Appendix 2. Table. Definitions Used for Assessing Risk of Bias Items in Individual Randomized Trials

Risk of bias item	Risk of bias judgment	Definition
Sequence generation	*Low*	Central randomization Computer random-number generator Minimization Random number table Coin tossing, shuffling cards or envelops
	High	Date of birth Date of hospital admission
	Unclear	Not reported
Allocation concealment	*Low*	Central randomization Sequentially numbered, opaque, sealed envelopes Sequentially numbered drug containers of identical appearance
	High	Allocation based on date of birth, alternation Open random allocation schedule Unsealed envelopes
	Unclear	Not reported
Blinding participants and personnel[1]	*Low*	Blinding of participants and personnel Low likelihood that blinding could have been broken
	High	Any situation where blinding of participants and personnel is not possible (e.g. surgical treatment) Subjective outcome likely to be influenced by lack of blinding
	Unclear	Incomplete information
Blinding outcome assessor[1]	*Low*	No blinding but with objective outcome Blinding of outcome assessor
	High	Subjective outcome likely to be influenced by lack of blinding
	Unclear	Incomplete information

INCOMPLETE OUTCOME DATA

Attrition bias due to amount, nature or handling of incomplete outcome data.

Criteria for a judgement of 'Low risk' of bias.

Any one of the following:

- No missing outcome data;
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;
- Missing data have been imputed using appropriate methods.

Criteria for the judgement of 'High risk' of bias.

Any one of the following:

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;

- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization;
- Potentially inappropriate application of simple imputation.

Criteria for the judgement of 'Unclear risk' of bias.

Any one of the following:

- Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided);
- The study did not address this outcome.

[1] In a secondary analysis the two items related to blinding were also reconsidered as low risk of bias in the case of objective outcomes. Results remained unchanged.