Study ID		**Kim 2005**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Microsoft Excel 2000, a random number-generation program.
	1.2	NI	Allocation concealment not reported
	1.3	N	The demographic and total symptom severity scores did not differ between groups at baseline, nor were there significant differences between groups
		Some concerns	**Some concerns due to the lack of reporting on allocation concealment**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	identical placebo spray
	2.2	PY	not specified as double blind, possible people delivering the intervention were aware
	2.3	PN	No information
	2.4	NA	
	2.5	NA	
	2.6	PY	Modified ITT interpreted
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	During the first 2 weeks, 6 patients dropped out of the study, including 2 (10%) in the homeopathic group and 4 (20%) in the placebo group.
	3.2	N	no analysis method or sensitivity analysis which corrected for bias
	3.3	Y	Authors note discontinuation was primarily due to lack of response to treatment
	3.4	Y	as above
		High	**Due to the discontinuation of patients due to lack of response to treatment**
Bias in measurement of the outcome	4.1	N	validated measures specific to allergic rhinitis were used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	patient reported outcomes, patients blind to treatment allocation
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Liu 2013**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Patients assigned intervention using computer generated code
	1.2	PY	All physicians and staff were blinded to allocation
	1.3	PN	Baseline clinical characteristics were similar in both groups, except p-specific IgE - intervention group more allergic to dust mites. Not considered likely to be due to the randomisation process.
		Low	**Randomisation sequence likely truly random, allocation sequence concealed and baseline characteristics appear balanced**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Blinded study with identical placebo
	2.2	N	Study staff were blind to allocation
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	PY	Modified ITT interpreted
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	46 enrolled, 36 available for analysis. Missing data for 2/25 participants in the intervention group and 8/21 in the control group.
	3.2	N	no analysis for missing outcome data
	3.3	Y	Could be related to ineffective therapy, although no reason is provided
	3.4	Y	Imbalanced rate of drop out between groups, considered likely to be related to the outcome.
		High	**Due to the substantial and imbalanced rate of drop out.**
Bias in measurement of the outcome	4.1	N	
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double-blind study
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

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Study ID		**Reilly 1984**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Patients were allocated by random numbers
	1.2	PY	Study pharmacist held the code
	1.3	N	No major differences between groups at baseline
		Low	**Randomisation sequence likely truly random, allocation sequence concealed and baseline characteristics appear balanced**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Blinded study with identical placebo
	2.2	N	Double blinded
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	PN	Unclear method of analysis, as the returned outcome measures exceeded the number of participants randomised to each group.
	2.7	PY	Unclear how many participants were potentially inappropriately analysed.
		High	**Due to the potentially inappropriate analysis method**
Bias due to missing outcome data	3.1	N	Authors report that 114/156 participants randomised were included in the analysis. 108/158 had complete week 55 data.
	3.2	N	no analysis for missing outcome data
	3.3	Y	plausible that withdrawals in treatment phases are due to ineffective treatment, although reasons not provided
	3.4	PN	Rate of drop out is balanced between groups. Reasons not provided but no evidence to suggest that missingness is due to the outcome.
		Some concerns	Due to the proportion of missing outcome data, which is balanced between groups
Bias in measurement of the outcome	4.1	N	
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double blinded study - participant reported outcomes
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the reported result	5.1	NI	Pre-study power calculation reported, no pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

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Study ID		**Taylor 2000**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Restricted technique, permuted blocks of two, stratified by allergen
	1.2	NI	Allocation concealment not reported
	1.3	N	baseline characteristics similar in both groups
		Some concerns	**Some concerns due to lack of information regarding allocation concealment**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	identical placebo
	2.2	PN	Single blind during the run-in period (all participants received placebo), double blind during intervention period.
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis used
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	Y	One patient (homoeopathy group) was lost to follow up
	3.2	NA	
	3.3	NA	
	3.4	NA	
		Low	
Bias in measurement of the outcome	4.1	N	Youlten nasal inspira-tory peak flow meter - validated measure of nasal obstruction. VAS-100 mm also used to assess patient experience
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double blinded study - objective measures and participant reported outcomes
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the reported result	5.1	Y	Pre-study power calculation reported, no pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Due to lack of pre-specified analysis plan**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

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Study ID		**Aabel 2000a**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	Statistician conducted randomisation, but no details provided on the method of generating the randomisation sequence.
	1.2	PY	The vials were sent to a statistician for random coding. Interpreted that this results in allocation concealment.
	1.3	N	Similar baseline characteristics of patients treated with Betula 30c or placebo
		Low	**Randomisation sequence likely truly random, allocation sequence concealed and baseline characteristics appear balanced**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Identical placebo
	2.2	N	Double blinded. The lead investigator was aware of the run-in treatment.
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	Modified ITT interpreted. Ineligible participants excluded after randomisation and 1 participant who dropped out not included in the final analysis.
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	PY	Outcome data available for 66/70 participants.
	3.2	NA	
	3.3	NA	
	3.4	NA	
		Low	
Bias in measurement of the outcome	4.1	PN	3 point scale for various symptoms, not validated
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double blinded study - participant reported outcomes
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Due to lack of pre-specified analysis plan**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

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Study ID		**Aabel 2000b**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	Statistician conducted randomisation, but no details provided on the method of generating the randomisation sequence.
	1.2	Y	The vials were sent to a statistician for random coding. Interpreted that this results in allocation concealment.
	1.3	N	Similar baseline characteristics of patients treated with Betula 30c or placebo
		Low	**Randomisation sequence likely truly random, allocation sequence concealed and baseline characteristics appear balanced**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	identical placebo
	2.2	N	Double blinded
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	Modified ITT interpreted, those who did not return outcome data were not included in the analysis
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	Missing data for 7/80 participants
	3.2	N	no analysis for missing outcome data
	3.3	PY	It is plausible that missing outcome data is related to symptoms
	3.4	PN	Reasons for drop out suggest this is unlikely, those that did not return registration forms in prophylactic phase may have done so due to lack of effectiveness of intervention
		Some concerns	**Due to the proportion of missing outcome data**
Bias in measurement of the outcome	4.1	N	VAS-100mm
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double blinded study - participant reported outcomes
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Due to lack of pre-specified analysis plan**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

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Study ID		**Aabel 2001**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Statistician conducted randomisation, but no details provided on the method of generating the randomisation sequence.
	1.2	PY	Only the statistician knew the code
	1.3	NI	Not reported
		High	**Due to the lack of information on randomisation method and baseline characteristics**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double blinded
	2.2	N	Double blinded
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	Modified ITT interpreted, those who did not return outcome data were not included in the analysis
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	NI	Rate of drop out not reported
	3.2	NI	
	3.3	PN	Assumed no drop out
	3.4	NA	
		Low	
Bias in measurement of the outcome	4.1	N	VAS-100mm
	4.2	PY	Because of low pollen counts, participants were asked to continue measuring their outcomes for as long as possible. Variable duration of reporting between groups was observed.
	4.3	NA	
	4.4	NA	
	4.5	NA	
		High	**due to variations in the method of outcome assessment**
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

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Study ID		**Naidoo 2013**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Simple random sampling
	1.2	PY	Randomisation performed by laboratory separate from study staff
	1.3	NI	Baseline characteristics not reported in a manner that permit comparison
		Some concerns	**Due to the lack of information on baseline characteristics**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double blinded
	2.2	N	Double blinded
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis performed
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	Y	Data available for all participants
	3.2	NA	
	3.3	NA	
	3.4	NA	
		Low	
Bias in measurement of the outcome	4.1	N	SPT is validated for measuring allergic reaction
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double blinded study - objective measures
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Due to lack of pre-specified analysis plan**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

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Study ID		**Wiesenauer 1995**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	Stratified randomisation, no mention of how the randomisation sequence was generated. Physician defined the strata and no mention of the stratification process was provided.
	1.2	Y	Patient numbers affixed to medicine bottles and manufacturer labels removed
	1.3	N	No significant difference at baseline
		Some concerns	
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double blinded
	2.2	N	Double blinded
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	N	Per protocol analysis excluding participants who used other medicines including antiallergics, anti-inflammatories and antiphlogistics.
	2.7	Y	32 participants excluded
		High	**Due to the inappropriate method of analysis**
Bias due to missing outcome data	3.1	N	32 cases (18 in verum and 14 in placebo group) were excluded from the study
	3.2	N	no analysis for missing outcome data
	3.3	PY	Reason for withdrawal include incomplete documentation, self-medication or additional hay fever medication administered by the physician
	3.4	PY	additional medication could have been required due to ineffective therapy
		High	**High risk of bias due to the large proportion of patients not included in the analysis**
Bias in measurement of the outcome	4.1	N	patient reported 4 point scale
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double blinded study - participant reported outcomes
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

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Study ID		**Carello 2017**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Children who satisfied the eligibility criteria were randomized using software with a 128 random list for the two groups (A and B) in a 1:1 ratio
	1.2	PN	Allocation concealment not specified. Subjects allocated group according to sequential order of enrolment, considered possible that allocation was not concealed at enrolment.
	1.3	N	No significant difference at baseline
		Some concerns	**Due to potential issues with allocation concealment**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double blinded
	2.2	N	Double blinded
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis specified. mITT conducted based on complete data.
	2.7	NA	
		Low	
Bias due to missing outcome data	3.1	N	Thirteen discontinued medication (6 in Group A and 7 in Group B), and one child in Group B experienced an adverse event.
	3.2	N	No analysis for missing outcome data
	3.3	PY	Possibly due to ineffective treatment - authors note that drop outs were probably due to the long-term nature of the study
	3.4	PN	Considering the duration of the study, the rate of missing data is not considered likely to be due to the true value
		Some concerns	**Due to the proportion of missing data, not considered likely to be due to the true outcome**
Bias in measurement of the outcome	4.1	N	Disease severity was assessed with the Scoring Atopic Dermatitis (SCORAD) index
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double blinded study - objective measures and participant reported outcomes
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

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Study ID		Dey 2022	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	A permuted block randomization method (6 blocks of n = 10; i.e., 6 × 10 = 60) used to generate a random sequence
	1.2	Y	allocation by a third party who were not allowed to influence the study
	1.3	PN	Except age (higher in placebo group) and socioeconomic status (middle class people higher in homeopathy group and affluent higher in placebo). Not considered likely to be due to the randomisation process.
		Low	
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double blinded
	2.2	N	Double blinded
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis
	2.7	NA	
		Low	
Bias due to missing outcome data	3.1	N	During the course of intervention, 9 patients dropped out (3 in the active, 6 in the control)
	3.2	N	Missing values were replaced by the last observation carried forward method
	3.3	NI	Limited reasons for drop out available.
	3.4	NI	No evidence to suggest that missingness is related to the true value of the outcome
		Some concerns	**Due to the proportion of missing data, not considered likely to be due to the true outcome**
Bias in measurement of the outcome	4.1	N	Disease severity was assessed with the Scoring Atopic Dermatitis (SCORAD) index
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double blinded study - objective measures and participant reported outcomes
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

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Study ID		**Vickers 2000**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Randomisation in permuted blocks of 8 and 12 is by a computer system designed to ensure allocation concealment
	1.2	Y	
	1.3	N	There were no statistically significant differences at baseline between completers in the four groups, and no notable differences in homeopathic medicines prescribed
		Low	**Randomisation sequence likely truly random, allocation sequence concealed and baseline characteristics appear balanced**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	Y	four arms in trial - one arm of unblinded homeopathy
	2.2	PY	Treatment allocation was concealed from clinical staff by holding the randomisation list on a secure database system to which they had no access. Subjects in the fast track open verum group received unblinded homeopathic medication immediately
	2.3	Y	Blinded patients appeared more likely to withdraw: 11 of 38 (29%) blinded patients dropped out compared to 3 of 38 (8%) unblinded
	2.4	Y	Blindness appeared to have a positive effect on outcome, however this was confounded by the proportion of missingness
	2.5	N	
	2.6	Y	ITT analysis specified
	2.7	NA	
		Low	**Low risk of bias in the blinded group. High risk in the open label arm.**
Bias due to missing outcome data	3.1	N	14 lost to follow up
	3.2	N	No analysis for missing outcome data
	3.3	Y	Blinded patients appeared more likely to withdraw: 11 of 38 (29%) blinded patients dropped out compared to 3 of 38 (8%) unblinded
	3.4	Y	As above
		High	**Due to thew impact of blinding on drop out**
Bias in measurement of the outcome	4.1	N	Appropriate outcome measures
	4.2	N	Outcome measurements consistent between groups
	4.3	PY	Patient reported measures - unblinded group are aware of intervention
	4.4	Y	Patient reported outcome measures could be effected by knowledge of the intervention
	4.5	Y	Authors note it is likely that blind patients who did not notice an improvement were most likely to drop out, while those who did improve continued to provide data, hence the apparent positive effect of blinding
		Low	**Low risk of bias in the blinded group. High risk in the open label arm.**
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

