
  - e.g. a cohort study examined the influence of folate acid supplementation on the risk of fetal neural tube defects
  - However data were only collected on live births (still births and therapeutic abortions were excluded)
  - The problem is that the probability of a live birth is influenced by both folate acid supplementation (intervention) and neural tube defects (outcome)
  - The association between intervention and outcome in the live-born babies is biased compared with the effect of intervention in all babies

Bias due to selection of follow up time

- This can occur when **prevalent users**, rather than new (incident) users of intervention are included in analyses



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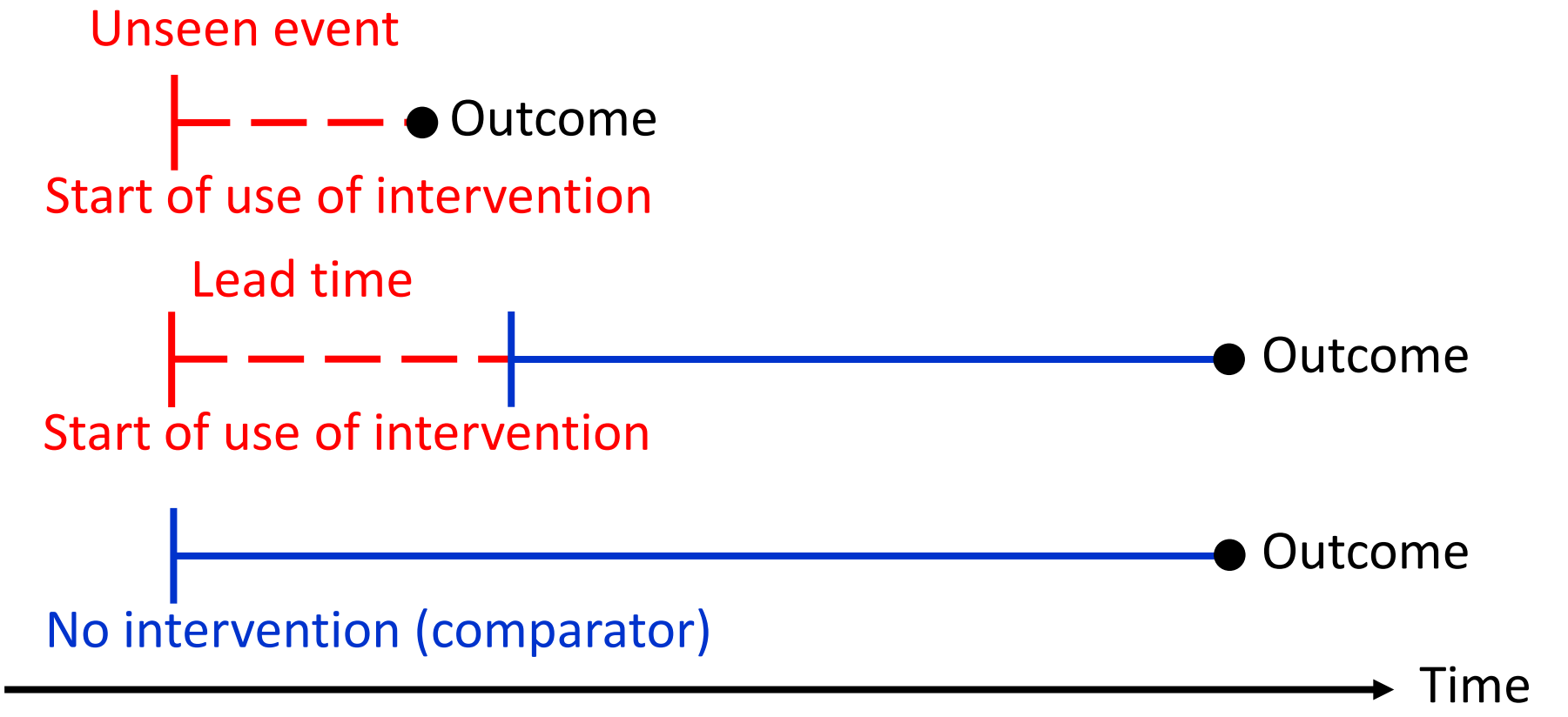

From SQs to risk of bias judgements: bias due to selection of participants

- For each signalling question, the rationale is explained and there is guidance on how to answer to the question

Signalling question	Rationale/Remark
2.1. Was selection of participants into the study (or into the analysis) based on variables measured after the start of intervention? **If N/PN to 2.1: go to 2.4**	This is a preamble to the next two questions. Go straight to question 2.4 if the answer is N / PN.
2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced eligibility associated with intervention? **2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced eligibility influenced by the outcome or a cause of the outcome?**	Selection bias occurs when selection is related to an effect of either intervention or a cause of intervention *and* an effect of either the outcome or a cause of the outcome. There is a risk of bias due to selection of participants if the answers to *both* 2.2 and 2.3 are Y / PY.
2.4. Do start of follow-up and start of intervention coincide for most participants?	If subjects are not followed from the start of the intervention then a period of follow up has been excluded, and individuals who experienced the outcome soon after intervention will be missing from analyses. This problem may occur when prevalent, rather than new (incident), users of the intervention are included in analyses.

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Brief description of other bias domains

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Bias in classification of intervention

- Example: vaccine study in Burkina-Faso, researchers visited families every 6-12 months and collected information from vaccination cards
- Non-differential misclassification
  - Vaccinated: Vaccination recorded on vaccination card
  - Unvaccinated: “When the card was not seen, we assumed that the child had not been vaccinated”
- Differential misclassfication:
  - Vaccination status is updated retrospectively, and vaccination cards are destroyed when a child dies

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Post-intervention biases

- Bias due to departures from intended interventions
  - In RCTs, the primary mechanism to prevent such bias is blinding (of participants and trial personnel). Blinding is not usually employed in NRSI;
  - Addressing such bias in NRSI gives rise to the same issues as in non-blinded RCTs.
- Bias due to missing data
  - Issues relating to missing **outcome** data seem similar for RCTs and NRSI
  - Observational studies may present additional problems relating to missing data on interventions or confounders.

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Post-intervention biases

- Biases in measurement of outcomes
  - Outcome assessors can be blinded in both RCTs and NRSI;
  - Issues relating to bias in assessing outcomes appear similar;
- Bias in selection of the reported result
  - Applies to both RCTs and NRSI, but it may be possible to identify the planned comparisons in a trial protocol. Protocols for analyses of NRSI are typically not available;
  - There are additional issues more important in NRSI (e.g. selective reporting of analyses)

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Relevance to studies of exposures

- Is there an analogue of the “target trial”?
- How do we define and assess confounding and its control?
- Implications of long-term nature of many exposures (eg for definition and assessment of selection bias)?
- Are issues relating to bias in exposure measurement more complex than those relating to bias in measurement of interventions?
- Is the “departures from intended interventions” domain relevant to studies of exposures?

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Conclusions

- ROBINS-I is based on extensive and careful consideration of the domains of bias in the results of non-randomized studies of interventions
  - It is based on explicit comparisons with a "target" randomized trial
- A revised version will be posted at www.riskofbias.info soon, following submission of the paper to *BMJ*
- Ongoing work, funded by a new grant, will focus on:
  - Theoretical and empirical evaluation
  - Wider range of study designs
  - Production of an easy-to-use, interactive, online version integrating guidance and examples