Online Supplemental File 4

Risk of bias tools

Cochrane risk-of-bias tool for randomized trials (RoB 2)

Bias domain and signaling question	Response options		
	Lower risk of bias	**Higher risk of bias**	**Other**
1. Bias arising from the randomization process			
1.1 Was the allocation sequence random?	Yes/ Probably Yes	No/ Probably No	No Information
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Yes/ Probably Yes	No/ Probably No	No Information
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	No/ Probably No	Yes/ Probably Yes	No Information
Risk-of-bias judgment (low/high/some concerns)			
Optional: What is the predicted direction of bias arising from the randomization process?			
2. Bias due to deviations from intended interventions			
2.1 Were participants aware of their assigned intervention during the trial?	No/ Probably No	Yes/ Probably Yes	No Information
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	No/ Probably No	Yes/ Probably Yes	No Information

2.3 If Yes/ Probably Yes/ No Information to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	No/ Probably No	Yes/ Probably Yes	No Information/ Not Applicable
2.4 If Yes/ Probably Yes/ No Information to 2.3: Were these deviations likely to have affected the outcome?	No/ Probably No	Yes/ Probably Yes	No Information/ Not Applicable
2.5 If Yes/ Probably Yes to 2.4: Were these deviations from intended intervention balanced between groups?	Yes/ Probably Yes	No/ Probably No	No Information/ Not Applicable
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	Yes/ Probably Yes	No/ Probably No	No Information
2.7 If No/ Probably No/ No Information to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyses participants in the group to which they were randomized?	No/ Probably No	Yes/ Probably Yes	No Information/ Not Applicable
Risk-of-bias judgment (low/high/some concerns)			
Optional: What is the predicted direction of bias due to deviations from intended interventions?			
3. Bias due to missing outcome data			
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Yes/ Probably Yes	No/ Probably No	No Information
3.2 If No/ Probably No/ No Information to 3.1: Is there evidence that the result was not biased by missing outcome data?	Yes/ Probably Yes	No/ Probably No	Not Applicable
3.3 If No/ Probably No to 3.2: Could missingness in the outcome depend on its true value?	No/ Probably No	Yes/ Probably Yes	No Information/ Not Applicable
3.4 If Yes/ Probably Yes/ No Information to 3.3: Is it likely that missingness in the outcome depended on its true value?	No/ Probably No	Yes/ Probably Yes	No Information/ Not Applicable
Risk-of-bias judgment (low/high/some concerns)			
Optional: What is the predicted direction of bias due to missing outcome data?			
4. Bias in measurement of the outcome			

4.1 Was the method of measuring the outcome inappropriate?	No/ Probably No	Yes/ Probably Yes	No Information
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	No/ Probably No	Yes/ Probably Yes	No Information
4.3 If No/ Probably No/ No Information to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	No/ Probably No	Yes/ Probably Yes	No Information
4.4 If Yes/ Probably Yes/ No Information to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	No/ Probably No	Yes/ Probably Yes	No Information/ Not Applicable
4.5 If Yes/ Probably Yes/ No Information to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	No/ Probably No	Yes/ Probably Yes	No Information
Risk-of-bias judgment (low/high/some concerns)			
Optional: What is the predicted direction of bias in measurement of the outcome?			
5. Bias in selection of the reported result			
5.1 Were the data that produced this result analyzed in accordance with a prespecified analysis plan that was finalized before unblinded outcome data were available for analysis?	Yes/ Probably Yes	No/ Probably No	No Information
Is the numerical result being assessed likely to have been selected, on the basis of the results, from:			
5.2 ... multiple eligible outcome measurements (eg, scales, definitions, time points) within the outcome domain?	No/ Probably No	Yes/ Probably Yes	No Information
5.3 ... multiple eligible analyses of the data?	No/ Probably No	Yes/ Probably Yes	No Information
Risk-of-bias judgment (low/high/some concerns)			
Optional: What is the predicted direction bias due to selection of the reported results?			
6. Overall bias			
Risk-of-bias judgment (low/high/some concerns)			
Optional: What is the overall predicted direction of bias for this outcome?			

Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I)

Major Components	Response options			
Part 1: Bias due to confounding				
1.1 Is there potential for confounding of the effect of intervention in this study? If No/ Probably No to 1.1: the study can be considered to be at low risk of bias due to confounding and no further signaling questions need be considered If Yes/ Probably Yes to 1.1: determine whether there is a need to assess time-varying confounding:	Yes/ Probably Yes	No/ Probably No		
1.2. Was the analysis based on splitting participants' follow up time according to intervention received? If No/ Probably No, answer questions relating to baseline confounding (1.4 to 1.6) If Yes/ Probably Yes, go to question 1.3.	Yes/ Probably Yes	No/ Probably No	No Information	Not Applicable
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? If No/ Probably No, answer questions relating to baseline confounding (1.4 to 1.6) If Yes/ Probably Yes, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)	Yes/ Probably Yes	No/ Probably No	No Information	Not Applicable
Questions relating to baseline confounding only (1.4 to 1.6)				

1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Yes/ Probably Yes	No/ Probably No	No Information	Not Applicable
1.5. If Yes/ Probably Yes to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Yes/ Probably Yes	No/ Probably No	No Information	Not Applicable
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	Yes/ Probably Yes	No/ Probably No	No Information	Not Applicable
Questions relating to baseline and time-varying confounding (1.7to 1.8)				
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Yes/ Probably Yes	No/ Probably No	No Information	Not Applicable
1.8. If Yes/ Probably Yes to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Yes/ Probably Yes	No/ Probably No	No Information	Not Applicable
Risk of bias judgement:	Low risk of bias/ Moderate risk of bias/ Serious risk of bias/ Critical risk of bias/ No information			
Optional: What is the predicted direction of bias due to confounding?	Favors experimental/ Favors comparator/ Unpredictable			
Part 2: Bias in selection of participants into the study				
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If No/ Probably No to 2.1: go to 2.4	Yes/ Probably Yes	No/ Probably No	No Information	
2.2. If Yes/ Probably Yes to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Yes/ Probably Yes	No/ Probably No	No Information	Not Applicable
2.3 If Yes/ Probably Yes to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Yes/ Probably Yes	No/ Probably No	No Information	Not Applicable

2.4. Do start of follow-up and start of intervention coincide for most participants?	Yes/ Probably Yes	No/ Probably No	No Information	
2.5. If Yes/ Probably Yes to 2.2 and 2.3, or No/ Probably No to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Yes/ Probably Yes	No/ Probably No	No Information	Not Applicable
Risk of bias judgement:	Low risk of bias/ Moderate risk of bias/ Serious risk of bias/ Critical risk of bias/ No information			
Optional: What is the predicted direction of bias due to selection of participants into the study?	Favors experimental/ Favors comparator/ Towards null/ Away from null/ Unpredictable			
Part 3: Bias in classification of interventions				
3.1 Were intervention groups clearly defined?	Yes/ Probably Yes	No/ Probably No	No Information	
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Yes/ Probably Yes	No/ Probably No	No Information	
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Yes/ Probably Yes	No/ Probably No	No Information	
Risk of bias judgement:	Low risk of bias/ Moderate risk of bias/ Serious risk of bias/ Critical risk of bias/ No information			
Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?	Favors experimental/ Favors comparator/ Towards null/ Away from null/ Unpredictable			
Part 4: Bias due to deviations from intended interventions				
If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2				
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Yes/ Probably Yes	No/ Probably No	No Information	

4.2. If Yes/ Probably Yes to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Yes/ Probably Yes	No/ Probably No	No Information	Not Applicable
If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6				
4.3. Were important co-interventions balanced across intervention groups?	Yes/ Probably Yes	No/ Probably No	No Information	
4.4. Was the intervention implemented successfully for most participants?	Yes/ Probably Yes	No/ Probably No	No Information	
4.5. Did study participants adhere to the assigned intervention regimen?	Yes/ Probably Yes	No/ Probably No	No Information	
4.6. If No/ Probably No to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Yes/ Probably Yes	No/ Probably No	No Information	Not Applicable
Risk of bias judgement:	Low risk of bias/ Moderate risk of bias/ Serious risk of bias/ Critical risk of bias/ No information			
Optional: What is the predicted direction of bias due to deviations from the intended interventions?	Favors experimental/ Favors comparator/ Towards null/ Away from null/ Unpredictable			
Part 5: Bias due to missing data				
5.1 Were outcome data available for all, or nearly all, participants?	Yes/ Probably Yes	No/ Probably No	No Information	
5.2 Were participants excluded due to missing data on intervention status?	Yes/ Probably Yes	No/ Probably No	No Information	
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Yes/ Probably Yes	No/ Probably No	No Information	
5.4 If No/ Probably No to 5.1, or Yes/ Probably Yes to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Yes/ Probably Yes	No/ Probably No	No Information	Not Applicable
5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Yes/ Probably Yes	No/ Probably No	No Information	Not Applicable
Risk of bias judgement:	Low risk of bias/ Moderate risk of bias/ Serious risk of bias/ Critical risk of bias/ No information			