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Study ID		Harrison 1999	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	The study was conducted in two locations. In Swindon, randomisation was done on an alternate basis. In the Isle of Wright, sealed envelopes were used. No further details were provided.
	1.2	PN	Study authors suggest that the study may have been compromised by the possibility that randomisation was unconcealed
	1.3	Y	Study authors note the uneven distribution of hearing loss at baseline suggests potential issues with the randomisation process
		High	**Due to baseline differences suggesting an issue with the randomisation process**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	Y	Participants were aware of treatment allocation
	2.2	PY	Only the homeopathy treatment group received homeopathic consultations, so it is presumed the homeopaths were aware of the treatment allocation
	2.3	PN	Only deviations reported were non-completion by some participants. Not considered to be due to the trial context.
	2.4	NA	
	2.5	NA	
	2.6	Y	Presumed ITT analysis
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	2/33 participants withdrew from the study
	3.2	N	No adjustment for missing data reported
	3.3	NI	Reasons for participant drop-out were not provided
	3.4	PN	It is unable to be determined if participant drop-out was due to health status
		Some concerns	**Due to missing outcome data with no adjustments presented**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Persons conducting the audiometric and tympanometry measurements were blinded to treatment allocations
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan available for comparison
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		Jacobs 2001	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Study medications were randomised into coded bottles by a homeopathic pharmacist. Coded bottles were randomised to contain either active medication or placebo by random number generator and pattern blocks of 4 and 6. Participants were given the next bottle in the sequence
	1.2	Y	Concealment code was not broken until analysis was completed
	1.3	PN	Some slight baseline differences noted Not considered likely to be due to the randomisation process.
		Low	**Randomisation sequence likely truly random, allocation sequence concealed and Some slight baseline differences likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo-controlled
	2.2	N	Double-blind
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis performed
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	3/75 participants withdrew from the study
	3.2	N	No adjustment for missing data reported
	3.3	PN	3/3 participants were lost to follow up. Drop-out was not due to health status
	3.4	NA	
		Some concerns	**Some concerns due to missing outcome data**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double-blind
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan available for comparison
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Due to lack of pre-specified analysis plan**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Pedrero-Escalas 2016**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Treatment assignment was set up with a permuted-block randomisation algorithm and a masking plan was followed to guarantee the double-blindness
	1.2	PY	Not specifically stated, but presumed due to the nature of the study
	1.3	PN	Some slight baseline differences noted, and adjusted for through multivariate regression analysis. Not considered due to the randomisation process
		Low	**Randomisation sequence likely truly random, allocation sequence concealed and Some slight baseline differences likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo-controlled
	2.2	N	Double-blind
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis performed
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	10/96 participants withdrew from the study
	3.2	N	No adjustment for missing data reported
	3.3	PY	5/10 participants dropped out due to adverse events, 2/10 due to surgical procedures, 2/10 voluntarily withdrew (explanation unknown), 1/10 abandoned trial (explanation unknown)
	3.4	PY	Health status was among the reasons for participant drop out. 4 participants in the placebo group and 1 in the treatment group dropped out due to adverse events
		High	**Due to participant drop out relating to health status**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double-blind
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the reported result	5.1	Y	Trial protocol available for comparison
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Low	
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Sinha 2012**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated random numbers
	1.2	PY	Not specifically stated, but presumed due to the nature of the study
	1.3	PN	Some slight baseline differences noted, not considered due to the randomisation process
		Low	**Randomisation sequence likely truly random, allocation sequence concealed and Some slight baseline differences likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo-controlled
	2.2	N	The parent/guardians and the research personnel remained unaware of the treatment allocation throughout the study
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis performed
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	3/81 participants had missing data
	3.2	PN	ITT analysis performed, last observation carried forward principle applied
	3.3	PY	1/3 participants in the control group withdrew due to convulsions, 2/3 participants in the homeopathy group withdrew due to reasons unspecified
	3.4	PY	Health status was among the reasons for participant drop out
		High	**Due to participant drop out relating to health status**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Researchers were not aware of treatment allocations
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan avaialable for comparison
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		Taylor 2011	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated randomisation schedule. Randomization was stratified by antibiotic treatment plan (immediate or delayed therapy) and in blocks of 4
	1.2	PY	Not specifically stated, but presumed
	1.3	PY	No statistically significant differences reported at baseline, however randomisation was stratified by antibiotic treatment plan, and this was not presented in the baseline characteristics. It is therefore possible that this was unbalanced between the treatment groups. Antibiotic treatment plan is likley to have an affect on the outcomes reported
		Some concerns	**Due to missing baseline characteristics that might be unbalanced between groups**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	Y	Open trial
	2.2	Y	Open trial
	2.3	PN	Only deviations reported were non-completion. Not considered due to the trial context
	2.4	NA	
	2.5	NA	
	2.6	PY	Presumed modified ITT analysis was performed
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	26/120 participants had missing data
	3.2	N	No adjustment for missing data reported
	3.3	NI	Reasons for participant non-completion were not provided. It is not known whether it was related to health status
	3.4	PN	10/26 in the control group and 15/26 in the homeopathy group did not return symptom diaries. Reasons for non-completion not specified
		Some concerns	**Some concerns due to missing outcome data**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	Y	Open trial
	4.4	PY	It is possible knowledge of the intervention could have biased outcome measures
	4.5	PY	Knowledge of intervention could bias self-reported outcomes, and influence whether participants chose to fill their antibiotic prescriptions or not. The proportion who filled their prescriptions was greater in the control group (36.5%) compared to the homeopathy group (7.1%). Antibiotic use is likely to affect outcomes
		High	**Due to knowledge of intervention that influences outcome measured**
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan avaialable for comparison
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Taylor 2014**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Randomisation was performed using a computerised database; randomisation was stratified by study site and in blocks of 4
	1.2	NI	Not specifically stated, but presumed
	1.3	PN	Baseline characteristics only provided for participants whom provided outcome data. So unable to determine if there were imbalances, but any imbalances would probably not be due to the randomisation process
		Some concerns	**Baseline characteristics missing for some participants, but any imbalances unlikely due to randomisation process**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	Y	Open trial
	2.2	Y	Open trial
	2.3	PN	Only deviations reported were non-completion. Not considered due to the trial context
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis performed
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	4/210 participants had missing data for the primary outcome measure. 35/210 participants had missing severity (ETG-5) data at 5-7 days
	3.2	N	No adjustment for missing data reported
	3.3	NI	Reasons for participant non-completion were not provided. It is not known whether it was related to health status
	3.4	PN	1/4 participants in the homeopathy group and 3/4 in the control group had missing data for the primary outcome. 35/210 had missing severity outcome data (treatment group distribution balanced)
		Some concerns	**Some concerns due to missing outcome data**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	Y	Open trial
	4.4	PY	It is possible knowledge of the intervention could have biased outcome measures
	4.5	PY	Knowledge of intervention could bias outcomes. Due to the open nature of the trial, the higher proportion of participants in the control group choosing to fill their antibiotic prescription (41.2% vs 26.9%) is likely explained by knowledge they were in the control group
		High	**Due to knowledge of intervention that influences outcome measured**
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan avaialable for comparison
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**de Lange de Klerk 1993**	
	SQ *	**Judgement**	**Signalling question**
Bias arising from the randomisation process	1.1	Y	Participants randomised using permuted blocks (size 4) stratified by age
	1.2	Y	Code was not broken until data analysis stage
	1.3	N	Study authors report no baseline differences between groups
		Low	**Randomisation sequence likely truly random, allocation sequence concealed and any baseline differences likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo-controlled
	2.2	N	Double-blind
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	Presumed ITT analysis
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	61/170 participants had some missing daily symptom outcome data. Of those, 53 participants had missed fewer than 8 days and 4 missed more than a month over the course of the year. All 170 participants were included in data analysis
	3.2	N	Presumed ITT analysis as all 170 participants included in analysis
	3.3	PY	5 participants dropped out and 3 stopped treatment after 26 weeks. The main reason for stopping treatment was no improvement in clinical course
	3.4	PY	2 participants in the homeopathy and 3 in the placebo group dropped out due to no improvement in clinical course
		High	**Due to treatment discontinuation relating to health status**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double-blind
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan available for comparison
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		Furuta 2017	
	SQ *	**Judgement**	**Furuta 2017**
Bias arising from the randomisation process	1.1	PY	Randomisation was performed by the homeopathic pharmacist who prepared the medicine (no further details provided)
	1.2	Y	The code was broken only after the end of the treatment of all patients
	1.3	PY	Baseline characteristics were not provided other than the sex distribution, which was unbalanced.
		Some concerns	**Due to uncertainty surrounding baseline characteristics**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo-controlled
	2.2	N	Double-blind
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	PY	ITT analysis presumed
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	7/40 participants withdrew from the study
	3.2	N	No adjustments presented for missing data
	3.3	PY	1/7 participants dropped out due to tonsillitis and febrile seizures, 3/7 due to living too far away and 3/7 due to unknown causes
	3.4	PY	1/7 participants in the placebo group dropped out due to health reasons. The 3/7 who dropped out due to unknown reasons were also in the placebo group, it is possible drop out was due to health status
		High	**Due to missing outcome data and reasons relating to health status**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Both investigators and patients were blinded to intervention
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan available for comparison
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Steinsbekk 2004**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	An independent trial service office provided the randomisation using a computer-based block randomisation with stratification for age groups. The size of the blocks were concealed until the end of the study. Separate randomisation lists were created for arms 3 and 4 of the trial
	1.2	Y	Allocation sequence managed by independent
	1.3	PN	Some slight baseline differences noted, not considered due to the randomisation process
		Low	**Randomisation sequence likely truly random, allocation sequence concealed and Some slight baseline differences likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	PY	Patients were not blinded in treatment arm 1 and 2, but were blinded in arm 3 and 4
	2.2	PY	Those delivering the interventions were aware of allocations in treatment arm 1 and 2, but arm 3 and 4 were double-blinded
	2.3	PN	The only deviations were non-completion by some participants. Not considered due to the trial context
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis performed
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	79/420 participants withdrew from the study
	3.2	PN	Values for the missing days for those who were lost to follow-up were replaced with the mean for the period they had participated
	3.3	PY	1/79 participants dropped out due to 'disease', 4/79 participants dropped out as they had 'been healthy'. Other reasons for drop-out were reasons not related to health status
	3.4	PN	Health status was among the reasons for participant drop out. This was generally evenly distributed across the treatment arms
		High	**Due to missing outcome data and reasons relating to health status**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	PY	Treatment arms 1 and 2 were not subject to any blinding, treatment arms 3 and 4 were double-blinded
	4.4	PY	It is possible knowledge of the intervention in treatment arms 1 and 2 could have biased outcome measures
	4.5	PN	Knowledge of intervention could have influenced outcomes, but there is no evidence to suggest that this is likely
		Some concerns	**Knowledge of intervention could bias outcome measures**
Bias in selection of the reported result	5.1	Y	Study protocol available for comparison
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Low	
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Palm 2017**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Randomisation was performed centrally and in blocks of 2, 4 and 6 using the randomization tool RANSCH. The 3 types of blocks were randomly distributed within each study centre and the investigators did not know the block sizes
	1.2	Y	Randomisation was done via an electronic data capture system which ensured a proper allocation concealment
	1.3	N	No significant baseline differences noted
		Low	**Randomisation sequence likely truly random, allocation sequence concealed and any baseline differences likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	Y	Open-label study
	2.2	Y	No one was blinded to treatment allocation
	2.3	PN	The only deviations were non-completion by some participants. Not considered due to the trial context
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT and per-protocol analysis performed
	2.7	N	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	74/256 participants had missing or incomplete/partially incomplete data
	3.2	PY	Missing data of the prematurely withdrawn patients were adequately addressed in the statistical models used in the primary outcome analysis (time to-event analyses based on Cox model) and in the sensitivity analysis on ATI event count data (Poisson regression)
	3.3	NA	
	3.4	NA	
		Low	
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	Y	No blinding
	4.4	PY	It is possible knowledge of the intervention could have biased outcome measures
	4.5	PN	Knowledge of intervention could have influenced outcomes, but there is no evidence to suggest that this is likely
		Some concerns	**Knowledge of intervention could bias outcome measures**
Bias in selection of the reported result	5.1	PN	The study makes reference to a study protocol but it had not been uploaded on the ISRCTN registry for comparison
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Due to lack of pre-specified analysis plan**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Pannek 2019**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PN	Patients randomised (method not provided) until 10 participants in the control group completed the study. Recruitment then stopped and allocation by randomisation was abandoned
	1.2	PN	Allocation by randomisation was abandoned
	1.3	PN	Some slight baseline imbalances noted
		High	**High concerns relating to the randomisation process**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	Y	Participants were not blinded
	2.2	Y	No blinding
	2.3	PN	Only deviations reported were non-completion by some participants. Not due to the trial context
	2.4	NA	
	2.5	NA	
	2.6	PY	Modified ITT - participants who dropped out were not analysed
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	11/46 participants had missing data
	3.2	N	No adjustments made for missing data
	3.3	NI	Reasons for drop out in each group not provided. Knowledge of treatment allocation could be a reason for drop out in control group
	3.4	NI	No information on reasons for drop out provided, unknown if it was due to health status
		Some concerns	**Due to missing data, no adjustments made and no information on reasons for participant drop-out**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcomes were measured in the same way between the intervention and control groups
	4.3	Y	Outcome assessors were not blinded
	4.4	Y	Knowledge of intervention could have influenced outcome assessment
	4.5	PN	Knowledge of intervention could bias outcome measures, but there is no evidence to suggest that this is likely
		Some concerns	**Knowledge of intervention could bias outcome measures**
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan provided
	5.2	PN	The number of UTIs experienced was measured multiple ways (patient history, questionnaire and dipstick tests)
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Due to lack of pre-specified analyis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Witt 2009**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated random numbers
	1.2	NI	Not specified
	1.3	NI	Baseline clinical characteristics were similar in both groups, except Der p-specific IgE - intervention group more allergic to dust mites. Not considered likely to be due to the randomisation process.
		Some concerns	**Due to missing information on allocation concealment and baseline characteristics**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	NI	Not specified
	2.2	NI	Not specified
	2.3	PN	Only deviations reported were non-completion by some participants
	2.4	NA	
	2.5	NA	
	2.6	PY	Per-protocol analysis based on data for those who completed full 12-month follow up. No adjustments made
	2.7	NA	
		Some concerns	**Due to method of analysis with no adjustments for missing data**
Bias due to missing outcome data	3.1	N	79/150 participants had missing data
	3.2	N	No adjustments made for missing data
	3.3	PY	2 participants in itraconazole group dropped out due to diarrhoea and pregnancy, 4 in homeopathy group due to use of co-medication with antimycotics. Missing data for other participants was due to withdrawal or lost to follow up (reasons not specified)
	3.4	PN	Participant withdrawal fairly evenly distributed across treatment groups
		High	**Due to very high proportion of missing data and reasons relating to health status**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcomes were measured in the same way between the intervention and control groups
	4.3	NI	Not specified
	4.4	NI	No information to make determination
	4.5	NI	No information to make determination
		High	**Due to lack of information provided on blinding and if this may have influenced the outcome measures**
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan provided
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Due to lack of pre-specified analyis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Baker 2003**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	A randomisation schedule (blocks of four subjects) was generated by a staff member independent of the study using a random number generator program (Microsoft Excel, Microsoft Corp., Redmond, Washington, USA)
	1.2	Y	Bottles containing the study preparations were numbered according to the schedule and distributed to subjects in numerical order. Access to the randomisation schedule was not available to researchers until all data had been collected
	1.3	NI	No table of baseline characteristics presented.
		Some concerns	**Due to lack of baseline characteristics**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	The placebo preparation was indistinguishable from the other preparations.
	2.2	N	A randomised, double blind, placebo-controlled clin ical study with three parallel arms was undertaken.
	2.3	NA	Not applicable
	2.4	NA	Not applicable
	2.5	NA	Not applicable
	2.6	N	Per protocol analysis. Of the three withdrawals, one subject failed to comply with the study protocol, one subject left the university and one subject withdrew after commencing medication for illness. Data relevant to those who withdrew was not included in the analysis.
	2.7	PN	Per-protocol analysis. Not specified which group subjects withdrew from.
		Some concerns	**Some concerns due to the analysis method used and lack of details re the participants who withdrew.**
Bias due to missing outcome data	3.1	N	Data was available for 62/70 subjects originally randomised.
	3.2	N	Information was not provided on which groups these participants had been allocated to. Three withdrew and five were lost to follow-up. Data relevant to those who withdrew was not included in the analysis.
	3.3	Y	One participant withdrew from the study after commencing medication for a non-specified illness.
	3.4	PY	Participants may not have completed the study due to the lack of effect of the homeopathic intervention on their level of test anxiety.
		High	**More than 5% of participant data was missing from the analysis and this was not accounted for.**
Bias in measurement of the outcome	4.1	Y	Revised Test Analysis a validated measure for test anxiety.
	4.2	Y	Outcome measurement may have taken place at different times of the year (e.g. around exam time). No information was provided by study authors on blinding of outcome assessors.
	4.3	NA	
	4.4	NA	
	4.5	NA	
		High	**methods of outcome assessment were not comparable across intervention groups;**

