Appendix 3. Criteria for risk of bias assessment

1. Random sequence generation

Criteria for a judgement of "Low risk":

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;
- Minimisation. ^*Minimization may be implemented without a random element, and this is considered to be equivalent to being random.

Criteria for a judgement of "High risk":

Sequence generation process involves 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.

Sequence generation process involves judgement or some method of non-random categorisation 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 a judgement of "Unclear risk":

Insufficient information about sequence generation process

2. Allocation concealment

Criteria for a judgement of "Low risk":

Participants and investigators enrolling participants could not foresee assignment because a successful method of allocation concealment, for example:

- Central allocation (including telephone, web-based, and pharmacy-controlled, randomisation);
- Sequentially numbered drug containers of identical appearance;
- Sequentially numbered, opaque, sealed envelopes.

Criteria for a judgement of "High risk":

Participants and investigator enrolling participants could possibly foresee assignments and thus introduce selection bias, for example:

- 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;
- Any other explicitly unconcealed procedure.

Criteria for a judgement of "Unclear risk":

Insufficient detail to permit judgement of "Low risk" or "High risk".

3. Blinding of participants

Criteria for a judgement of "Low risk":

Any one of the following:

- No blinding, but the review authors judge that the outcomes are not likely to be influenced by lack of blinding;
- Blinding of participants ensured, and unlikely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Criteria for a judgement of "High risk":

Any one of the following:

- No blinding or incomplete blinding, and the outcomes are 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;
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Criteria for a judgement of "Unclear risk":

Any one of the following:

- Insufficient information to permit judgement of "Low risk" or "High risk",
- The study did not address this outcome.

4. Blinding of key study personnel

Criteria for a judgement of "Low risk":

Any one of the following:

- No blinding, but the review authors judge that the outcomes are not likely to be influenced by lack of blinding;
- Blinding of key study personnel (physicians/pharmacists/care givers/trial coordinators) ensured, and unlikely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

Criteria for a judgement of "High risk":

Any one of the following:

- No blinding or incomplete blinding, and the outcomes are likely to be influenced by lack of blinding;
- Blinding of key study personnel attempted, but likely that the blinding could have been broken;
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Criteria for a judgement of "Unclear risk":

Any one of the following:

- Insufficient information to permit judgement of "Low risk" or "High risk";
- The study did not address this outcome.

5. Blinding of outcome assessment

Criteria for a judgement of "Low risk":

Any one of the following:

- 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 a judgement of "High risk":

Any one of the following:

- No blinding or incomplete blinding, and the outcome assessment 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 a judgement of "Unclear":

Any one of the following:

- Insufficient information to permit judgement of "Low risk" or "High risk";
- The study did not address this outcome.

6. Incomplete outcome data

Criteria for a judgement of "Low risk":

Any one of the following:

- No missing outcome data;
- Reasons for missing outcome data unlikely to be related to true outcome;
- 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;
- The percentage of withdrawal and drop-outs does not exceed 20% with reasons documented and missing data have been imputed using appropriate methods.

Criteria for a judgement of "High risk":

Any one of the following:

- Reason for missing outcome data is 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 randomisation;

- Potentially inappropriate application of simple imputation.

Criteria for a judgement of "Unclear":

- Insufficient reporting of attrition/exclusions to permit judgement of "Low risk" or "High risk";
- The study did not address this outcome.

7. Selective outcome reporting:

Criteria for a judgement of "Low risk":

Any of the following:

- 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 a judgement of "High risk":

Any one of the following:

- 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 a judgement of "Unclear":

Insufficient information to permit judgement of "Low risk" or "High risk".

8. Imbalance in baseline covariates

Criteria for a judgement of "Low risk":

Groups are similar at baseline regarding demographics, severity of pain, and value of main outcome measure(s).

Criteria for a judgement of "High risk":

Groups are obviously dissimilar at baseline regarding demographics, severity of pain, and value of main outcome measure(s).

Criteria for a judgement of "Unclear":

If baseline characteristics are described in the text but data are not presented.

9. Treatment compliance

Criteria for a judgement of "Low risk":

Participants' compliance with the treatment allocation was measured or documented. The level of treatment compliance based on reported dosage, duration and frequency is acceptable. Analyses were performed on an intention-to-treat basis.

Criteria for a judgement of "High risk":

Any one of the following:

- Participants' compliance with the treatment allocation was not measured;
- Over 50% of participants did not comply with the allocated treatment;
- Participants were excluded from analysis for variety of reasons, or only per protocol analysis was performed as the primary analysis.

Criteria for a judgement of "Unclear":

Insufficient reporting in treatment compliance to permit judgement of "Low risk" or "High risk".

10. Timly outcome assessment

Criteria for a judgement of "Low risk":

Timing of outcome assessment is identical or closely similar for all treatment groups and for all important outcomes.

Criteria for a judgement of "High risk":

Timing of outcome assessment is obviously different among participants due to variety reasons.

Criteria for a judgement of "Unclear":

Insufficient reporting to permit judgement of "Low risk" or "High risk".

Overall risk of bias

A - low risk of bias:

Low risk for all sources of bias (1-10).

B - moderate risk of bias:

One of more high risk in other sources of bias (8-10). Low risk or unclear risk for key sources of bias (1-7).

C - high risk of bias:

High risk for one or more key sources of bias (1-7).