Risk Of Bias instrument for Use in SysTematic reviews-for Randomized Controlled Trials (ROBUST-RCT)

Study reference:

State the outcome(s) that are being assessed for risk of bias:

Item 1: Random sequence generation

Step 1: **Was the allocation sequence adequately generated***	**Step 2:** **Judge risk of bias related to sequence generation***	**Instructions**
☐ **Definitely Yes**	☐ **Definitely Low**	Trial explicitly stated use of an adequate method of generating the random allocation sequence. Examples include: random number table; random number generator; throwing dice; drawing of lots; minimization.
☐ **Probably Yes**	☐ **Probably Low**	Trial was described as "randomized" without further details regarding the method of generating the allocation sequence, and: - the text mentioned simple randomization, block randomization, or stratified randomization; or - the text described the allocation concealment method (stated using central allocation, drug containers, or envelopes).
☐ **Probably No**	☐ **Probably High**	Trial was described as "randomized" without further details regarding the method of generating the allocation sequence, and it does not meet any of the criteria for "Probably Yes/Low".
☐ **Definitely No**	☐ **Definitely High**	Trial used a non-randomized allocation sequence that would be recognized as "quasi-randomization". Examples include: allocation based on dates of birth or admission; patient's hospital record number; alteration or rotation; allocation decided by clinicians or participants; allocation based on the results of a laboratory test; allocation by availability of the intervention.

*Instructions for step 1 and step 2 are the same because no additional judgement is involved.

Support for judgement:

Item 2: Allocation concealment

Step 1: **Was the allocation adequately concealed***	**Step 2:** **Judge risk of bias related to allocation concealment***	**Instructions**
☐ **Definitely Yes**	☐ **Definitely Low**	Trial used a clearly satisfactory allocation concealment method: central allocation (e.g., telephone, web-based); pharmacy-controlled randomization (stated using sequentially numbered sealed drug containers); trial explicitly stated using sequentially numbered opaque sealed envelopes *with evidence that they were opened sequentially*.
☐ **Probably Yes**	☐ **Probably Low**	• Trial explicitly stated using sequentially numbered, opaque, sealed envelopes *without further details*. • *Drug trial in which participants and healthcare providers were blinded*: - with no further information on the allocation concealment method; or - stated using envelopes but it remains unclear whether the envelopes were sequentially numbered opaque and sealed; or - stated using drug containers but it remains unclear whether the drug containers were sequentially numbered and sealed.
☐ **Probably No**	☐ **Probably High**	• *Unblinded drug trial or non-drug trial*: - with no further information on the allocation concealment method; or - stated using envelopes but it remains unclear whether the envelopes were sequentially numbered opaque and sealed; or - stated using drug containers but it remains unclear whether the drug containers were sequentially numbered and sealed.
☐ **Definitely No**	☐ **Definitely High**	• Trial used an open random allocation schedule. • Trial used a non-randomized allocation sequence that would be recognized as “quasi-randomization”.

*Instructions for step 1 and step 2 are the same because no additional judgement is involved.

Support for judgement:

Item 3: Blinding of participants

Step 1: Were participants blinded

☐ **Definitely Yes**	Trial explicitly stated that participants were blinded.
☐ **Probably Yes**	No explicit statement about blinding of participants, and: - it is a placebo-controlled drug trial; or - it is an active control drug trial (A vs. B) and mention of "double dummy" or that medications were identical or matched; or - trial was described as "single blinded", "double blinded" or "triple blinded", and the best judgment is that one of the blinded groups is the participants; or - participants not capable of distinguishing if they are receiving active or control intervention (e.g., neonates, severely demented).
☐ **Probably No**	No explicit statement about blinding of participants, and: - it is an active control drug trial (A vs. B) and no mention of "double dummy" or that medications were identical or matched; or - it is a non-drug trial; or - trial was described as "single blinded" and the best judgement is that the single blinded group is someone other than the participants.
☐ **Definitely No**	• Trial explicitly stated that participants were not blinded. • Trial was described as "open-label" or "unblinded".