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Baker 2003**	
	SQ *	**Judgement**	**Comments**
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	
	5.3	N	
		Some concerns	**Due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		Bonne 2003	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	A senior member of the psychiatry outpatient clinic performed randomisation, which was stratified for sex with simple random assignment within each subgroup.
	1.2	NI	Not specified by study authors.
	1.3	N	Sociodemographic measures were similar for both groups, baseline outcome values appear comparable.
		Some concerns	**Due to the lack of information regarding allocation concealment and generation of the randomisation sequence.**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Drug/placebo code was revealed after all participants completed the study.
	2.2	N	The secreatry, psychiatrist and homeopath remained blind to patient group assignment throughout the study. The code was held only by the physician responsible for randomisation. Drug/placebo code was revealed after all participants completed the study.
	2.3	NA	Not applicable
	2.4	NA	Not applicable
	2.5	NA	Not applicable
	2.6	PY	Modified ITT is interpretted. Participants who did not have outcome data available were not included in the analysis.
	2.7	NA	Not applicable
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	Data was available for 39/44 participants originally randomised.
	3.2	PY	LOCF should not be assumed to correct for missingness, however results using LOCF did not differ significantly from the base case.
	3.3	NA	
	3.4	NA	
		Some concerns	
Bias in measurement of the outcome	4.1	N	HAM-A is a validated measure of anxiety.
	4.2	NI	
	4.3	N	The psychiatrist remained blind to patient group assignment throughout the study.
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Bonne 2003**	
	SQ *	**Judgement**	**Comments**
Bias in selection of the reported result	5.1	Y	Drug/placebo code was revealed after all participants completed the study.
	5.2	N	
	5.3	N	
		Low	
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Parewa 2021**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Permuted randomization method restricted by blocks was used to generate random sequence by a third party who was not permitted to persuade the study in any way. Blocks were of variable size, but maintained 1:1 allocation.
	1.2	Y	The random number chart was presented to the blinded pharmacist confidentially to dispense medicines as per code from identically coded vials and was not revealed either to the patients, attending homeopaths, or outcome assessors under any circumstances.
	1.3	N	12 variables were analysed to check baseline comparability between groups. There was no significant difference between groups. Multiple linear regression models were developed to examine whether the variables statistically significantly influences outcomes and in both groups none of the variables did so.
		Low	
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double-blinding was checked by the postgraduate trainees before, during, and after commencement of the intervention by asking the patients in which group they believed they were in.
	2.2	N	Double blinding method was adopted; that is, the patients, investigators, outcome assessors, and the data entry operator remained blind about the allocation concealment. Both medicines and placebos were re-packed in identical glass bottles and labelled with codes of either 1 or 2, name of medicine, and potency, and were dispensed according to the randomization list by the blinded pharmacist.
	2.3	NA	Not applicable
	2.4	NA	Not applicable
	2.5	NA	Not applicable
	2.6	Y	Intent-to-treat analysis was used to detect group differences.
	2.7	NA	Not applicable
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	Three participants in each group dropped out resulting in 56/62 participants completing the study.
	3.2	PN	Missing values were estimated using regression means.Study authors have not presented evidence to show results were not biased by missing outcome data.
	3.3	N	Equal numbers of participants dropped out in both studies.
	3.4	NA	
		Low	
Bias in measurement of the outcome	4.1	N	Generalised Anxiety Disorder 7 questionnaire is a validated measure of anxiety.
	4.2	N	
	4.3	N	The random number chart was not revealed to the patients, attending homeopaths, or outcome assessors under any circumstances.
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Parewa 2021**	
	SQ *	**Judgement**	**Comments**
Bias in selection of the reported result	5.1	Y	Randomization codes were broken at the end of the trial after the data set was frozen.
	5.2	N	
	5.3	N	
		Low	
Overall risk of bias		**Low**	The study does not have any bias considered to seriously alter the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Foy-Nux 2018**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	Randomization was done by toss of a coin.
	1.2	PY	The code was kept in signed envelope until the end of the study.
	1.3	Y	Both salivary cortisol and α-amylase before treatment were lower in the homeopathic combination group.
		Some concerns	**Due to the presence of baseline differences between groups.**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Both the patient and the dentist were blind to the remedy administrated.
	2.2	N	Combination and placebo bottles were identical in appearance and their contents had similar taste, they were marked 1 or 2 and the code was kept in signed envelope until the end of the study.
	2.3	NA	Not applicable
	2.4	NA	Not applicable
	2.5	NA	Not applicable
	2.6	N	11 of the 22 randomised participants dropped out, leaving 11 participants whose results were analysed.
	2.7	Y	50% of the participants who were originally randomised did not finish the trial.
		High	**Per protocol analysis was used by study authors which increases risk of bias.**
Bias due to missing outcome data	3.1	N	11 of 22 participants dropped out of the study. Seven children didn't take the combination at home, two missed the second appointment, one child would not allow a saliva sample to be taken and one child would not cooperate on the first appointment resulting in oral sedation being used.
	3.2	N	
	3.3	PY	Compliance in children is strongly influenced by their parents' views and motivation for compliance.
	3.4	PY	Participants were children with a degree of anxiety around the dentist and so any task related to this could have reduced compliance by its association and not the true value of the intervention itself.
		High	**Data from 50% of the study participants was not available for analysis and this was not accounted for. This was largely due to non-compliance.**
Bias in measurement of the outcome	4.1	Y	Salivary cortisol and salivary a-amylase are not validated methods for measuring anxiety. They have been proposed as biomarkers for reaction to stress.
	4.2	N	The salivary cortisol and α-amylase levels were measured in the lab using enzyme immunoassay kits.
	4.3	NI	No information was provided by the study authors.
	4.4	N	The salivary cortisol and α-amylase levels were measured in the lab using enzyme immunoassay kits.
	4.5	NA	
		High	**The outcome measures used are not validated methods for measuring anxiety.**

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Foy-Nux 2018**	
	SQ *	**Judgement**	**Comments**
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	
	5.3	N	
		Some concerns	**Due to no information being provided on unblinding of outcome data for analysis.**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Dimpfel 2016**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	NI	No information was provided by study authors.
	1.2	NI	No information was provided by study authors.
	1.3	N	Baseline values do not differ from each other in a statistically significant way suggesting that both groups placebo and verum have a similar starting position.
		Some concerns	**Due to the lack of information provided.**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	PN	The study was double-blinded but no processes of ensuring this was implemented were discussed.
	2.2	PN	The study was double-blinded but no processes of ensuring this was implemented were discussed.
	2.3	NA	Not applicable
	2.4	NA	Not applicable
	2.5	NA	Not applicable
	2.6	PY	No method of analysis was discussed and no participants withdrew from the study.
	2.7	NA	
		Some concerns	**Some concerns due to lack of details re the participants who withdrew.**
Bias due to missing outcome data	3.1	Y	
	3.2	NA	
	3.3	NA	
	3.4	NA	
		Low	
Bias in measurement of the outcome	4.1	PY	EnkephaloVision is a new approach to quantitative EEG recording. There is evidence that emotional states directly relate to brain electric activity but this is not a validated method for measuring anxiety.
	4.2	Y	Interpretation of spectral EEG changes depends on the recording conditions.
	4.3	NA	
	4.4	NA	
	4.5	NA	
		High	**The outcome measures used are not validated methods for measuring anxiety.**

