**Key concepts in clinical epidemiology: addressing and reporting sources of bias in randomised controlled trials**

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**ABSTRACT**

Randomised controlled trials are widely considered the most robust design for evaluating the effects of clinical interventions. While generalisability is often limited, randomisation aims to ensure that effects observed are genuine. However, there are common sources of bias, even in well-conducted trials, that pose a threat to this interpretation. The revised Cochrane risk-of-bias tool for trials (RoB 2) distinguishes five domains of bias that can affect the results of trials stemming from (1) the randomisation process, (2) deviations from intended interventions, (3) missing outcome data, (4) outcome measurement, and (5) reporting of findings. We use RoB 2 as a framework for recommendations to help researchers mitigate these sources of bias and ensure transparency in reporting so that users of research are aware of them.

**Key words**

Randomised controlled trial; bias; research transparency

1. **BACKGROUND**

Randomised controlled trials are widely considered the most robust design for evaluating the effects of clinical interventions because randomisation can potentially eliminate bias resulting from differences in pre-existing characteristics of participants – prognostic factors in particular – in intervention and comparator conditions. If designed and conducted well, trials have high internal validity, meaning that inferences of causal relationships (i.e., that an intervention causes a change in outcome) are free of systematic error (or bias).[1] However, in many areas of clinical research practical issues with trials can compromise the integrity of randomisation and lead to bias. In addition, there remain sources of bias that cannot be addressed by randomisation and which can occur during the whole process of research (during design, conduct, analysis, and report of trials).[2-4] Such bias can reduce the internal validity of a trial, leading to a distortion of the true treatment effect.[3] Importantly, the risk of bias may differ for different outcomes within the same trial.

The revised Cochrane risk-of-bias tool for trials (RoB 2) distinguishes five domains of bias that can affect the results of trials stemming from (1) the randomisation process, (2) deviations from intended interventions, (3) missing outcome data; (4) outcome measurement, and (5) reporting of findings

 ([www.riskofbias.info](http://www.riskofbias.info)).[3, 5] The tool was designed to assess the risk of bias of trials included in systematic reviews (other tools exist[6]). Here, we use RoB 2 as a framework for recommendations to help researchers planning or conducting trials to mitigate these sources of bias and ensure transparency in reporting so that users of research are aware of them. It may also provide readers of trial reports with guidance for critical appraisal of trial reports.

1. **SOURCES OF BIAS AND RECOMMENDATIONS FOR PREVENTION AND MITIGATION**

Bias can arise from the randomisation process when unreliable methods are used for generating the random allocation sequence, when treatment allocation is not adequately concealed, or when the randomisation process is not well implemented. This can result in potentially confounding variables being unbalanced between trial arms at baseline.[7] Lack of concealment of treatment assignment (blinding) often cannot be avoided and does not necessarily lead to bias but it should be reported so that risk of bias can be adequately assessed.

Bias due to deviations from intended interventions can arise when treatments are not delivered fully as intended (lack of fidelity). It can also arise from exposure of participants to factors influencing the outcome other than the intervention to which they have been assigned, including accidental exposure to an intervention in another trial arm. This ‘contamination’ can arise, for example, when participants fail to receive a hoped-for benefit from their intervention and seek an alternative treatment. Bias can also arise from participants not adhering fully to the treatment regimen. This is very common and often cannot be avoided, but level of adherence should always be assessed and reported. Finally, bias can arise because those delivering an intervention in one arm are more enthusiastic about their intervention than those in another arm. This ‘allegiance bias’ can affect fidelity and even within the parameters set for delivery of the intervention, can inflate or reduce the effect size.[8]

Missing outcome data are a ubiquitous problem in clinical trials, often because participants no longer wish to engage with the trial. If outcome data are missing ‘at random’, i.e., in a way that is unrelated to the outcome, the effect is only to reduce the statistical power because of reduced sample size for analysis. However, if outcome data are missing in a way that could be related to the outcome of interest, this breaks the randomisation and undermines the key strength of the trial design.[9] If outcome data are missing to different extents, or for different reasons, in different arms of the trial this can lead to an underestimate or overestimate of any effects.