Optional: What is the predicted direction of bias due to missing data?	Favors experimental/ Favors comparator/ Towards null/ Away from null/ Unpredictable			
Part 6: Bias in measurement of outcomes				
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Yes/ Probably Yes	No/ Probably No	No Information	
6.2 Were outcome assessors aware of the intervention received by study participants?	Yes/ Probably Yes	No/ Probably No	No Information	
6.3 Were the methods of outcome assessment comparable across intervention groups?	Yes/ Probably Yes	No/ Probably No	No Information	
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Yes/ Probably Yes	No/ Probably No	No Information	
Risk of bias judgement:	Low risk of bias/ Moderate risk of bias/ Serious risk of bias/ Critical risk of bias/ No information			
Optional: What is the predicted direction of bias due to measurement of outcomes?	Favors experimental/ Favors comparator/ Towards null/ Away from null/ Unpredictable			
Part 7: Bias in selection of the reported result				
Is the reported effect estimate likely to be selected, on the basis of the results, from...				
7.1. ... multiple outcome measurements within the outcome domain?	Yes/ Probably Yes	No/ Probably No	No Information	
7.2 ... multiple analyses of the intervention-outcome relationship?	Yes/ Probably Yes	No/ Probably No	No Information	
7.3 ... different subgroups?	Yes/ Probably Yes	No/ Probably No	No Information	
Risk of bias judgement:	Low risk of bias/ Moderate risk of bias/ Serious risk of bias/ Critical risk of bias/ No information			
Optional: What is the predicted direction of bias due to selection of the reported result?	Favors experimental/ Favors comparator/ Towards null/ Away from null/ Unpredictable			

Overall bias	
Risk of bias judgement:	Low risk of bias/ Moderate risk of bias/ Serious risk of bias/ Critical risk of bias/ No information
Optional: What is the overall predicted direction of bias for this outcome?	Favors experimental/ Favors comparator/ Towards null/ Away from null/ Unpredictable

Methodological index for non-randomized studies (MINORS)*

Major Components	Response options		
1. A clearly stated aim	Not reported (0 point)	Reported but inadequate (1 point)	Reported and adequate (2 point)
2. Inclusion of consecutive patients	Not reported (0 point)	Reported but inadequate (1 point)	Reported and adequate (2 point)
3. Prospective collection of data	Not reported (0 point)	Reported but inadequate (1 point)	Reported and adequate (2 point)
4. Endpoints appropriate to the aim of the study	Not reported (0 point)	Reported but inadequate (1 point)	Reported and adequate (2 point)
5. Unbiased assessment of the study endpoint	Not reported (0 point)	Reported but inadequate (1 point)	Reported and adequate (2 point)
6. Follow-up period appropriate to the aim of the study	Not reported (0 point)	Reported but inadequate (1 point)	Reported and adequate (2 point)
7. Loss to follow up less than 5%	Not reported (0 point)	Reported but inadequate (1 point)	Reported and adequate (2 point)
8. Prospective calculation of the study size	Not reported (0 point)	Reported but inadequate (1 point)	Reported and adequate (2 point)
9. An adequate control group	Not reported (0 point)	Reported but inadequate (1 point)	Reported and adequate (2 point)
10. Contemporary groups	Not reported (0 point)	Reported but inadequate (1 point)	Reported and adequate (2 point)
11. Baseline equivalence of groups	Not reported (0 point)	Reported but inadequate (1 point)	Reported and adequate (2 point)
12. Adequate statistical analyses	Not reported (0 point)	Reported but inadequate (1 point)	Reported and adequate (2 point)
Total score			

*The first eight apply to both non-comparative and comparative studies, while the remaining four relate only to studies with two or more groups. The global ideal score being 16 for non-comparative studies and 24 for comparative studies.