Appendix

The seven domains of bias addressed in the ROBINS-I assessment tool

Confounding

(Related terms: Selection bias as it is sometimes used in relation to clinical trials; Allocation bias; Case-mix bias; Channelling bias.)

In contrast to randomized trials, the characteristics of participants in NRSI will typically differ between intervention groups. The assessment of risk of bias arising from uncontrolled confounding is therefore a major component of ROBINS-I. Confounding of intervention effects occurs when one or more prognostic variables (variables that predict the outcome of interest) also predict whether an individual receives one or the other of the interventions of interest.

Baseline confounding, which occurs when one or more prognostic variables predicts the intervention received at start of follow up, is likely to be an issue in most NRSI. For example, a non-randomized study comparing two antiretroviral drug regimens should control for CD4 cell count measured before the start of antiretroviral therapy, because this is strongly prognostic for AIDS and death and is likely to influence choice of regimen. Appropriate methods to control for measured confounders include stratification, regression, matching, standardization, g-estimation, and inverse probability weighting. They may control for individual variables or for the estimated propensity score.

ROBINS-I also addresses time-varying confounding.\(^1\) This only needs to be considered in studies that partition follow up time for individual participants into time spent in different intervention groups. Time-varying confounding occurs when the intervention received can change over time (for example, if individuals switch between the interventions being compared), and when post-baseline prognostic factors affect the intervention received after baseline. For example, CD4 cell count measured after start of antiretroviral therapy (a post-baseline prognostic variable) might influence switches between the regimens of interest.\(^2\) When post-baseline prognostic variables are affected by the interventions themselves (for example, antiretroviral regimen may influence post-baseline CD4 count), conventional adjustment for them in statistical analyses is not appropriate as a means of controlling for confounding.\(^2\)\(^3\) Note that when individuals switch between the interventions being compared the effect of interest is that of starting and adhering to intervention, not the effect of assignment to intervention.

Selection bias

(Related terms: Selection bias as usually used in relation to observational studies and sometimes used in relation to clinical trials; Inception bias; Lead-time bias; Immortal time bias.)

When exclusion of some eligible participants, or the initial follow up time of some participants, or some outcome events, is related to both intervention and outcome, there will be an association between interventions and outcome even if the effects of the interventions are identical. This type of bias is called selection bias\(^4\) and is distinct from confounding, although the terms are sometimes confused. As an example, studies of folate supplementation to prevent neural tube defects were biased because they were restricted to live births.\(^4\) The bias arises because stillbirths and therapeutic abortions (which were excluded from the sample), are related to both the intervention and the outcome.\(^2\)\(^4\) Another example is that the apparently increased risk of venous thromboembolism with
the newer oral contraceptive progestogens when investigated in NRSI. Users of the newer agents had started treatment more recently than users of older agents and the risk of venous thromboembolism is greatest early in the course of treatment. Contemporary methodological standards emphasize the importance both of identifying cohorts of new users of health technologies and of commencing follow-up from the date of the treatment decision, not commencement of treatment, in order to avoid biases like the so-called “immortal time bias”.

Our use of the term selection bias refers only to biases that are internal to the study, and not to issues of indirectness (generalizability, applicability or transferability to people who were excluded from the study). For example, restricting the study to individuals free of comorbidities may limit the generalizability of its findings to clinical practice, where comorbidities are common. However it does not bias the estimated effect of intervention, compared to a target trial in which participants were free of comorbidities.

**Bias in measurement classification of interventions**

(Related terms: Misclassification bias; Information bias; Recall bias; Measurement bias; Observer bias.)

Misclassification of assignment to intervention is seldom a problem in randomized trials, but misclassification of intervention received may occur in NRSI. For example, the absence of a record of vaccination does not guarantee that no vaccination was administered. Non-differential misclassification is unrelated to the outcome and will usually bias the estimated effect of intervention towards the null. Differential misclassification occurs when misclassification of intervention status is related to the outcome or the risk of the outcome, and is likely to lead to bias. It is therefore important that, wherever possible, interventions are defined and categorized without knowledge of subsequent outcomes. A well-known example is recall bias in a case-control study, whereby knowledge of case-control status may affect recall of previous intervention. Differential misclassification can also occur in cohort studies, if information (or availability of information) on intervention status is influenced by outcomes. For example, in a cohort study of elderly people in which the outcome is dementia, some participants may have had mild cognitive impairment at inception. The recall of previous interventions at study inception may be affected in these participants.