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Dimpfel 2016**	
	SQ *	**Judgement**	**Comments**
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available.
	5.2	PY	Interpretation of spectral EEG changes depends on the recording conditions.
	5.3	PY	Interpretation of spectral EEG changes depends on the recording conditions.
		High	**Due to the lack of pre-specified analysis plan available and the potential for differences in outcome assessment methods used.**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Fibert 2015**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer-based randomisation
	1.2	Y	Independent statistician responsible for randomisation and allocation
	1.3	N	
		Low	**Randomisation sequence likely truly random, allocation sequence concealed and Some slight baseline differences likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	Y	Participants are offered consultation with either a homeopath or nutritionist
	2.2	Y	
	2.3	Y	Patients were able to refuse or withdraw from the offered treatment after randomisation
	2.4	PN	Reasons for non-participation do not suggest this (uncontactable, withdrew, refused)
	2.5	NI	Reasons for non-participation in treatment were not specified per intervention group
	2.6	Y	Both ITT and per protocol results presented
	2.7	NA	
		Some concerns	**Some concerns due to participant awareness of interventions and non-participation in assigned treatments however unlikely to have affected the outcome**
Bias due to missing outcome data	3.1	N	9/29 Hom; 4/28 NT 6-month questionnaires and 6/22 hom; 3/19 NT 12-month questionnaires not returned. There were 5 instances of missing data in the few paper Carer Questionnaires. Out of 100 potential teacher questionnaires, 72 baseline, 34 6-month, and 58 12-month Teacher Questionnaires were returned. Schools did not return questionnaires consistently: 31 paired baseline and 6-month questionnaires, 14 paired 6 and 12-month questionnaires, and 21 paired baseline and 12-month questionnaires were returned. Thirty-five percent of paired questionnaires were returned by different teachers
	3.2	N	Last observation carried forward was used to impute missing data in questionnaires. Both ITT and per protocol results presented. For teacher ratings, positive direction of improvements in NT according to ITT analysis became a negative direction according to per protocol analysis
	3.3	PY	Reasons for non-participation in treatment do not suggest this however missing teacher outcomes for 4 home schooled children could relate with higher symptom severity precluding from school attendance
	3.4	PN	Home schooled children for which teacher outcomes were missing could mean higher symptom severity
		High	**Due to missing data and potential for missingness in the outcome to depend on its true value**
Bias in measurement of the outcome	4.1	N	Valid outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	Y	Carers were aware of treatment offered
	4.4	Y	Knowledge of intervention received could have influenced assessment of symptoms and response
	4.5	PN	Knowledge of intervention could bias outcomes, but there is no evidence to suggest that this is likely
		Some concerns	**Due to outcome assessment by non-blinded carers**
Bias in selection of the	5.1	Y	Pre-specified analysis plan in protocol
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Fibert 2015**	
	SQ *	**Judgement**	**Comments**
reported result		**Low**	
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		Oberai 2013	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer-based randomisation
	1.2	NI	No information provided regarding allocation concealment
	1.3	N	Both the groups were comparable at baseline ($p \geq 0.05$)
		Some concerns	**Due to lack of information regarding allocation concealment**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Patients were blinded
	2.2	N	Doses administered by parents/guardians. All manners of interventions and process of administration were the same.
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	Modified ITT analysis with LOCF
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	7 patients excluded from analysis for not following randomisation (observed to be wrongly randomised at baseline during site visit); 12/54 dropouts (5 homeopathy, 7 placebo), majority during the first half of the follow-up period
	3.2	N	Modified ITT analysis with missing data replaced by last assessed value as per the last observation carry forward method**.** No analysis to address missing outcome data presented.
	3.3	NI	Reasons for dropouts not reported
	3.4	NI	Reasons for dropouts not reported
		High	**Due to missing data and reasons for dropout not specified**
Bias in measurement of the outcome	4.1	N	Valid outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	Y	Investigators who assessed CGI-SS and SCGI-IS were not blinded to treatment assignment
	4.4	Y	Knowledge of intervention received could have influenced assessment of symptoms and response. CGI-SS and SCGI-IS were assessed by the investigator who was not blinded
	4.5	PN	Knowledge of intervention could bias outcomes, but there is no evidence to suggest that this is likely
		Some concerns	**Due to outcome assessment by non-blinded investigator**
Bias in selection of the	5.1	NI	No information on whether analysis plan was pre-specified
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Oberai 2013**	
	SQ *	**Judgement**	**Comments**
reported result		**Some concerns**	**Due to lack of information on any pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		Frei 2005	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer-based randomisation
	1.2	Y	Random assignments provided in sealed envelopes to manufacturer who prepared and mailed the medication to the participating families
	1.3	N	
		Low	**Randomisation sequence likely truly random, allocation sequence concealed and Some slight baseline differences likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double-blind crossover
	2.2	N	Patients and carers unaware of treatment assignment during crossover phase
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	4/62 withdrawn (3 crossover period 1, 1 crossover period 2; 3 verum, 1 placebo; 1 increasing tics, 2 behavioural disorders, 1 reactive depression)
	3.2	PN	To take into account potential dropouts, sample size was estimated using t-test for two parallel groups in the first period. For correlated data analysis (within patient outcome assessments), patients who dropped out after the first crossover period were included in the analysis by assuming missing at random. For other types of analyses, patients with missing values were excluded.
	3.3	Y	Reasons for withdrawal include tics, behavioural disorders and reactive depression
	3.4	Y	Reasons for dropout could be related to treatment outcomes
		High	**Due to potential for missingness in the outcome to depend on its true value**
Bias in measurement of the outcome	4.1	N	Valid outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Patients, their parents, the investigators and the treating physician were blind to the assigned treatments and the treating physician had no contact with patients and parents during the crossover trial.
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the	5.1	Y	Pre-specified analysis plan indicated
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Frei 2005**	
	SQ *	**Judgement**	**Comments**
reported result		**Low**	
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Jacobs 2005**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer-based randomisation
	1.2	Y	Allocation controlled by homeopathic pharmacist
	1.3	N	
		Low	**Randomisation sequence likely truly random, allocation sequence concealed and Some slight baseline differences likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Triple blind study
	2.2	N	Triple blind study
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	37/43 completed all study interventions, with 2 dropouts in the homeopathy group, 3 dropouts in the placebo group, and 1 placebo-group subject lost to follow-up
	3.2	PN	An analysis of only those who completed the study found no differences in results
	3.3	NI	Reasons for dropouts not reported
	3.4	NI	Reasons for dropouts not reported
		Some concerns	**Some concerns due to missing data**
Bias in measurement of the outcome	4.1	N	Valid outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Triple blind study
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the	5.1	NI	No information on whether analysis plan was pre-specified
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Jacobs 2005**	
	SQ *	**Judgement**	**Comments**
reported result		**Some concerns**	**Some concerns as unclear if analysis plan was pre-specified**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Strauss 2000**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	Described only as participants being randomly divided into groups
	1.2	NI	No information provided regarding allocation concealment
	1.3	NI	No information provided on baseline characteristics of intervention groups
		Some concerns	**Due to lack of information on allocation concealment and baseline characteristics**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double blind study
	2.2	N	Double blind study
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	NI	Method of analysis not reported
	2.7	NI	Sample size randomised into each group was reported however numbers analysed were not specified
		Some concerns	**Some concerns due to lack of information on method of analysis and number of participants analysed in each group**
Bias due to missing outcome data	3.1	NI	No information provided on any missing data
	3.2	N	No analysis to address any missing data presented
	3.3	NI	No information provided on any missing data
	3.4	NI	No information provided on any missing data
		High	**Due to lack of information on missing outcome data**
Bias in measurement of the outcome	4.1	N	Valid outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double blind study
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the	5.1	NI	No information on whether analysis plan was pre-specified
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Strauss 2000**	
	SQ *	**Judgement**	**Comments**
reported result		**Some concerns**	**Due to lack of information on any pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Lamont 1997**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	N	Alternate assignment in order of referral
	1.2	N	Investigator aware of allocation due to alternate assignment method
	1.3	NI	No information provided on baseline characteristics of intervention groups
		High	**Due to non-random assignment and lack of allocation concealment**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double blind study (subjects and persons administering treatment were blinded)
	2.2	N	Carers were not informed of the use of placebos in the study
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	NI	Method of analysis not reported
	2.7	NI	Numbers analysed were not specified
		Some concerns	**Some concerns due to lack of information on method of analysis and number of participants analysed in each group**
Bias due to missing outcome data	3.1	N	3/43 participants were excluded from the study. Not specified whether the data was included in the analysis
	3.2	N	No analysis to address any missing data presented
	3.3	NI	No information provided on any missing data
	3.4	NI	No information provided on any missing data
		High	**Due to lack of information on missing outcome data**
Bias in measurement of the outcome	4.1	N	Valid outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	Y	Ratings were done by carers who were blinded to treatment, however the investigator was not blinded and contacted the carers to obtain their ratings and conducted the 2 month follow up interviews.
	4.4	Y	It is conceivable that, in recording their ratings, the investigator could have inadvertently influenced outcomes in favour of the hypothesis.
	4.5	PY	Study authors raised concerns that knowledge of intervention could have influenced the outcome
		High	**Due to knowledge of intervention potentially influencing outcomes**
Bias in selection of the	5.1	NI	No information on whether analysis plan was pre-specified
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Lamont 1997**	
	SQ *	**Judgement**	**Comments**
reported result		**Some concerns**	**Due to lack of information on any pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		Dhawale 2014	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	Participants were divided into two groups as per their enrolment. Specific details on the process of randomisation were not provided
	1.2	NI	No information on allocation concealment was provided
	1.3	NI	Baseline characteristics were not provided
		Some concerns	**Due to lack of information provided on randomisation, allocation concealment and baseline characteristics**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Participants and their parents were blinded
	2.2	Y	The senior research fellow who conducted the homeopathic treatments was aware of treatmnet allocations
	2.3	NI	Insufficient information provided to determine if any deviations occurred. No information on non-completion
	2.4	NA	
	2.5	NA	
	2.6	N	Method of analysis not reported and not able to be determined from the results presented
	2.7	NI	Numbers analysed were not specified
		Some concerns	**Some concerns due to lack of information on method of analysis and number of participants analysed in each group**
Bias due to missing outcome data	3.1	NI	No information provided on any missing data
	3.2	N	No analysis to address any missing data presented
	3.3	NI	No information provided on any missing data
	3.4	NI	No information provided on any missing data
		High	**High risk due to lack of information on missing outcome data**
Bias in measurement of the outcome	4.1	NI	No details provided on how the outcomes were measured
	4.2	PY	It is possible this could have differed between intervention groups as no details of how the outcome was measured were provided. No evidence to suggest this is likely though
	4.3	NA	
	4.4	NA	
	4.5	NA	
		High	**High risk due to lack of information on how the outcomes were measured**
Bias in selection of the	5.1	N	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Dhawale 2014**	
	SQ *	**Judgement**	**Comments**
reported result		**Some concerns**	**Due to lack of information on any pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Adler 2009**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Generated using computer software (randomizer.org) with the code 1 or 2 from a set of 100 non-unique numbers
	1.2	Y	Only the senior author and pharmacist had access to the code of the randomised sequence during the study. After completion of treatment allocation was revealed to the PI by the pharmacist
	1.3	N	Baseline characteristics were similar between the 2 groups
		Low	**Randomisation sequence likely truly random, allocation sequence concealed and Some slight baseline differences likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double-blind trial with matching placebos
	2.2	N	Double-blind trial with matching placebos
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	Full analysis set of all randomised patients used
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	Full analysis set used without filling in missing data (40% of randomised participant data is missing)
	3.2	PN	No significant difference in discontinuation rates between groups
	3.3	PY	More patients randomised to fluoxetine discontinued due to adverse effects, more patients randomised to homeopathy discontinued due to worsening of symptoms
	3.4	Y	More patients randomised to fluoxetine discontinued due to adverse effects, more patients randomised to homeopathy discontinued due to worsening of symptoms
		High	**Due to missing data considered likely to be due to the true value of the outcome**
Bias in measurement of the outcome	4.1	N	MADRS is a validated measure of depression and treatment induced change
	4.2	N	
	4.3	N	Person measuring outcome was blind to treatment groups or outcomes
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Due to the lack of information on pre-specified analysis**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		Adler 2011	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	The randomisation list was generated with SAS/BASE Software (SAS Inc., Cary NC, USA) by a statistician not further involved in the study
	1.2	Y	Sealed opaque envelopes
	1.3	Y	Significant differences between groups exist e.g. in age, duration of depression and reasons for participation
		Some concerns	**Some concerns due to baseline differences between groups**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Patients remained blind to the identity of the 4 treatment groups until the end of the study
	2.2	N	The whole study team including the psychiatrist, the psychologist who assessed the HAM-D and the statistician remained blinded to the identity of the four treatment groups until the end of the study
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	PY	Unclear but likely modified ITT
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	7/44 (16%) participants did not complete the intervention
	3.2	N	No evidence to suggest outcomes were not biased by missing data
	3.3	NI	Reasons for drop out are not reported
	3.4	NI	Reasons for drop out are not reported
		High	**Due to missing data with no reasons provided for drop out**
Bias in measurement of the outcome	4.1	N	HAM-D is a validated measure of depression severity
	4.2	N	Severity of symptoms assessed by a blinded psychologist supervised by the clinic
	4.3	N	Assessor was blinded to intervention received
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the reported result	5.1	N	The preplanned sample size could not be reached and so the analysis plan was adapted and the trial terminated early
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Low	
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Katz 2005**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Randomisation to 3 groups by the Royal London Homeopathic Hospital pharmacy using a computer-generated random number list
	1.2	PY	The randomisation code was broken after completion of the trial
	1.3	NI	No information given on baseline characteristics
		Low	**Randomisation sequence likely truly random, allocation sequence concealed and Some slight baseline differences likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double-blind trial with matching placebos
	2.2	N	Double-blind trial with matching placebos
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	Completer and ITT analysis presented
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	Some secondary outcome data not reported and no data provided for those who dropped out (90% of randomised participant data is missing)
	3.2	N	No analysis for missing data was presented
	3.3	NI	Reasons for drop out are not reported
	3.4	NI	Reasons for drop out are not reported
		High	**Due to missing data with no reasons provided for drop out**
Bias in measurement of the outcome	4.1	N	HAM-D and CGI are validated measures of depression severity
	4.2	N	Both homeopath and psychiatrist saw all patients
	4.3	N	Assessor was blinded to intervention received
	4.4	NA	
	4.5	NA	
		Low	**Any error in measuring the outcome is judged unrelated to intervention status**
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan available and some secondary outcomes predefined were not reported on
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	PY	Some secondary outcome data not reported
		High	**Due to change in outcomes measured**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Viksveen 2014**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Random selection was carried out by a statistician not otherwise involved in the trial, using a computer software program
	1.2	Y	Randomisation carried out by a statistician not otherwise involved who only had access to participant ID
	1.3	N	Baseline characteristics were comparable in both groups
		Low	**Randomisation sequence was truly random, allocation sequence concealed and any baseline difference likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	Y	The trial was not blinded apart from the random selection process
	2.2	Y	The trial was not blinded apart from the random selection process
	2.3	PN	The only reported deviations were non completion by some participants. This is in line with what would be expected in routine practice.
	2.4	NA	
	2.5	NA	
	2.6	Y	Modified ITT, only including those who completed the follow up questionnaire
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	Significant dropouts in both groups (44% participants excluded from analysis)
	3.2	PN	Four approaches to deal with missing data used. Little's missing completely at random (MCAR) test did not suggest any systematic patterns in missing data. However, missingness was substantially different between those who accepted the offer of homeopathy vs those who did not.
	3.3	Y	Those who accepted the offer of homeopathy were more likely to complete the follow up questionnaire and be included in the analysis. These participants were likely more motivated to complete the trial.
