Appendix 1: Definitions used for assessing the risk of bias in individual randomised controlled trials.

Domain	Risk of bias	Definition
Sequence generation	Low	- Random number table - Computer random-number generator - Coin tossing - Shuffling cards or envelopes - Minimization
	High	- Sequence generated by odd or date of birth or date of admission
	Unclear	- Method used to generate sequence of randomisation not reported
Allocation concealment	Low	- Central allocation - Sequentially numbered drug containers of identical appearance - Sequentially numbered, opaque, sealed envelopes
	High	- Predictable assignment (date of birth, alternation, open random allocation schedule, unsealed envelopes)
	Unclear	- Method to maintain allocation concealment not reported
Blinding of participants and personnel	Low	- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken - Either participants or some key personnel were not blinded but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias
	High	- No blinding or incomplete blinding and the outcome measurement is likely to be influenced by lack of blinding (i.e., subjective outcome) - Blinding of participants and personnel attempted but likely that the blinding could have been broken (differences in co-interventions among groups) - Either participants or personnel were not blinded, and the non-blinding likely to introduce bias
	Unclear	- Insufficient information to permit judgement of "low risk" or "high risk" - Insufficient information about co-interventions to assess whether lack of blinding or incomplete blinding was likely to influence the outcome
Blinding of outcome assessment	Low	- No blinding but objective outcome (i.e., mortality, biological tests) - Blinding of outcome assessor and unlikely that the blinding could have been broken
	High	- No blinding or incomplete blinding and the outcome measurement is likely to be influenced by lack of blinding (i.e., subjective outcome) - 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
	Unclear	- Insufficient information regarding outcome assessment blinding
Incomplete outcome data	Low	- No missing outcome data - Missing data have been imputed using appropriate methods (worst-case analysis) - Missing data balanced in numbers across intervention groups with similar reasons for missing data across groups - The proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate (< 10% of the number of patients randomised or < the number of outcomes)
	High	- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups - The proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate (≥ 10% of patients randomised or ≥ the number of outcomes) - As-treated analysis performed with substantial departure of the intervention received from that assigned at randomisation (≥ 10% of patients randomised or ≥ the number of outcomes)
	Unclear	- Insufficient reporting of attrition/exclusion (i.e., number of participants randomised and analysed not stated, no reason for missing data provided)