Support for judgement:

Step 2: Judge risk of bias related to blinding of participants

Issues to consider:

i) Were participants blinded (step 1)

ii) If unblinded, how likely unblinding of participants has influenced the outcome

- *How likely are participants expectations regarding effect of intervention to have influenced the outcome*
- *How likely are participant-initiated co-interventions to have influenced the outcome*

☐ **Definitely Low**	• Participants were definitely blinded; OR • Unblinding of participants *very unlikely* to have influenced the outcome because: very unlikely participants expectations regarding effect of intervention have influenced the outcome and very unlikely participant-initiated co-interventions have influenced the outcome.
☐ **Probably Low**	• Participants were probably blinded; OR • Unblinding of participants *unlikely* to have influenced the outcome because: unlikely participants expectations regarding effect of intervention have influenced the outcome and unlikely participant-initiated co-interventions have influenced the outcome.
☐ **Probably High**	Participants were definitely or probably not blinded, AND unblinding of participants *likely* to have influenced the outcome because participants expectations regarding effect of intervention likely to have influenced the outcome or participant-initiated co-interventions likely to have influenced the outcome.
☐ **Definitely High**	Participants were definitely or probably not blinded, AND unblinding of participants *very likely* to have influenced the outcome through participants expectations regarding effect of intervention or through participant-initiated co-interventions.

Support for judgement:

Item 4: Blinding of healthcare providers

Step 1: Were healthcare providers blinded

☐ **Definitely Yes**	Trial explicitly stated that healthcare providers were blinded.
☐ **Probably Yes**	No explicit statement about blinding of healthcare providers, and: - it is a placebo-controlled drug trial; or - it is an active control drug trial (A vs. B) and mention of "double dummy" or that medications were identical or matched; or - trial was described as "single blinded", "double blinded" or "triple blinded", and the best judgment is that one of the blinded groups is the healthcare providers.
☐ **Probably No**	No explicit statement about blinding of healthcare providers, and: - it is an active control drug trial (A vs. B) but no mention of "double dummy" or that medications were identical or matched; or - it is a non-drug trial; or - trial was described as "single blinded" and the best judgement is that the single blinded group is someone other than the healthcare providers.
☐ **Definitely No**	• Trial explicitly stated that healthcare providers were not blinded. • Trial was described as "open-label" or "unblinded".

Support for judgement:

Step 2: Judge risk of bias related to blinding of healthcare providers

Issues to consider:

i) Were healthcare providers blinded (step 1)

ii) *If unblinded, how likely unblinding of healthcare providers has influenced the outcome*

- *How likely healthcare provider-initiated co-interventions have influenced the outcome*

☐ **Definitely Low**	Healthcare providers were definitely blinded.
☐ **Probably Low**	• Healthcare providers were probably blinded; OR • Unblinding of healthcare providers unlikely to have influenced the outcome because: - Unlikely there is any healthcare provider-initiated co-intervention that could potentially influence the outcome; or - Investigators have documented all healthcare provider-initiated co-interventions that could potentially influence the outcome and demonstrated similarity in use of all these co-interventions between groups.
☐ **Probably High**	• Healthcare providers were definitely or probably not blinded, AND unblinding of healthcare providers likely to have influenced the outcome because there are healthcare provider-initiated co-interventions that could potentially influence the outcome.
☐ **Definitely High**	• Healthcare providers were definitely or probably not blinded, AND unblinding of healthcare providers very likely to have influenced the outcome because there are healthcare provider-initiated co-interventions that could potentially influence the outcome and investigators have documented dissimilarity in any of these co-interventions between groups.

Support for judgement:

Item 5: Blinding of outcome assessors

Step 1: Were outcome assessors blinded

When the outcome is participants self-report, e.g., completing a questionnaire (such as quality of life, disability index), participants are the outcome assessors.