	3.4	Y	Those who accepted the offer of homeopathy were more likely to complete the follow up questionnaire and be included in the analysis. These participants were likely more motivated to complete the trial.
		High	**Due to large proportion of missing data which could be related to the true outcome value**
Bias in measurement of the outcome	4.1	N	The PHQ-9 is a validated measure for use in depression
	4.2	N	The outcome was self-reported
	4.3	Y	Outcome assessors were aware of the intervention received
	4.4	Y	Those who accepted the offer of homeopathy were more likely to complete the follow up questionnaire. These participants were likely more motivated to receive treatment and had belief in the effectiveness of treatment.
	4.5	Y	As above.
		High	**Due to deviations in outcomes measured and lack of blinding**
Bias in selection of the reported result	5.1	N	Outcomes were changed
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	PY	Some secondary outcomes changed
		High	**Due to change in outcomes measured**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Harrison 2013**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	A randomisation schedule (blocks of four subjects) was generated by a staff member independent of the study using a random number generator program (Microsoft Excel, Microsoft Corp., Redmond, Washington, USA)
	1.2	PN	The authors do not report on allocation concealment.
	1.3	PN	Some differences in baseline characteristics, not considered likely due to issues with randomisation
		Some concerns	**Some concerns due to quasi randomisation and slight baseline imbalances**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double-blind
	2.2	N	Double-blind
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	PN	Per protocol interpreted as participants who did not comply with the intervention or who received insomnia medication were excluded from the analysis
	2.7	PY	2 participants (12%) in the placebo group excluded due to intake of insomnia medication. Unknown number of participants in the homeopathy group excluded due to non-compliance.
		High	**High risk of bias due to inappropriate method of analysis**
Bias due to missing outcome data	3.1	N	6/34 (17%) of participants were not included in the analysis.
	3.2	N	No adjustment for missing data was presented
	3.3	Y	Some participants lost to follow up due to intake of insomnia medication
	3.4	Y	Some participants lost to follow up due to intake of insomnia medication
		High	**High risk of bias due to missing data considered likely to be due to the true value of the outcome**
Bias in measurement of the outcome	4.1	N	
	4.2	N	
	4.3	N	Self-reported outcomes by blinded participants
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**James 2019**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Random number generator
	1.2	Y	"Confidentiality of the random number code was maintained". Only the pharmacist was aware of the code.
	1.3	PN	Some differences in baseline characteristics noted, but not considered to be due to the randomisation process
		Low	
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Patients were kept blinded
	2.2	N	Treating homeopaths were blinded
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT is conducted
	2.7	NA	
		Low	
Bias due to missing outcome data	3.1	N	5/60 participants (8%) had missing data
	3.2	Y	Missing values replaced using regression means, last observation carried forward and multiple imputations using linear regression model
	3.3	NA	
	3.4	NA	
		Low	
Bias in measurement of the outcome	4.1	N	
	4.2	N	
	4.3	N	Outcome assessors and patients kept blinded to treatment status
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	PY	No pre-specified analysis plan available, however it is reported that the trial protocol was published as part of a postgraduate thesis
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Low	
Overall risk of bias		**Low**	The study does not have any bias considered to seriously alter the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Jong 2016**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Random code generated by external centre
	1.2	Y	Sealed envelopes to conceal allocation
	1.3	N	No baseline imbalances reported
		Low	
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Open-label
	2.2	N	Open-label
	2.3	N	The only reported deviations were non-completion, in line with what would be expected in routine practice
	2.4	NA	
	2.5	NA	
	2.6	PY	Modified ITT, participants who did not complete post-baseline assessments not included
	2.7	N	
		Low	
Bias due to missing outcome data	3.1	Y	4/180 (2.2%) had missing outcome data at Day 28
	3.2	NA	
	3.3	NA	
	3.4	NA	
		Low	
Bias in measurement of the outcome	4.1	N	
	4.2	N	
	4.3	Y	Open-label study
	4.4	Y	Subjective outcome measures reported by non-blinded participants
	4.5	PY	There is no evidence to suggest biased outcome reporting
		Some concerns	**Some concerns due to subjective outcomes being reported by non-blinded participants**
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Naude 2010**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	Drawing numbers from a hat
	1.2	PY	Participants were assigned a number as they entered the study, dispensing was performed according to the randomisation list
	1.3	N	No baseline imbalances noted
		Some concerns	**Some concerns due to potentially inadequate randomisation and allocation concealment**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Participants were kept blinded
	2.2	N	Researchers were kept blinded
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	PN	Per protocol, one participant with non-compliance to treatment medication was excluded
	2.7	N	1/33 participants excluded for non-compliance
		Some concerns	**Some concerns due to method of analysis**
Bias due to missing outcome data	3.1	N	3/33 (9%) had missing outcome data
	3.2	N	No adjustment for missing data was presented
	3.3	PY	One participant excluded due to non-compliance with medication, which could plausibly be due to perceived lack of effectiveness
	3.4	N	It is not considered likely that missingness is related to the outcome
		Some concerns	**Some concerns due to missing outcome data, with no adjustment presented to account for this**
Bias in measurement of the outcome	4.1	N	
	4.2	N	
	4.3	N	Outcome assessors and patients kept blinded to treatment status
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Straumsheim 1997**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	A randomisation schedule (blocks of four subjects) was generated by a staff member independent of the study using a random number generator program (Microsoft Excel, Microsoft Corp., Redmond, Washington, USA)
	1.2	Y	homeopathic medicines and placebos provided in identical glass bottles, coded by a statistician who was otherwise uninvolved in trial - pharmacist responsible for storage and distribution of medicine also had code
	1.3	PN	Some differences in baseline characteristics, not considered likely due to issues with randomisation
		Low	**Randomisation sequence was truly random, allocation sequence concealed and any baseline difference likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	homeopathic and placebo indistinguishable
	2.2	PN	Pharmacist distributing medicine had access to code
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	N	modified intent to treat - 1 excluded no migraine in month before treatment, two pregnant, 1 hypertension, 1 lost to follow up
	2.7	PN	not specified which group they withdrew from
		Some concerns	**Some deviations from intended intervention and effect on the outcome is slight; method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	73 included, 3 removed before randomisation, no data for two that left assumed post randomisation
	3.2	NI	No analysis for missing data
	3.3	PY	One hypertensive patient, one lost to follow up
	3.4	Y	drop out reasons could be result of treatment
		High	
Bias in measurement of the outcome	4.1	N	
	4.2	N	
	4.3	N	Patient self-report outcomes in diary, assessed by neurologist
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Low	
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Gaus 1992**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Patients randomised to treatment by dice-roll
	1.2	Y	Homeopathy or identical placebo mailed to patients
	1.3	PY	Some differences in baseline characteristics noted, but not considered to be due to the randomisation process
		Some concerns	**Due to the lack of information regarding allocation concealment and generation of the randomisation sequence.**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	homeopathic and placebo indistinguishable
	2.2	N	Double blinded
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	Y	Data for 6 drop out included in trial
	3.2	NA	
	3.3	NA	
	3.4	NA	
		Low	
Bias in measurement of the outcome	4.1	N	
	4.2	N	
	4.3	N	Patient self-reported outcomes
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Low	
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		Whitmarsh 1997	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	NI	only information about randomization methods is a statement that the study is randomized.
	1.2	NA	
	1.3	Y	Mean migraine attack frequency 38% higher in placebo, placebo group significantly more likely to record mild attack
		High	**Missing information and baseline imbalances suggest a problem with randomisation**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	homeopathic and placebo indistinguishable
	2.2	N	Double blinded
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	No statistical analysis plan specified, chi squared t test and % change analysis
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	Data for 3 drop out not included
	3.2	NI	No analysis for missing data
	3.3	Y	One failed to attend 2nd follow up, one lung tumour, one began opiate analgesia, one felt it was not worthwhile continuing
	3.4	Y	drop out reasons could be result of treatment
		High	
Bias in measurement of the outcome	4.1	N	
	4.2	N	
	4.3	N	Patient self-reported outcomes
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Lewith 2002**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	Randomisation described - first 10 participants randomised to treatment A or B using sealed envelope, all subsequent participants were allocated to A or B by a process of minimisation according to age, sex, smoking status and severity of asthma
	1.2	Y	Codes were not broken until completion of study
	1.3	N	No significant difference at baseline
		Low	
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo-controlled
	2.2	N	Double blinded
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT specified and conducted
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	40/242 participants withdrew from the study
	3.2	N	No analysis for missing outcome data
	3.3	PY	Reasons for withdrawal include protocol violation (oral steroid) (17/40), self withdrawal (15/40), concomitant illness (5/40), exacerbation of asthma (1/40) and other (2/40)
	3.4	PY	Oral steroid use is likely related to asthma status and accounts for a substantial proportion of missing data
		High	**High concerns due to missing data and reasons for drop out related to health status**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double blind trial
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan was available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Some concerns due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Qutubuddin 2019**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated random numbers
	1.2	Y	Allocation concealment managed by an independent third party
	1.3	PN	Some baseline imbalances were noted but not considered likely to be due to randomisation
		Low	
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo-controlled
	2.2	N	No, third party managed allocation concealment
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT specified and conducted
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	18/140 participants had missing data
	3.2	PN	ITT sample was analysed using last value carried forward method
	3.3	PY	9/18 participants dropped out due to worsening symptoms. 6/18 dropped out due to no improvement. Other reasons for drop out were lost to follow up moved away
	3.4	PY	Worsening symptoms reported as a reason for drop out
		High	**High concerns due to missing data and reasons for drop out related to health status**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double blind trial
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	Y	Trial protocol available for comparison
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Low	
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Topcu 2010**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated random numbers
	1.2	Y	Treatment allocation codes given to patients by staff not otherwise involved in the study
	1.3	PN	Some baseline imbalances were noted but not considered likely to be due to randomisation
		Low	
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	Y	Participants not blinded to treatment allocation
	2.2	PY	Those delivering interventions (homeopaths and reflexologists) were aware of treatment allocation. Study investigators were blinded
	2.3	PN	Only deviations reported were non-completion by some participants. Not considered to be due to the trial context.
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT specified and conducted
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	14/84 participants had missing data
	3.2	PN	ITT sample was analysed using last value carried forward method
	3.3	PY	Primary reasons for drop out were withdrawal of consent (4/14), non-compliance (6/14) and lost to follow up (4/16)
	3.4	PN	Study does not describe what 'non-compliance' as a reason for drop out means. It is possible that drop out could be due to health status
		Some concerns	**Some concerns due to missing data and drop out potentially relating to health status**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	PY	Outcome assessors blinded to treatment for objective outcomes. Participants aware of treatment allocation for self-reported outcomes.
	4.4	PY	Self-reported outcome measures could have been influenced by knowledge of intervention
	4.5	PN	Knowledge of intervention could bias self-reported outcomes, but there is no evidence to suggest that this is likely
		Some concerns	**Some concerns that knowledge of intervention could bias outcome measures**
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Some concerns due to lack of pre-specified analysis plan**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		White 2003	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated random numbers
	1.2	Y	Treatment allocation codes only given to homeopathic pharmacists. Codes not broken until data had been analysed
	1.3	PN	Some very slight baseline imbalances noted but not considered likely due to randomisation
		Low	
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo-controlled
	2.2	N	Double blinded
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT specified and conducted
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	19/93 participants did not complete the final questionnaire
	3.2	PN	ITT sample was analysed, missing data managed by carried forward the baseline value
	3.3	PY	1/19 participants dropped out due to worsening symptoms, 3/19 dropped out due to no improvement.
	3.4	PY	One participant in placebo group dropped out due to worsening symptoms. One dropped out in placebo group and 2 dropped out in the homeopathy group due to no improvement
		High	**HIgh concerns due to missing data and reasons for drop out related to health status**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double blind trial
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Some concerns due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Thompson 2008**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	Described as randomised, but details not specified
	1.2	Y	A staff member not otherwise involved in the study ensured allocation concealment
	1.3	PN	Some slight baseline imbalances noted
		Low	
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	Y	Open trial
	2.2	Y	Open trial
	2.3	PN	Only deviations reported were non-completion by some participants. Not considered to be due to the trial context.
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT specified and conducted
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	4/39 participants withdrew from the study
	3.2	PN	ITT sample was analysed using last value carried forward method
	3.3	PN	Primary reasons for drop out were time commitment, moving away and not completing forms (not considered due to health status)
	3.4	NA	
		Some concerns	**Some concerns due to missing data**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	Y	Open trial
	4.4	PY	Outcomes measures were self-reported. Due to the open nature of the study it is possible that subjective outcome assessments could have been influenced by knowledge of treatment allocation
	4.5	PN	Knowledge of intervention could bias self-reported outcomes, but there is no evidence to suggest that this is likely
		Some concerns	**Some concerns that knowledge of intervention could bias outcome measures**
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Some concerns due to lack of pre-specified analysis plan**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Reilly 1994**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Permuted block randomisation stratified for the indicated allergen and daily dosage of inhaled steroid
	1.2	Y	Only the pharmacist had access to the code which was not broken until after analysis
	1.3	PN	Some baseline imbalances were noted but not considered likely to be due to randomisation
		Low	**Randomisation sequence was truly random, allocation sequence concealed and any baseline difference likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo-controlled
	2.2	N	Double blinded
	2.3	NA	Patients were supposed to alter their drug use however 1 placebo patient required oral prednisolone 3 and 4 weeks after treatment
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT specified and conducted
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	4/28 participants withdrew from the study and a further 6/28 participants did not complete pulmonary function testing
	3.2	N	No adjustment for missing data reported
	3.3	PY	1 participant withdrew due to worsening symptoms. 3 withdrew due to social reasons and reported no change in symptoms. 4 were unable to complete end of treatment pulmonary function testing due to poor health status
	3.4	PY	Worsening symptoms reported as a reason for drop out
		High	**High concerns due to missing data and reasons for drop out related to health status**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double blind trial
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Some concerns due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Jacobs 1993**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	Described as randomised, but details not specified
	1.2	PN	Double-blinded but details not specified.
	1.3	PN	No significant imbalance between groups, however specific demographics not provided.
		Some concerns	**No details on allocation sequence randomisation, concealment, or baseline demographics.**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double-blinded, randomised allocation, and placebo identical in appearance and odour.
	2.2	N	Double-blinded, randomised allocation, and placebo identical in appearance and odour.
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	Intent-to-treat (modified) analysis as one participant was randomised, but not included in analysis. Details not specified.
	2.7	N	As only missing data for one participant, unlikely for substantial impact or slight impact expected. Details not specified.
		Low	**Any deviations from intended intervention reflect usual practice with their impact on the outcome expected to be slight AND the analysis was appropriate.**
Bias due to missing outcome data	3.1	Y	All but one randomised participant (<5%) included. No details specified regarding discontinuation.
	3.2	NA	
	3.3	NA	
	3.4	NA	
		Low	**Data were available for all, or nearly all, participants.**
Bias in measurement of the outcome	4.1	PN	Mostly subjective outcomes based on recall. One objective health worker evaluation.
	4.2	N	The same measurement or ascertainment of outcomes across groups.
	4.3	N	Double-blinded, randomised allocation, and placebo identical in appearance and odour.
	4.4	NA	
	4.5	NA	
		Low	**The outcome assessors were unaware of the intervention received by study participants AND any error in measuring the outcome is unrelated to the intervention.**
Bias in selection of the reported result	5.1	PN	No pre-specified analysis plan available, but indication of some level of pre-approval.
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain.
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Outcomes are clearly defined AND there is no indication of selection/reporting of outcomes on the basis of the results**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