Bias in outcome measurement can be due many factors, such as expectations favouring an intervention or incentives to produce data that confirm predictions. Clinical trials often rely on subjective outcome measures that are potentially subject to bias and error. Differential bias can arise from different methods being used to assess outcomes in different trials arms. Bias can also arise from repeated testing or changes in reference points used to judge outcomes (‘response shift’).

Bias in selection of findings to report or highlight is common and not fully addressed by requirements to register study protocols or analysis plans prior to analysing the data. Subgroup analyses are particularly vulnerable to this bias as they provide multiple opportunities to find and select or highlight findings that accord with a desired outcome.[10] Underpowered studies are also particularly vulnerable to reporting bias, compounded by a tendency of journals to be more inclined to accept articles reporting positive findings. The funding source or sponsor of a study can also be a factor contributing to reporting bias.

Table 1 provides an overview of the sources of bias outlined, together with recommendations for prevention, mitigation, and reporting. Regarding the latter, a trial report should be written in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines and relevant extensions (see for a full list of reporting guidelines: www.equator-network.org).[11] A new, free online Paper Authoring Tool (<https://paperauthoringtool.com>) has used these guidelines and extensive experience in writing up clinical trials to provide authors with a way to ensure that trial protocols and reports are prepared in a way that maximises transparency. We recommend to report any additional measures that were taken to reduce the risk of bias, e.g., how treatment preferences, adherence and fidelity were enhanced. The trial report should provide data that have been collected in relation to the different sources of bias, if any, and results from analyses incorporating these (e.g., results from sensitivity analyses). Finally, authors should not only discuss *if* a relevant form of bias could have been introduced but also *how* this would affect the interpretation of the study findings.

1. **CONCLUSION**

While randomised controlled trials can provide a high degree of confidence that outcomes are caused by interventions, in practice there are major, often unavoidable, sources of bias. Trialists must pay close attention to all of these and take steps to mitigate them where possible and always to report them to allow users of research to form a judgement about the extent to which findings can be relied upon. Our concise overview of important sources of bias – based on Cochrane’s risk-of-bias (RoB 2) framework – together with our list of recommendations for their prevention, mitigation, and reporting may provide guidance in this respect.

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**FURTHER READING**

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*Review of published trials to assess whether they utilised methods for reducing the risk of selection bias*