☐ **Definitely Yes**	Trial explicitly stated that the outcome assessors or adjudicators (people making the measurement or assessment) were blinded.
☐ **Probably Yes**	No explicit statement about blinding of outcome assessors or adjudicators, and: - it is a placebo-controlled drug trial; or - it is an active control drug trial (A vs. B) and mention of "double dummy" or that medications were identical or matched; or - trial was described as "single blinded", "double blinded" or "triple blinded", and the best judgement is that one of the blinded groups is the outcome assessors.
☐ **Probably No**	No explicit statement about blinding of outcome assessors or adjudicators, and: - it is an active control drug trial (A vs. B) but no mention of "double dummy" or that medications were identical or matched; or - it is a non-drug trial; or - trial was described as "single blinded" and the best judgement is that the single blinded group is someone other than the outcome assessors.
☐ **Definitely No**	• Trial explicitly stated that the outcome assessors or adjudicators were not blinded. • Trial was described as "open-label" or "unblinded".

Support for judgement:

Step 2: Judge risk of bias related to blinding of outcome assessors

Issues to consider:

i) Were outcome assessors blinded (step 1)

ii) If unblinded, how likely unblinding of outcome assessors has influenced the outcome assessment

- *Degree of judgement/subjectivity involved in the outcome assessment (more judgment/subjectivity more likelihood of bias)*

☐ **Definitely Low**	• Outcome assessors were definitely blinded; OR • Outcome is all-cause mortality.
☐ **Probably Low**	• Outcome assessors were probably blinded; OR • Unblinding of outcome assessors likely could not have influenced the outcome assessment because the outcome assessment involves minimal judgement (other objective outcomes, e.g., laboratory measurement, hospital admission, mechanical ventilation).
☐ **Probably High**	Outcome assessors were definitely or probably not blinded, AND unblinding of outcome assessors likely could have influenced the outcome assessment because the outcome assessment involves some judgment (e.g., cause-specific mortality).
☐ **Definitely High**	Outcome assessors were definitely or probably not blinded, AND unblinding of outcome assessors could have influenced the outcome assessment because the outcome assessment involves considerable judgment by participant or adjudicator (e.g., symptoms and symptom scores, quality of life, seizure occurrence).

Support for judgement:

Item 6: Outcome data not included in analysis

Step 1: Extract the number of participants who were not included in analysis in each group

Note: For time-to-event outcomes, also count the participants who were censored because of missing follow-up data in 'N not analyzed'.

	N not analyzed	N total (usually N randomized)	Percentage not analyzed (N not analyzed / N total)
Intervention group _____			
Control group _____			
Overall			

Step 2: Judge risk of bias related to the overall percentage of participants not included in analysis

Issue to consider: Was the overall percentage of participants not included in analysis acceptably low

Note: Systematic review teams need to set and fill in the threshold for each response option. See manual for instructions and example thresholds.

☐ **Definitely Low**	Percentage of participants not included in analysis is < %
☐ **Probably Low**	• Percentage of participants not included in analysis is % to < % • If the trial did not mention whether there were participants not included in analysis, a substantial loss to follow-up is unlikely (e.g., ICU mortality)
☐ **Probably High**	• Percentage of participants not included in analysis is % to < % • If the trial did not mention whether there were participants not included in analysis, a substantial loss to follow-up is likely (e.g., 1-year quality of life)
☐ **Definitely High**	Percentage of participants not included in analysis is ≥ %

Support for judgement:

Which if any optional item(s) to assess

We provide eight optional items (see manual).

We strongly recommend that the systematic review teams consider each of the optional items carefully and judge whether they are relevant to their particular reviews.

If systematic review teams decide to include optional item(s), specify the optional items that need to be considered and provide instructions for assessing the items (see examples in manual).

Optional item	Instruction	Judgement	Support for judgement