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Study ID		**Jacobs 2000**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Random numbers table was used to determine randomisation.
	1.2	Y	All study personnel in Nepal were blinded as to treatment allocation, as was the statistician.
	1.3	PY	Some baseline imbalances were noted but not considered likely to be due to randomisation
		Some concerns	**Due to the lack of information regarding allocation concealment and generation of the randomisation sequence.**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double-blinded, randomised allocation, and placebo identical in taste, odour, appearance, and packaging.
	2.2	N	All study personnel in Nepal were blinded as to tretment allocation, as was the statistician.
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	Intent-to-treat (modified) as some subjects did not complete follow up but were considered in Kaplan-Meier plot. Reasons for discontinuation specified.
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice with their impact on the outcome expected to be slight AND the analysis was appropriate.**
Bias due to missing outcome data	3.1	PN	>5% missingness (10/126), but considered accounted for in Kaplan-Meier plot.
	3.2	PY	Despite >5% missingness (10/126), ITT analysis and missing data considered accounted for in Kaplan-Meier plot.
	3.3	NA	
	3.4	NA	
		Low	**The analysis addressed missing data and is likely to have removed any risk of bias.**
Bias in measurement of the outcome	4.1	PN	Mostly subjective outcomes based on recall and parent's record of daily stools on diary cards
	4.2	N	The same measurement or ascertainment of outcomes across groups.
	4.3	N	All study personnel in Nepal were blinded as to treatment allocation, as was the statistician.
	4.4	NA	
	4.5	NA	
		Low	**The outcome assessors were unaware of the intervention received by study participants AND any error in measuring the outcome is unrelated to the intervention.**
Bias in selection of the reported result	5.1	Y	Predefined measures were based on a previous study.
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain.
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurement.
		Low	**There is clear evidence that all reported results correspond to all intended outcomes, analyses, and sub-cohorts**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Jacobs 2006**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Randomised by sequential assignment to previously coded vials (which were also randomised using a random-numbers table).
	1.2	Y	Study participants, investigators, study nurses, and data analysts were blinded to the treatment group assignment.
	1.3	N	Children in the treatment and placebo groups were similar in distribution of baseline demographic and clinical characteristics.
		Low	
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double-blinded, randomised allocation, and placebo identical in taste, odour, appearance, and packaging.
	2.2	N	Study participants, investigators, study nurses, and data analysts were blinded to the treatment group assignment.
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	Intent-to-treat (modified) as some subjects did not complete follow up but were considered in Kaplan-Meier plot. Reasons for discontinuation specified.
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice with their impact on the outcome expected to be slight AND the analysis was appropriate.**
Bias due to missing outcome data	3.1	PN	>5% missingness (27/301), but considered accounted for in Kaplan-Meier plot.
	3.2	PY	Despite >5% missingness (27/301), ITT analysis and missing data considered accounted for in Kaplan-Meier plot.
	3.3	NA	
	3.4	NA	
		Low	**The analysis addressed missing data and is likely to have removed any risk of bias.**
Bias in measurement of the outcome	4.1	PN	Mostly subjective outcomes based on recall and parent's record of daily stools on cards, and also reviewed by nurses
	4.2	N	The same measurement or ascertainment of outcomes across groups.
	4.3	N	Study participants, investigators, study nurses, and data analysts were blinded to the treatment group assignment.
	4.4	NA	
	4.5	NA	
		Low	**The outcome assessors were unaware of the intervention received by study participants AND any error in measuring the outcome is unrelated to the intervention.**
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain.
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurement.
		Some concerns	**Outcomes are clearly defined AND there is no indication of selection/reporting of outcomes on the basis of the results BUT there is no pre-specified analysis plan available**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Patel 2010**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	Described as randomised, but details not specified
	1.2	PN	Described as single-blinded, but details not specified
	1.3	NI	Baseline details and differences not specified.
		High	**Due to allocation sequence potentially not truly concealed, and no information on baseline characteristics**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	PN	Described as single-blinded, but details not specified
	2.2	PY	Described as single-blinded, but details not specified
	2.3	N	No information suggesting there were deviations from the intended intervention
	2.4	NA	
	2.5	NA	
	2.6	N	The method of analysis used is unclear. 42 participants (12%) were excluded from the analysis as they withdrew from the study. An additional 24 cases were withdrawn due to worsening requiring hospitalisation.
	2.7	PY	Yes due to high levels of potentially inappropriate exclusion and unclear whether this was balanced between groups.
		High	**Analysis was not appropriate and unclear whether participants and researchers were aware of the intervention being received**
Bias due to missing outcome data	3.1	N	>5% missingness (42/342)
	3.2	N	There is no evidence that the result was not biased by missing outcome data
	3.3	Y	24 cases withdrawn from the study due to clinical worsening who were admitted to hospital. It is unclear whether this was balanced between groups.
	3.4	Y	24 cases withdrawn from the study due to clinical worsening who were admitted to hospital. It is unclear whether this was balanced between groups.
		High	**High risk of bias due to missing data that is definitely related to the outcome**
Bias in measurement of the outcome	4.1	N	Clinical grading of diarrhoea
	4.2	N	Clinical grading of diarrhoea between groups
	4.3	PY	Described as single-blinded, but details not specified
	4.4	Y	Described as single-blinded, but details not specified. Clinical grading included subjective assessment.
	4.5	NI	No evidence to suggest biased outcome assessment, but insufficient detail provided
		High	**Unclear blinding therefore participants and researchers measuring the outcome may have been influenced by knowledge of intervention received**
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain.
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurement.
		Some concerns	**Outcomes are clearly defined AND there is no indication of selection/reporting of outcomes on the basis of the results BUT there is no pre-specified analysis plan available**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Paterson 2003**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Randomisation was in blocks of four, and serially numbered opaque envelopes were used to achieve concealed allocation. However, patients nominated preference of homeopathy and acupuncture and were then randomised.
	1.2	Y	Randomisation was in blocks of four, and serially numbered opaque envelopes were used to achieve concealed allocation. However, patients nominated preference of homeopathy and acupuncture and were then randomised.
	1.3	N	No major difference in baseline characteristics between groups.
		Low	
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	Y	As patients nominated preference of homeopathy and acupuncture and then randomised, participants knew what treatment arm they were assigned to during the trial.
	2.2	Y	As patients nominated preference of homeopathy and acupuncture and then randomised, participants knew what treatment arm they were assigned to during the trial.
	2.3	N	No evidence of deviations from the intended intervention that arose because of the trial context.
	2.4	NA	
	2.5	NA	
	2.6	Y	Intent-to-treat (modified) analysis conducted
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	Y	<5% missingness
	3.2	NA	
	3.3	NA	
	3.4	NA	
		Low	
Bias in measurement of the outcome	4.1	PY	One of two primary outcomes (MYMOP) inappropriate.
	4.2	Y	One primary outcome measurement (MYMOP) varied between participants and intervention groups.
	4.3	N	
	4.4	NA	
	4.5	NA	
		High	**One of two primary outcomes (MYMOP) inappropriate and subject to participants experience.**
Bias in selection of the reported result	5.1	N	No information of pre-specified analysis plan for this study.
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**No information of pre-specified analysis plan for this study.**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		Dossett 2015	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Subjects were randomised using permuted blocks randomisation with randomly varying block sizes of four or eight.
	1.2	Y	The randomisation was double-blinded (neither the subject nor the research time knew the allocation assignment). The randomisation code was maintained by the study statistician and the centre research pharmacy.
	1.3	PY	Some difference in baseline characteristics between groups, however, unexpected to significantly influence the results.
		Some concerns	
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	The randomisation was double-blinded (neither the subject nor the research time knew the allocation assignment). The randomisation code was maintained by the study statistician and the centre research pharmacy.
	2.2	N	The randomisation was double-blinded (neither the subject nor the research time knew the allocation assignment). The randomisation code was maintained by the study statistician and the centre research pharmacy.
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	Intent-to-treat analysis conducted.
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	Y	<5% missingness
	3.2	NA	
	3.3	NA	
	3.4	NA	
		Low	
Bias in measurement of the outcome	4.1	N	Primary outcome measure assessed according to five point scale reported in subjective daily symptom diary, although average used for each participant
	4.2	N	
	4.3	N	
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	Y	
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
		Low	
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Raak 2019**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Block randomisation with a block size of 4 was electronically generated and 50% of patients allocated to either intervention or placebo. Information on medication to be given to the patients was contained in numbered, sealed, random envelopes.
	1.2	Y	After randomisation and patients' parents had provided informed consent, the investigator opened the envelopes.
	1.3	N	Baseline differences were comparable between groups.
		Low	**Randomisation sequence was truly random, allocation sequence concealed and any baseline difference likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	Y	Both investigators and patients' parents knew which medication the patient would receive.
	2.2	Y	Both investigators and patients' parents knew which medication the patient would receive.
	2.3	N	No deviations from the intended intervention reported.
	2.4	NA	
	2.5	NA	
	2.6	Y	Intent-to-treat analysis conducted.
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	Y	<5% missingness
	3.2	NA	
	3.3	NA	
	3.4	NA	
		Low	
Bias in measurement of the outcome	4.1	N	Complaints and objective symptoms were evaluated and scored by the investigator either according to patients' parents' self-report or according to the patients' examination results.
	4.2	N	
	4.3	Y	Both investigators and patients' parents knew which medication the patient would receive.
	4.4	Y	Both investigators and patients' parents knew which medication the patient would receive.
	4.5	PY	
		High	**Both investigators and patients' parents knew which medication the patient would receive which may have influenced the assessment of the outcome.**
Bias in selection of the reported result	5.1	NI	No information of pre-specified analysis plan for this study.
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
		Some concerns	**No information of pre-specified analysis plan for this study.**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Peckham 2012**	
Domain	**SQ ***	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PN	Shuffling of sealed envelopes
	1.2	Y	Sealed opaque envelope carried out by an independent administrator
	1.3	N	No baseline imbalances noted
		Some concerns	**Some concerns due to the quasi randomisation process**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	Y	Open label study
	2.2	Y	Open label study
	2.3	PN	The only deviations are non-completion by some participants, in line with what would be expected in routine practice
	2.4	NA	
	2.5	NA	
	2.6	Y	Modified ITT
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	12/94 (12.8%) of participants had missing data at follow up
	3.2	N	No analysis for missing data is presented
	3.3	NI	No reasons for missing outcome data presented, participants lost to follow up
	3.4	NI	No reasons for missing outcome data presented, participants lost to follow up
		Some concerns	
Bias in measurement of the outcome	4.1	N	
	4.2	N	
	4.3	Y	Self-reported outcomes by non-blinded participants
	4.4	PY	Given that participants elected to uptake the intervention, it is plausible that they would be biased in their reporting of the outcome. It was reported in the trial protocol that expectation of benefit would be measured, however these results are not reported due to low uptake of the interventions.
	4.5	PN	There is no evidence to suggest that participants were biased in their reporting of the outcome.
		Some concerns	**Some concerns due to self-reported outcomes by non-blinded participants.**
Bias in selection of the reported result	5.1	Y	Trial protocol available for comparison
	5.2	N	Outcome measures align with those pre-specified in the protocol
	5.3	N	Outcomes not reported for 52-week data despite being pre-specified. The primary outcome was to be measured at 26-weeks, and is reported. Justification for lack of follow-up data is provided.
		Low	
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Wiesenauer 1992**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	Participants legs randomised to either homeopathy or placebo. Process of randomisation not specified.
	1.2	PY	Tubes were delivered in unopened packages so the physician was unable to tell which ointment was assigned to which body side. Process of allocation sequence concealment not specified.
	1.3	NA	Intraindividual comparison between legs.
		Some concerns	**Randomisation sequence not clearly described. Allocation sequence likely concealed. Baseline likely comparable**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Participants legs randomised to either homeopathy or placebo. Tubes were delivered in unopened packages so the physician, and therefore participants, were unable to tell which ointment was assigned to which body side.
	2.2	N	Double blind, placebo controlled study.
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	Intent-to-treat analysis participants were analysed in the group to which they were randomised.
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice. Method of analysis appropriate.**
Bias due to missing outcome data	3.1	PY	<5% missingness and ITT analysis conducted.
	3.2	NA	
	3.3	NA	
	3.4	NA	
		Low	**Data were available for all, or nearly all, participants**
Bias in measurement of the outcome	4.1	PY	Main effect measures were very crude, and a three point scale may not be sensitive to small changes in disease course.
	4.2	N	Assessment of efficacy uniform for all participants, however relies on self-assessment versus physician assessment and therefore subjective.
	4.3	PY	"Double-blind", however process of randomisation and allocation sequence concealment not specified
	4.4	PY	"Double-blind", however process of randomisation and allocation sequence concealment not specified. Homeopathy intervention had a slight change in colour which authors report was only noticeable with direct comparison to placebo although this is not expected to bias the results.
	4.5	PY	As above.
		High	**The outcome measure was inherently subjective due to intraindividual self-assessment and authors reported the main effect measures were crude and may not be sensitive to small change.**
Bias in selection of the reported result	5.1	NI	No information of pre-specified analysis plan.
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**There is no indication of selection/reporting of outcomes/measures on the basis of the results**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID	Bernstein 2006	
	Judgement	**Comments**
Bias arising from the randomisation process	PY	Participants randomised to either homeopathy of placebo. Process of randomisation not specified.
	PY	"Double-blind", however allocation sequence concealment not specified
	N	No differences between treatment groups.
	Some concerns	**Randomisation sequence possibly truly random, allocation sequence likely concealed, and no differences between treatment groups.**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	N	"Double blind" and participants randomised to either homeopathy of placebo.
	N	Double blind, placebo controlled study.
	NA	
	NA	
	NA	
