Appendix 2. Modified Cochrane Risk of Bias tool[34]

Source of bias	Criteria for a judgment of "yes"	Criteria for a judgment of "no"
1. Was the randomisation procedure adequate?	***YES*** *– A random component in the sequence generation process is used, such as:* • *Using to a random number table* • *Using a computer random number generator* • *Tossing a coin* • *Shuffling cards or envelopes* • *Throwing dice* • *Drawing lots* • *Minimisation* • *Randomisation generated by outside statistician/central group* • *Random permuted block scheme*	***NO*** *– a non-random component is used in the allocation process, such as:* • *Sequence generated using odd or even date of birth* • *Sequence based on a rule based on date of admission or hospital number* • *Allocation decision is made by clinician or participant* • *Allocation is based on clinical or laboratory test findings*
	Unclear *– Study uses statements such as "we randomly allocated" or "using a randomised design", but insufficient detail is given of the process to allow a decision to be made regarding the adequacy of the method.*	
2. Was the treatment allocation adequately concealed?	***YES*** *– participants and physicians could not foresee allocation assignment, because an adequate method was used to conceal allocation. Adequate allocation concealment methods include:* • *Central allocation* • *Identical drug containers are sequentially numbered* • *Opaque, sealed, sequentially numbered assignment envelopes are used* • *Remotely labelled study kit with no indication of treatment within* • *Statement that allocation was concealed from investigators*	***NO*** *– participants or physicians could potentially foresee allocation. Inadequate allocation concealment procedures include:* • *The use of an open random allocation schedule* • *Assignment envelopes are not appropriate, such that envelopes may be unsealed, not sequentially numbered, or see-through* • *Rotation or alternation* • *Methods based on date of birth, case record number, or other patient identifiers*
	Unclear *– No mention of precautions taken to conceal treatment allocation.*	
3. Were participants blinded to the intervention?	***YES*** *– patients were adequately blinded and it is unlikely that the blinding could be broken. A statement describing that the treatments were identical or "matched" is expected to allow a decision.*	***NO*** *– No blinding, incomplete blinding, or blinding attempted but likely to have been broken*
	Unclear *– Study reported as single- or double-blinded but no description of the process of blinding, thereby not allowing a decision to be made regarding the adequacy.*	
4. Were physicians blinded to the intervention?	***YES*** *– physicians were adequately blinded and it is unlikely that the blinding could be broken. If the*	***NO*** *– No blinding, incomplete blinding, or blinding attempted but likely to have been broken*

		treatments are identical a statement that the physicians were blinded allows a yes ***Unclear*** *– Study reported as single- or double-blinded but no description of the process of blinding, thereby not allowing a decision to be made regarding the adequacy.*	
5.	**Were outcome assessors blinded to the intervention?**	***YES*** *– treatment choice is not evident when measuring outcome.* • *If outcome is patient-reported, then the answer for "Were participants blinded to the intervention?" will be the same for this question.* • *For physician-assessed outcomes, this is dependent on whether the treatment allocation can be identified from examination of the patient or their tests*	***NO*** *– treatment choice is likely to be evident when measuring outcome* • *If outcome is patient-reported, then the answer for "Were participants blinded to the intervention?" will be the same for this question.* • *For physician-assessed outcomes, this is dependent on whether the treatment allocation can be identified from examination of the patient or their tests*
6.	**Incomplete outcome data: Is the attrition rate <15%?**	***YES*** *– drop-out rate is less than 15%* ***Unclear*** *– flow of patients not given. Unable to ascertain number of withdrawals*	***NO*** *– drop-out rate is greater than 15%*
7.	**Are all pre-specified outcomes of interest reported in the pre-specified way?**	***YES*** *– all the study's pre-specified outcomes of interest are reported in the pre-specified way*	***NO*** *– Outcome measures were not pre-specified, such as:* • *Not all the pre-specified outcomes have been reported* • *Outcomes are not reported using the measurements or methods pre-specified* • *Outcomes reported had not been pre-specified, such as post-hoc analyses* • *Outcomes of interest have been incompletely reported* • *The report does not report outcomes that would be expected from such a study*
8.	**Was intention-to-treat analysis used?**	***YES*** *– all randomised participants are analysed according to the group they were allocated to, regardless of non-compliance, protocol violations, drop-outs etc.* ***Unclear*** *– does not mention if ITT or PP used and n for each outcome not presented*	***NO*** *– the study states that ITT was used, but patients have been excluded from analysis, post-randomisation, for variety of reasons. Alternatively, per-protocol analysis is used to analyse only participants that adhered fully to their allocated treatment, excluding any drop-outs or moves between treatment groups.*
9.	**Were the treatment and control group similar at baseline?**	***YES*** *– treatment and control group were similar regarding patient demographics and baseline parameters.*	***NO*** *– Treatment and control groups were dissimilar with regards to patient demographics and baseline parameters. Alternatively, characteristics are not presented in either text or table*

***Unclear**- if characteristics are mentioned in text, but data are not presented*

34. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. *The Cochrane Collaboration* 2011.