

Criteria for judging risk of bias

1. Random sequence generation (selection bias)

Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence

There is a low risk of selection bias if 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 (minimization may be implemented without a random element, and this is considered to be equivalent to being random).

There is a high risk of selection bias if the investigators describe a non-random component in the sequence generation process, such as: sequence generated by odd or even date of birth, date (or day) of admission, hospital or clinic record number; or allocation by judgement of the clinician, preference of the participant, results of a laboratory test or a series of tests, or availability of the intervention.

2. Allocation concealment (selection bias)

Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment

There is a low risk of selection bias if the 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; or sequentially numbered, opaque, sealed envelopes.

There is a high risk of bias if 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 non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; or other explicitly unconcealed procedures.

3. Blinding of participants

Performance bias due to knowledge of the allocated interventions by participants during the study

There is a low risk of performance bias if blinding of participants was ensured and it was unlikely that the blinding could have been broken; or if there was no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.

4. Blinding of personnel/ care providers (performance bias)

Performance bias due to knowledge of the allocated interventions by personnel/care providers during the study.

There is a low risk of performance bias if blinding of personnel was ensured and it was unlikely that the blinding could have been broken; or if there was no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.

5. Blinding of outcome assessor (detection bias)

Detection bias due to knowledge of the allocated interventions by outcome assessors

There is low risk of detection bias if the blinding of the outcome assessment was ensured and it was unlikely that the blinding could have been broken; or if there was no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.; or:

- *for patient-reported outcomes* in which the patient was the outcome assessor (e.g., pain, disability): *there is a low risk of bias* for outcome assessors if there is a low risk of bias for participant blinding.*
- *for outcome criteria that are clinical or therapeutic events* that will be determined by the interaction between patients and care providers (e.g., co-interventions, length of hospitalization, treatment failure), in which the care provider is the outcome assessor: *there is a low risk of bias* for outcome assessors if there is a low risk of bias for care providers.*
- *for outcome criteria that are assessed from data from medical forms*: *there is a low risk of bias* if the treatment or adverse effects of the treatment could not be noticed in the extracted data.*

6. Incomplete outcome data (attrition bias)

Attrition bias due to amount, nature or handling of incomplete outcome data

There is a low risk of attrition bias if there were no missing outcome data; reasons for missing outcome data were unlikely to be related to the true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data were balanced in numbers, with similar reasons for missing data across groups**; for dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk was not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, the plausible effect size (difference in means or standardized difference in means) among missing outcomes was not enough to have a clinically relevant impact on observed effect size, or missing data were imputed using appropriate methods. (*Note*: if drop-outs are very large, imputation using even "acceptable" methods may still suggest a high risk of bias)[#]

**The percentage of withdrawals and drop-outs should not exceed 20% for short-term follow-up and 30% for long-term follow-up and should not lead to substantial bias. (*Note*: these percentages are commonly used but arbitrary, not supported by literature)[#]

7. Selective Reporting (reporting bias)

Reporting bias due to selective outcome reporting

There is low risk of reporting bias if 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, or if 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).

There is a high risk of reporting bias if 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.

8. Group similarity at baseline[#] (selection bias)

Selection bias due to dissimilarity at baseline for the most important prognostic indicators

There is low risk of selection bias if groups are similar at baseline for demographic factors, value of main outcome measure(s), and important prognostic factors (examples in the field of back and neck pain are duration and severity of complaints, vocational status, percentage of patients with neurological symptoms)

9. Co-interventions[#] (performance bias)

Performance bias because co-interventions were different across groups.

There is low risk of performance bias if there were no co-interventions or they were similar between the index and control groups.

10. Compliance[#] (performance bias)

Performance bias due to inappropriate compliance with interventions across groups.

There is low risk of performance bias if compliance with the interventions was acceptable, based on the reported intensity/dosage, duration, number and frequency for both the index and control intervention(s). For single-session interventions (e.g., surgery), this item is irrelevant.

11. Intention-to-treat-analysis

Bias due to incomplete reporting and analysis according to group allocation.

There is low risk of bias if all randomised patients were reported/analyzed in the group to which they were allocated by randomisation.

12. Timing of outcome assessments[#] (detection bias)

Detection bias because important outcomes were not measured at the same time across groups.

There is low risk of detection bias if all important outcome assessments for all intervention groups were measured at the same time.

13. Other Bias

Bias due to problems not covered elsewhere in the table.

There is a low risk of bias if the study appears to be free of other sources of bias not addressed elsewhere (e.g., study funding).

[#] *Note: These instructions are adapted from van Tulder 2003[#], Boutron et al, 2005 (CLEAR NPT)* and the Cochrane Handbook of Systematic Reviews of Interventions, Chapter 8 (Version 5.1, updated March 2011).*