	Y	Intent-to-treat analysis participants were analysed in the group to which they were randomised.
	NA	
	Low	**Intent-to-treat analysis participants were analysed in the group to which they were randomised.**
Bias due to missing outcome data	N	>5% missingness.
	N	Patients with missing outcome data were imputed with the worst possible score for each outcome. This has the potential to substantially bias the result. Unequal distribution in discontinuation, with a greater number in placebo group (n=26).
	Y	Inappropriate imputation of missing outcome data leads to high risk of bias.
	Y	Inappropriate imputation of missing outcome data leads to high risk of bias.
	High	**Significant missingness, inappropriate imputation, and unequal distribution of missing outcome data leads to high risk of bias for this domain.**
Bias in measurement of the outcome	N	Primary outcome objectively indicates the severity of psoriasis; and validated quality of life questionnaire used.
	N	Outcomes measures are objective and consistent between groups.
	PN	"Double-blind", however allocation sequence concealment not specified
	NA	
	NA	
	Low	**The methods of assessment were appropriate, comparable across intervention groups, and the outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants**
Bias in selection of the reported result	NI	No information of pre-specified analysis plan.
	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
	Some concerns	**There is no indication of selection/reporting of outcomes/measures on the basis of the results**
Overall risk of bias	**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Khitrov 2009**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	NI	Method of generating the randomisation sequence not specified
	1.2	NI	The authors do not report on allocation concealment
	1.3	NI	Baseline characteristics not suffciently reported to make an assessment. There appeared to be no difference in the number of pariticipants with concomitant diseases
		High	**High risk of bias due to insufficient information reported**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	PY	Authors report this was an open trial
	2.2	PY	Authors report this was an open trial
	2.3	NI	No CONSORT diagram presented to assess deviations
	2.4	NA	
	2.5	NA	
	2.6	NI	Method of statistical analysis not reported
	2.7	NI	The number of participants potentially analysed in each group was not reported
		High	**High risk of bias due to lack of blinding and insufficient information regarding the method of analysis**
Bias due to missing outcome data	3.1	NI	The number of participants randomised and the rate of drop out is not reported
	3.2	N	No evidence presented to account for any potential missing data
	3.3	NI	No information presented
	3.4	NI	No information presented
		High	**High risk of bias due to insufficient reporting of missing data**
Bias in measurement of the outcome	4.1	N	
	4.2	PN	
	4.3	Y	Authors report this was an open trial
	4.4	PY	Non-blinded participants could plausibly differentially report their outcomes
	4.5	PN	There is no evidence to suggest differential reporting of outcomes between treatment groups
		Some concerns	**Some concerns due to outcome measurement by non-blinded participants and trialists**
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Some concerns due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Koley 2015**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated random numbers
	1.2	PY	Authors report that confidentiality of the code was maintained by the statistician however the method is not reported
	1.3	PN	Difference in stiffness VAS at baseline, not considered likely due to randomisation
		Low	**Randomisation sequence was truly random, allocation sequence concealed and any baseline difference likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Participants were blinded to intervention status
	2.2	N	Trialists were blinded to intervention status
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis specified and conducted
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	6/60 participants did not have outcome data available
	3.2	N	Last observation carried forward should not be assumed to account for missing outcome data
	3.3	Y	It is reported that 5/6 participants dropped out due to deterioration
	3.4	Y	It is reported that 5/6 participants dropped out due to deterioration
		High	**High risk of bias due to missing data that is known to be related to the true value of the outcome**
Bias in measurement of the outcome	4.1	N	
	4.2	N	
	4.3	N	Participants and trialists were blinded to intervention status
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan
	5.2	N	Reported results correspond with those in the clinical trial registry
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Some concerns due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Shealy 1998**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	Method of generating the randomisation sequence not specified
	1.2	PY	The authors do not report on allocation concealment, however it is noted that staff did not know which intervention group participants were assigned.
	1.3	PY	No baseline characteristics presented, however it is noted that groups were comparable in terms of age, gender and pain at baseline
		Some concerns	**Some concerns relating to the lack of information on randomisation and baseline characteristics**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo controlled trial, participants were not aware of their treatment allocation
	2.2	N	Staff were not aware of treatment allocation
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	NI	Method of statistical analysis not reported
	2.7	NI	The number of participants potentially analysed in each group was not reported
		High	**High risk of bias due to lack of information regarding method of statistical analysis**
Bias due to missing outcome data	3.1	NI	The number of participants randomised and the rate of drop out is not reported
	3.2	N	No evidence presented to account for any potential missing data
	3.3	NI	No information presented
	3.4	NI	No information presented
		High	**High risk of bias due to insufficient reporting of missing data**
Bias in measurement of the outcome	4.1	N	
	4.2	N	
	4.3	N	Participants and trialists were blinded to intervention status
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Some concerns due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Shipley 1983**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	Method of generating the randomisation sequence not specified
	1.2	NI	The authors do not report on allocation concealment
	1.3	NI	Baseline characteristics not sufficiently reported to make an assessment. There appeared to be no difference in the number of participants with concomitant diseases
		High	**High risk of bias due to insufficient information reported**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	PN	Placebo controlled trial, likely that participants were not aware of their treatment allocation
	2.2	PN	Double-blind, likely that trialists were unaware of intervention group
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	NI	Method of statistical analysis not reported
	2.7	NI	The number of participants potentially analysed in each group was not reported
		High	**High risk of bias due to lack of information regarding method of statistical analysis**
Bias due to missing outcome data	3.1	N	3/36 participants did not complete the study
	3.2	N	No evidence presented to account for any potential missing data
	3.3	N	2/3 participants dropped out due to aggravation of symptoms
	3.4	N	2/3 participants dropped out due to aggravation of symptoms
		High	**High risk of bias due to missing data that is known to be related to the true value of the outcome**
Bias in measurement of the outcome	4.1	N	
	4.2	N	
	4.3	N	Participants and trialists were likely blinded to intervention status
	4.4	N	
	4.5	N	
		Low	
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Some concerns due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Strosser 2000**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	Method of generating the randomisation sequence not specified
	1.2	NI	The authors do not report on allocation concealment
	1.3	NI	Baseline characteristics not sufficiently reported to make an assessment. There appeared to be no difference in the number of participants with concomitant diseases
		High	**High risk of bias due to insufficient information reported**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	PN	Placebo controlled trial, likely that participants were not aware of their treatment allocation
	2.2	PN	Double-blind, likely that trialists were unaware of intervention group
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	NI	Method of statistical analysis not reported
	2.7	NI	The number of participants potentially analysed in each group was not reported
		High	**High risk of bias due to lack of information regarding method of statistical analysis**
Bias due to missing outcome data	3.1	NI	The number of participants randomised and the rate of drop out is not reported
	3.2	N	No evidence presented to account for any potential missing data
	3.3	NI	No information presented
	3.4	NI	No information presented
		High	**High risk of bias due to insufficient reporting of missing data**
Bias in measurement of the outcome	4.1	N	
	4.2	N	
	4.3	N	Participants and trialists were likely blinded to intervention status
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Some concerns due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**vanHaselen 2000**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated random numbers
	1.2	PY	Treatment allocation was done at inclusion by the clinical metrologist, and was done based on the lowest unused number.
	1.3	N	Baseline characteristics were similar in both groups
		Low	
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double-blind trial. Participants were unaware of their intervention status. It was reported that 4 participants (two in each group) deliberately opened the covering to reveal their intervention group.
	2.2	N	Double-blind trial. Study staff were unaware of intervention group.
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis specified.
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	Y	Data available for 172/184 participants randomised
	3.2	NA	
	3.3	NA	
	3.4	NA	
		Low	
Bias in measurement of the outcome	4.1	N	
	4.2	N	
	4.3	N	Participants and trialists were likely blinded to intervention status
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Some concerns due to lack of pre-specified analysis plan**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Widrig 2007**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated random numbers
	1.2	NI	The authors do not report on allocation concealment
	1.3	N	No differences between groups at baseline
		Some concerns	**Some concerns due to lack of information regarding allocation concealment**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double-blind study, participants were not aware of their allocated treatment
	2.2	N	Double-blind study, considered likely that study staff were not aware of treatment allocation
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis specified and presented
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	Y	Data available for 198/204 participants
	3.2	NA	
	3.3	NA	
	3.4	NA	
		Low	
Bias in measurement of the outcome	4.1	N	
	4.2	N	
	4.3	N	Participants and trialists were likely blinded to intervention status
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Some concerns due to lack of pre-specified analysis plan**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Brien 2004**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated random numbers
	1.2	Y	Yes, sealed envelopes
	1.3	N	No baseline imbalances reported
		Low	
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	PN	Participants were aware of their allocation to consultation, but not to their allocation of remedy
	2.2	PN	Staff were aware of allocation to consultation, but not to remedy
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	27/83 participants did not complete treatment and it is interpreted that they also did not complete follow up
	3.2	N	No analysis to test for the effect of missing data was presented
	3.3	PY	Reasons for drop out are provided and related to intramuscular steroid injections and wishing to discontinue
	3.4	PY	Drop out due to intramuscular steroid injection is likely due to disease activity
		High	**High risk of bias due to rate of drop out considered likely related to the outcome**
Bias in measurement of the outcome	4.1	N	
	4.2	N	
	4.3	N	Participants and trialists were blinded to intervention status
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	N	Trial protocol available
	5.2	N	Results presented align with those pre-specified in the trial protocol
	5.3	N	Results presented align with those pre-specified in the trial protocol
		Low	
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Fisher 2001**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	Method of randomisation not specified
	1.2	NI	The authors do not report on allocation concealment
	1.3	NI	Baseline characteristics between groups not reported
		High	**High risk of bias due to unclear randomisation procedure and lack of baseline characteristics**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double-blind study, participants were not aware of their allocated treatment
	2.2	N	Double-blind study, considered likely that study staff were not aware of treatment allocation
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	PN	Per protocol analysis was interpreted, as participants who did not attend two follow up sessions were withdrawn
	2.7	Y	12/112 participants were withdrawn for failing to attend two consecutive follow up appointments
		High	**High risk of bias due to inappropriate method of analysis**
Bias due to missing outcome data	3.1	N	54/112 participants did not complete the trial
	3.2	N	No analysis to test for the effect of missing data was presented
	3.3	Y	Reasons for drop out are provided and include changes to conventional medicine which could plausibly be related to symptoms
	3.4	Y	Reasons for drop out are provided and include changes to conventional medicine which could plausibly be related to symptoms
		High	**High risk of bias due to rate of drop out considered likely related to the outcome**
Bias in measurement of the outcome	4.1	N	
	4.2	N	
	4.3	N	Participants and trialists were blinded to intervention status
	4.4	N	
	4.5	N	
		Low	
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Gupta 2020**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated random numbers
	1.2	Y	Allocation sequence concealed from study participants. The randomisation chart was available to the investigator and pharmacist only
	1.3	N	No significant baseline differences noted
		Low	**Randomisation sequence was truly random, allocation sequence concealed and any baseline difference likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo-controlled, double-blinded. The randomisation chart was available to the investigator and pharmacist only
	2.2	N	Placebo-controlled, double-blinded. The randomisation chart was available to the investigator and pharmacist only
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	N	Per protocol analysis used. Drop-outs were not included in the analysis of the outcomes.
	2.7	N	1 participant from each group dropped-out. Balanced discontinuation, so there is very minimal potential for a substantial impact.
		Some concerns	**Per protocol analysis used. Drop-outs were not included in the analysis of the outcomes, although they were balanced between groups.**
Bias due to missing outcome data	3.1	Y	<5% missingness (2/136 participants dropped out and per protocol analysis)
	3.2	NA	
	3.3	NA	
	3.4	NA	
		Low	**<5% missingness (2/136 participants dropped out and per protocol analysis)**
Bias in measurement of the outcome	4.1	N	Known outcome measures used
	4.2	N	Outcomes were measured in the same way between groups
	4.3	N	Allocation sequence concealed from study participants. The randomisation chart was available to the investigator and pharmacist only
	4.4	NA	
	4.5	NA	
		Low	**Methods of outcome assessment were appropriate and comparable across treatment groups. The outcome measure was unlikely to be influenced by knowledge of the intervention received by each group.**
Bias in selection of the reported result	5.1	PN	No pre-specified analysis plan available, but indication of some level of protocol.
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain.
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**There is no indication of selection/reporting of outcomes/measures on the basis of the results BUT there is no pre-specified analysis plan available.**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Morris 2016**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Double-blind, randomised control trial
	1.2	Y	The researchers and participants were blinded and were unaware of which bottles contained the homeopathy or placebo, ensuring allocation concealment and preventing selection bias.
	1.3	PY	Baseline differences in pain medication use, however, unlikely to be a result of the randomisation process.
		Low	**Randomisation sequence was truly random, allocation sequence concealed and any baseline difference likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	The researchers and participants were blinded and were unaware of which bottles contained the homeopathy or placebo, ensuring allocation concealment and preventing selection bias.
	2.2	N	The researchers and participants were blinded and were unaware of which bottles contained the homeopathy or placebo, ensuring allocation concealment and preventing selection bias.