**Table 1: Sources of bias and recommendations for their prevention, mitigation, and reporting**

| **Label\***  | **Prevention and mitigation**  | **Items to report** |
| --- | --- | --- |
| **Bias arising from the randomisation process**  | * Apply an appropriate method of randomisation, including an adequate random allocation sequence generation and allocation concealment mechanism during the course of the trial.
* Measure relevant potential confounders (in particular prognostically important factors) and assess potential baseline imbalances between trial arms after trial completion.
* In case of differences between trial arms in baseline characteristics or confounders, consider statistical adjustment for these in a sensitivity analysis.
 | * Method used to generate the random allocation sequence.#
* Mechanism used to implement the random allocation sequence.#
* Steps taken to conceal the sequence until interventions were assigned from individuals involved with implementation of the randomisation.#
* A table showing and comparing relevant baseline characteristics for each group.#
 |
| **Bias arising from deviations from intended interventions** | * Ensure that as many of those involved in running and participating in the trial as possible are blind to treatment allocation and at least ensure that the data set is locked and the analysis plan fixed and publicly registered before unblinding.
* When contamination is likely, consider an alternative design, e.g., a cluster randomised controlled trial.
* Offer participants in all trial arms an acceptable and relevant treatment; limit the burden of the treatment; and consider incentives for treatment completion in all arms.
* Inform participants fully about the trial procedures as they affect them prior to randomisation and ensure good communication with participants during the trial.
* Measure the preferences of participants for the different trial interventions prior to randomisation.
* In case of a behavioural intervention: develop an a priori list of potentially active ingredients of the intervention (i.e., behaviour change techniques), based on a standard taxonomy.
* Develop detailed protocols for delivery of intervention components (including descriptions of behaviour change techniques and personalisation or tailoring options) and implementation of trials procedures.
* Train all individuals involved with the trial on the trial protocols and procedures and evaluate their competence.
* Measure the fidelity of delivery of treatment components and any co-interventions during the trial (ideally as part of a larger process evaluation).
* Measure treatment adherence and, as far as possible, reasons for non-adherence.
* Consider using data on intervention preferences, adherence, and fidelity in sensitivity analyses.
* Use intention-to-treat as the primary analysis but undertake sensitivity analyses including treatment starters and treatment completers where possible.
 | * In a supplementary file or permanent publicly available online source, full specification of interventions in all study arms, including any control arms, in sufficient detail to be able to replicate the intervention.
* Full details on any deviations from the intervention and control specification in all study arms.
* Categories of individuals involved with the trial that were blinded, if any: individuals receiving the intervention (e.g., patients); individuals providing the intervention (e.g., healthcare providers); individuals assessing outcomes (e.g., researchers); individuals analysing data (e.g., statisticians).#
* Data on treatment preferences, adherence, and fidelity, as well as results from analyses incorporating these data.
* Results of sensitivity analyses in subgroups engaging with intervention to differing degrees.
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| **Bias arising from missing outcome data**  | * Put maximum available resources into preventing missing data and use evidence-based methods to prevent attrition.
* Collect complete and accurate data on the number of randomised participants that are not followed up in each trial arm at all measurement time points.
* Collect information about the reasons for attrition, as far as possible.
* Choose an appropriate method for dealing with missing data (including multiple imputation) based on analysis of possible reasons, and undertake sensitivity analyses to check the robustness of the findings to different missing value assumptions.
 | * For each study group, the numbers of participants who were assigned, began intended treatment, completed intended treatment, and were analysed for the each outcome.#
* For each group, losses and exclusions after randomisation, together with reasons.#
* The extent to which missing data occurred, reasons why data are missing, and how missing data were handled, with details of any imputation method.
* Results from analyses dealing with missing data in different ways.
 |
| **Bias arising from outcome measurement**  | * Clearly specify *a priori* outcomes.
* Differentiate primary outcomes from secondary outcomes. If more than one primary outcome is specified, use appropriate statistical adjustment to inferential statistics.
* Use standard objective outcomes measures and measures with demonstrated validity where possible.
* Ensure researchers collecting outcome measures are blind to study group allocation where possible.
 | * Precise and detailed descriptions of all outcome measures and how these were obtained, including instructions for researchers and the wording of any questions.
* Which of the outcome measures were primary and secondary outcome measures and which were pre-specified.#
* All deviations from the study protocol in terms of outcome measurement, including measures not used, measures added, and measured implemented in a different way from planned.#
* Provenance and validity of outcome measures where possible.
 |
| **Bias arising from reporting of findings** | * Use an ‘open science’ approach: share all relevant study materials such as case report forms, statistical analysis plans, and codes via supplements of trial publications and/or platforms such as Open Science Framework (<https://osf.io>).
* Unless ethical considerations militate against it, share full annotated data set.
* Consider a blinded interpretation of data.
* Apply criteria for the credibility of subgroup analyses: (1) the subgroup variable was measured at baseline or is time-invariant; (2) the subgroup hypothesis was specified a priori in a study protocol, including an expected direction of the effect; (3) a test of interaction between the subgroup variable and the group variable was performed; and (4) there is supporting evidence for the subgroup effect from previous research.
 | * Full study protocol (made publicly available prior to study completion), including details of all outcome measures.
* Detailed statistical analysis plan, including the command file for statistical analysis and recoding of variables (made publicly available prior to unblinding of the data set and running the analyses).
* Clearly distinguish planned from post-hoc analyses.
* Complete data for all pre-specified primary and secondary outcomes for each group, with estimated effect sizes and their precision (such as 95% confidence interval).#
* Completed checklist from the CONSORT guidelines[11] and relevant extensions.
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\*Based on the revised Cochrane risk-of-bias tool for randomised controlled trials (RoB 2).[3, 5] Items which are part of the CONSORT checklist.[11]