**Bias due to deviations from intended interventions**

(Related terms: Performance bias; Time-varying confounding)

This domain (sometimes known as “performance bias”) relates to biases that arise when there are systematic differences between the care provided to experimental intervention and comparator groups, beyond the assigned interventions. Bias may occur when these differences arise because of knowledge of the intervention applied and the expectation of finding a difference between experimental intervention and comparator consistent with the hypothesis being tested in the study. Deviations from intended interventions may arise because an intervention was not implemented successfully (for example if laboratory errors meant that the drugs administered did not have the intended formulation), because participants did not adhere to interventions, or because important co-interventions were not balanced between intervention groups.
Whether non-adherence or co-interventions lead to bias depends on the effect of interest: they will not lead to bias in the effect of assignment to intervention. By contrast, bias will arise if we are interested in the effect of starting and adhering to intervention, which is often the case when investigating adverse effects of drugs. For example, an open-label study compared respiratory tract infection (RTI) rates after minimally invasive or open surgery for oesophageal cancer. There were two important differences between intervention groups in the delivery of co-interventions. First, one-lung mechanical ventilation (which is thought to increase respiratory complications, including RTIs) was used in the open surgery group, whereas the minimally invasive group underwent two-lung ventilation. Second, epidural analgesia was used more frequently in the open surgery group: patients with epidurals are generally less mobile and thus at increased risk of developing an RTI.

Note that some deviations from intervention happen during usual clinical care (for example, cessation of a drug intervention because of acute toxicity), and can be considered to be part of the intended intervention.

**Bias due to missing data**
(Related terms: Attrition bias; Selection bias as it is sometimes used in relation to observational studies)

Reasons for missing data include attrition (loss to follow up), missed appointments, incomplete data collection and participants being excluded from analysis by primary investigators. In NRSI, data may be missing for interventions received, confounders or outcome measurements. Differences between intervention groups in the extent of and reasons for missing data are key.\(^{11}\) If the proportion of missing data is low and the reasons for missing data are similar across intervention groups, then the risk of bias is likely to be low. As the proportion of missing data rises, differences in treatment response between available and missing participants may increase the potential for bias.

**Bias in measurement of outcomes**
(Related terms: Detection bias; Recall bias; Information bias; Misclassification bias; Observer bias; Measurement bias)

Bias may be introduced if outcomes are misclassified or measured with error.\(^{12}\) Misclassification or measurement error is non-differential if it is unrelated to the intervention received.\(^{13}\) Random errors that do not depend on the intervention or the outcome (non-differential measurement errors) will not necessarily cause bias. Differential measurement errors (those related to intervention status) will bias the estimated effect of intervention-outcome relationship.\(^{11}\) This is sometimes referred to as detection bias.\(^{10}\) Detection bias can arise when outcome assessors are aware of intervention status, particularly when the outcome is subjective, if different methods (or intensities of observation) are used to assess outcomes in different intervention groups, or if measurement errors are related to intervention status or effects (or to a confounder of the intervention-outcome relationship). Blinding of outcome assessors aims to prevent systematic differences in measurements between intervention groups. However, blinding is frequently not possible or not performed for practical reasons, and is much less common in NRSI than in randomized trials.

**Bias in selection of the reported result**
(Related terms: Outcome reporting bias; Analysis reporting bias)
Selective reporting will lead to bias if it is based on the direction, magnitude or statistical significance of intervention effect estimates.\textsuperscript{14} This last bias domain includes three types of selective reporting. Selective outcome reporting occurs when an effect estimate for a particular outcome measurement is selected from among multiple measurements, for example a measurement made at one of a number of time points or based on one of multiple pain scales. Selective analysis reporting occurs when the reported results are selected from intervention effects estimated in multiple ways, such as analyses of both change scores and post-intervention scores adjusted for baseline, or multiple analyses with adjustment for different sets of potential confounders. Finally, there may be selective reporting of a subgroup of participants, selected from a larger cohort, for which results are reported on the basis of a more interesting finding.

References