Reviews

For main text:

Risk of bias

Two review authors (initials) independently assessed the risk of bias (low, high, or unclear) of all included trials using the Cochrane ‘Risk of bias’ tool (Higgins 2011) for the following domains:

* selection bias
* performance bias
* attrition bias
* reporting bias
* or any other bias

Any disagreements were resolved by discussion or by a third assessor. See [Appendix 2](https://archie.cochrane.org/sections/documents/view?version=z1602121707269037293463533411836&format=REVMAN#APP-02) for a more detailed description of risk of bias for each domain.

For Appendices:

**Appendix 2**

**Risk of bias tool**

The following issues were evaluated and entered into the risk of bias table:

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?   
     
   For each included study, we categorized the method used to generate the allocation sequence as:
   1. low risk (any truly random process e.g. random number table; computer random number generator);
   2. high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number);
   3. unclear risk.
2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?   
     
   For each included study, we categorized the method used to conceal the allocation sequence as:
   1. low risk (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
   2. high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
   3. unclear risk.
3. Blinding (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study? At study entry? At the time of outcome assessment?   
     
   For each included study, we categorized the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or classes of outcomes. We categorized the methods as:
   1. low risk, high risk or unclear risk for participants;
   2. low risk, high risk or unclear risk for personnel;
   3. low risk, high risk or unclear risk for outcome assessors.
4. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?   
     
   For each included study and for each outcome, we described the completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We categorized the methods as:
   1. low risk (< 20% missing data);
   2. high risk (≥ 20% missing data);
   3. unclear risk.
5. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?   
     
   For each included study, we described how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:
   1. low risk (where it is clear that all of the study’s pre-specified outcomes and all expected outcomes of interest to the review have been reported);
   2. high risk (where not all the study’s pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
   3. unclear risk.
6. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?   
     
   For each included study, we described any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:
   1. low risk;
   2. high risk;
   3. unclear risk.

If needed, we planned to explore the impact of the level of bias through undertaking sensitivity analyses.

### Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Protocols:

For main text:

Risk of bias

Two review authors will independently assess the risk of bias (low, high, or unclear) of all included trials using the Cochrane ‘Risk of bias’ tool (Higgins 2011) for the following domains:

* selection bias
* performance bias
* attrition bias
* reporting bias
* or any other bias

Any disagreements will be resolved by discussion or by a third assessor. See [Appendix 2](https://archie.cochrane.org/sections/documents/view?version=z1602121707269037293463533411836&format=REVMAN#APP-02) for a more detailed description of risk of bias for each domain.

For Appendices:

**Appendix 2**

**Risk of bias tool**

The following issues will be evaluated and entered into the risk of bias table:

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?   
     
   For each included study, we will categorize the method used to generate the allocation sequence as:
   1. low risk (any truly random process e.g. random number table; computer random number generator);
   2. high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number);
   3. unclear risk.
2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?   
     
   For each included study, we will categorize the method used to conceal the allocation sequence as:
   1. low risk (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);
   2. high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
   3. unclear risk.
3. Blinding (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study? At study entry? At the time of outcome assessment?   
     
   For each included study, we will categorize the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding will be assessed separately for different outcomes or classes of outcomes. We will categorize the methods as:
   1. low risk, high risk or unclear risk for participants;
   2. low risk, high risk or unclear risk for personnel;
   3. low risk, high risk or unclear risk for outcome assessors.
4. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?   
     
   For each included study and for each outcome, we will describe the completeness of data including attrition and exclusions from the analysis. We will note whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we will re-include missing data in the analyses. We will categorize the methods as:
   1. low risk (< 20% missing data);
   2. high risk (≥ 20% missing data);
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5. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?   
     
   For each included study, we will describe how we investigated the possibility of selective outcome reporting bias and what we found. We will assess the methods as:
   1. low risk (where it is clear that all of the study’s pre-specified outcomes and all expected outcomes of interest to the review have been reported);
   2. high risk (where not all the study’s pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
   3. unclear risk.
6. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?   
     
   For each included study, will describe any important concerns we have about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We will assess whether each study was free of other problems that could put it at risk of bias as:
   1. low risk;
   2. high risk;
   3. unclear risk.

If needed, we will explore the impact of the level of bias through undertaking sensitivity analyses.