Cochrane Risk of Bias Assessment Tool

Bias	Criteria for judging risk of bias in the Risk of Bias assessment tool
Random Sequence Generation (Selection Bias)	Criteria for a judgement of 'Low risk' of bias The investigators describe a random component in the sequence generation process such as: • Referring to a random number table; • Using a computer random number generator; • Coin tossing; • Shuffling cards or envelopes; • Throwing dice; • Drawing of lots; • Minimization. Criteria for the judgement of 'High risk' of bias The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: • Sequence generated by odd or even date of birth; • Sequence generated by some rule based on date (or day) of admission; • Sequence generated by some rule based on hospital or clinic record number. Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example: • Allocation by judgement of the clinician; • Allocation by preference of the participant; • Allocation based on the results of a laboratory test or a series of tests; • Allocation by availability of the intervention Criteria for the judgement of 'Unclear risk' of bias Insufficient information about the sequence generation process to permit judgement of 'Low risk' or 'High risk'.
Allocation Concealment (Selection Bias)	Criteria for a judgement of 'Low risk' of bias Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: • Central allocation (including telephone, web-based and pharmacy-controlled randomization); • Sequentially numbered drug containers of identical appearance; • Sequentially numbered, opaque, sealed envelopes.

	Criteria for the judgement of 'High risk' of bias Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: • Using an open random allocation schedule (e.g. a list of random numbers); • Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered); • Alternation or rotation; • Date of birth; • Case record number; • Any other explicitly unconcealed procedure. Criteria for the judgement of 'Unclear risk' of bias Insufficient information to permit judgement of 'Low risk' or 'High risk'.
Blinding of Participants And Personnel (Performance Bias) All Outcomes	Criteria for a judgement of 'Low risk' of bias • No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; • Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. Criteria for the judgement of 'High risk' of bias • No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; • Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding. Criteria for the judgement of 'Unclear risk' of bias • Insufficient information to permit judgement of 'Low risk' or 'High risk'; • The study did not address this outcome
Blinding of Outcome Assessment (Detection Bias) All Outcomes	Criteria for a judgement of 'Low risk' of bias • No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; • Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.

	Criteria for the judgement of 'High risk' of bias • No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; • Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding. Criteria for the judgement of 'Unclear risk' of bias • Insufficient information to permit judgement of 'Low risk' or 'High risk'; • The study did not address this outcome
Incomplete Outcome Data (Attrition Bias) All Outcomes	Criteria for a judgement of 'Low risk' of bias • No missing outcome data; • Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); • Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; • Missing data have been imputed using appropriate methods. Criteria for the judgement of 'High risk' of bias • Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; • For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; • For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization; • Potentially inappropriate application of simple imputation. Criteria for the judgement of 'Unclear risk' of bias • Insufficient information to permit judgement of 'Low risk' or 'High risk';

	• The study did not address this outcome
Selective Reporting (Reporting Bias)	Criteria for a judgement of 'Low risk' of bias • The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; • The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon). Criteria for the judgement of 'High risk' of bias • Not all of the study's pre-specified primary outcomes have been reported; • One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; • One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); • One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; • The study report fails to include results for a key outcome that would be expected to have been reported for such a study Criteria for the judgement of 'Unclear risk' of bias Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category.
Other Bias	Criteria for a judgement of 'Low risk' of bias Trials that did include statements on sources of funding. Criteria for the judgement of 'High risk' of bias Trials that did not include statements on sources of funding.