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	Intent-to-treat analysis and no participants excluded, discontinued, or lost to follow-up.
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	Y	Data available for all participants
	3.2	NA	
	3.3	NA	
	3.4	NA	
		Low	
Bias in measurement of the outcome	4.1	N	Appropriate and validated outcomes measures used
	4.2	N	Outcome measures were the same between groups
	4.3	N	The researchers and participants were blinded and were unaware of which bottles contained the homeopathy or placebo, ensuring allocation concealment and preventing selection bias.
	4.4	NA	
	4.5	NA	
		Low	**Methods of outcome assessment were appropriate and comparable across treatment groups. The outcome measure was unlikely to be influenced by knowedlge of the intervention received by each group.**
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain.
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurement.
		Some concerns	**Some concerns due to lack of pre-specified analysis plan**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Stam 2001**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Double-blind, randomised control trial
	1.2	Y	Blinding ensured as randomisation and allocation done by external provider and codes were broken only after completion of the analyses of the primary efficacy measures.
	1.3	N	There were no major differences between the treatment groups at baseline.
		Low	**Randomisation sequence was truly random, allocation sequence concealed and any baseline difference likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Blinding ensured as randomisation and allocation done by external provider and codes were broken only after completion of the analyses of the primary efficacy measures.
	2.2	N	Blinding ensured as randomisation and allocation done by external provider and codes were broken only after completion of the analyses of the primary efficacy measures.
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	N	Intent-to-treat analysis for primary efficacy measures, using 'last-value-carried-forward' method, however only if subjects had a baseline VAS as well as at least one follow-up VAS.
	2.7	PY	In analyses other than intent-to-treat, missing values were left blank.
		High	**Intent-to-treat analysis for primary efficacy measures possibly inappropriate and there was potential for a substantial impact on the result for failure to include missing values for secondary outcomes.**
Bias due to missing outcome data	3.1	Y	<5% missingness (6/161 participants dropped out)
	3.2	NA	
	3.3	NA	
	3.4	NA	
		Low	
Bias in measurement of the outcome	4.1	N	Appropriate and validated outcomes measures used
	4.2	N	Outcome measures were the same between groups
	4.3	N	Blinding ensured as randomisation and allocation done by external provider and codes were broken only after completion of the analyses of the primary efficacy measures.
	4.4	NA	
	4.5	NA	
		Low	**Methods of outcome assessment were appropriate and comparable across treatment groups. The outcome measure was unlikely to be influenced by knowedlge of the intervention received by each group.**
Bias in selection of the reported result	5.1	NI	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain.
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurement.
		Some concerns	**Some concerns due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Colau 2012**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated random numbers
	1.2	Y	Allocated sequence was kept in a sealed envelope that was not opened until the end of the study
	1.3	N	No significant baseline differences noted
		Low	**Randomisation sequence was truly random, allocation sequence concealed and any baseline difference likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo-controlled
	2.2	N	Double-blind trial
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis specified
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	7/108 participants withdrew from the study
	3.2	N	ITT population analysed, defined as all patients who took at least one dose of treatment and had at least one post-enrolment evaluation
	3.3	PN	7/7 participants that withdrew did so before taking treatment, reasons for withdrawal not provided
	3.4	NA	
		Some concerns	**Some concerns due to missing outcome data**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double-blind trial
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	PN	Clinical trial protocol available but not in English
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Some concerns due to inability to access trial protocol**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Andrade 2019**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Patients were asked to take one flask of medicine from a box. The flasks were randomly numbered, and the allocation list was held by another researcher, not involved with patient recruitment or assessment. The allocation list (simple randomization) was generated through a website
	1.2	Y	The allocation list was held by another researcher, not involved with patient recruitment or assessment.
	1.3	PN	Some slight baseline differences noted
		Low	**Randomisation sequence was truly random, allocation sequence concealed and any baseline difference likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo-controlled
	2.2	PN	All investigators but one were blinded to the intervention. They were responsible for study design, randomisation, data analysis and manuscript preparation
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis specified
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	7/40 participants withdrew from the study
	3.2	N	ITT analysis specified. Missing values due to voluntary dropouts were treated as worsening to the worst possible outcome in ITT analysis
	3.3	PY	6/7 participants dropped out due to lack of effect. 1/7 in the placebo group dropped out due to worsening symptoms
	3.4	PY	Drop-out was higher in the placebo group (6/7) compared to the homeopathy group (1/7)
		High	**High concerns due to missingness related to health status, which was unbalanced between treatment groups**
Bias in measurement of the outcome	4.1	PN	Participants were given a choice of secondary outcome domains to measure and report throughout the study
	4.2	N	Outcome measurements consistent between groups
	4.3	PY	All researchers but one were blinded to treatment allocation. It is not specified if the researcher collecting the outcome data was blinded
	4.4	PN	It is possible if the researcher collecting the data was not blinded, but there is no evidence to suggest this
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	PN	Reference made to a study protocol, however protocol not able to be located
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Some concerns due to inability to verify trial protocol**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Gupta 2019**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated random numbers
	1.2	Y	Participants and researchers unaware of allocation sequence
	1.3	N	No significant baseline differences noted
		Low	**Randomisation sequence was truly random, allocation sequence concealed and any baseline difference likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo-controlled
	2.2	N	Double-blind trial
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis presumed
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	Y	All randomised participants completed follow up
	3.2	NA	
	3.3	NA	
	3.4	NA	
		Low	
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double-blind trial
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	PN	Clinical trial protocol referenced, but not accessible (clinical trials registry India)
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Some concerns due to inability to access trial protocol**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Jacobs 2005**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated random numbers
	1.2	Y	Only the homeopathic pharmacist was aware of the randomisation code
	1.3	PN	Some slight baseline differences note, unlikely due to the randomisation process
		Low	**Randomisation sequence was truly random, allocation sequence concealed and any baseline difference likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo-controlled
	2.2	N	Double-blind trial
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis presumed
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	28/83 participants had missing data
	3.2	N	Presumed ITT analysis
	3.3	PY	11/28 participants dropped out due to no relief of symptoms, 5/28 due to study inconvenience, 4/28 due to cancer recurrence, 4/28 were lost to follow up, 3/28 due to other illness and 1/28 due to adverse event
	3.4	PY	Participant drop out was not balanced between groups, individualised homeopathy (6/28), non-individualised homeopathy (11/28) and placebo (11/28)
		High	**High concerns due to missing outcome data and drop-out due to health status**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double-blind trial
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Some concerns due to lack of pre-specified analysis plan**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Relton 2012**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	A random numbers sheet was generated by the statistician on a one to one basis using a block randomisation procedure, with blocks of 8
	1.2	Y	The random numbers were put into sealed numbered envelopes until treatment allocations were assigned
	1.3	PN	Some slight baseline differences note, unlikely due to the randomisation process
		Low	**Randomisation sequence was truly random, allocation sequence concealed and any baseline difference likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	Y	Post randomisation, the homeopathy treatment group were informed of their treatment allocation
	2.2	Y	Only the homeopathy group attended consultations with the homeopath, based on this, it is presumed the homeopath was aware of the participant's allocation
	2.3	PN	Deviations included refusal of treatment by some participants allocated to the treatment group (7/24), presumed due to knowledge of treatment allocation
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis specified, modified ITT analysis performed
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	4/48 participants had missing data
	3.2	N	ITT analysis of all those with complete and analysable data was performed
	3.3	PN	Reasons for participant non-completion are not provided
	3.4	NA	
		Some concerns	**Some concerns due to missing outcome data**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	Y	Outcomes were self-reported, and participants were aware of their treatment allocation
	4.4	PY	Knowledge of intervention may have influenced participant's assessment of self-reported outcomes
	4.5	PN	Knowledge of intervention could bias self-reported outcomes, but there is no evidence to suggest that this is likely
		Some concerns	**Some concerns that knowledge of intervention could bias outcome measures**
Bias in selection of the reported result	5.1	PN	Trial protocol available for comparison. Protocol lists some outcomes that were measured, but the results were not reported in the published trial
	5.2	PN	Some evidence of selective reporting. Some outcomes such as visits to hospital and other health professionals, and days off work, were measured but data not shown
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Some concerns due to non-reporting of outcomes**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**von Hagens 2012**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Lists for stratified randomised allocation to the three treatment groups with block length of 6 were created by an independent biometrician
	1.2	Y	Allocation sequence sent to a manufacturer who packed and labelled the medication and after final assessment of eligibility, participants were allocated to treatment
	1.3	PN	Baseline characteristics were similar between groups except for MRS 11 total scores between groups 1 and 3. Pooled results showed no difference between treatment and placebo group. Differences not considered due to randomisation processes
		Low	**Randomisation sequence was truly random, allocation sequence concealed and any baseline difference likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo-controlled
	2.2	N	Double-blind trial
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	PY	Both ITT analysis and per-protocol analysis methods were used
	2.7	N	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	18/102 participants had missing data at the end of the first treatment period (12 weeks)
	3.2	N	Both ITT analysis and per-protocol analysis methods were used
	3.3	PY	Reasons for participant drop out included; 8/18 due to no symptom relief, 6/18 withdrew consent, 1/18 lost to follow up, 1/18 adverse event, 2/18 other (not described)
	3.4	PY	Reasons for participants drop-out were related to health status
		High	**High concerns due to missing outcome data and drop-out due to health status**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double-blind trial
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	Y	Trial protocol available for comparison
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Low	
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Yakir 1994**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Medications were encoded prior to the study by random permutation
	1.2	Y	Allocation concealment managed by a third party. Code was not opened until the end of the study
	1.3	NI	No information. Assumed no significant difference as balanced by randomisation.
		Low	**Baseline characteristics not provided, presumed balanced due to randomisation process**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double-blind study
	2.2	N	Carers and people delivering the intervention were blinded
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	PY	Modified ITT analysis. 4 participants excluded from analysis
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	4/23 participants withdrew from the study
	3.2	N	Modified ITT analysis. 4 participants excluded from analysis due to drop out. No adjustments made
	3.3	PN	Reasons for drop out were withdrawel of consent (1/4), lost papers (2/4) and pregnancy (1/4). Reasons for withdrawen consent not provided. Drop out rates consistent across treatment arms
	3.4	NA	
		Some concerns	**Some concerns due to missing data**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double-blind study
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain.
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Some concerns due to lack of pre-specified analysis plan**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Charandabi 2016**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	An independent person managed the allocation sequence using computer generated random numbers with randomly unequal block sizes of 4 and 6
	1.2	PY	An associate researcher was the only person aware of the allocation. The homeopath, participants, and data analyser were blinded to group assignment
	1.3	PN	
		Low	**Some baseline imbalances but not likely due to the randomisation process**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double-blind study
	2.2	PN	An associate researcher was the only person who was aware of the group each person was assigned to. The homeopath, participants, and data analyser were blinded to group assignment.
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	PY	Modified ITT analysis. 7 participants excluded from analysis (6 from placebo group and 1 from homeopathy)
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	7/54 participants withdrew from the study
	3.2	N	Modified ITT analysis. 7 participants excluded from analysis (6 from placebo group and 1 from homeopathy)
	3.3	PY	Reasons for drop out were 'not accessible' (3/7) and 'unwilling to continue' (4/7). Reasons not provided
	3.4	PN	Reasons that participants were unwilling to continue were not provided, so this could have been due to health status. Dropout rate was higher in the placebo group (6/7) compared to the homeopathy group (1/7)
		Some concerns	**Some concerns due to missing data and reasons for drop out not specified**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double-blind study
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan available
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	PN	Mean differences and p-values not reported at the end of treatment for some outcomes (pain intensity and medication use). Reasons not specified
		Some concerns	**Some concerns due to lack of pre-specified analysis plan**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Teixeira 2017**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Sequence created by independent supervisor using a random number generator
	1.2	Y	Physician-investigators and participants blinded to the interventions for full duration of study and throughout data analysis
	1.3	PN	Some slight baseline imbalances noted. Not likely due to the randomisation process
		Low	**Some baseline imbalances but not likely due to the randomisation process**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Double-blind study
	2.2	N	Both physician-investigator and participants were blinded
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	PY	Primary outcome data were subjected to ITT and per-protocol analysis. For secondary outcomes, per-protocol analysis was used
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	9/50 participants withdrew from the study
	3.2	N	ITT and per protocol analysis used. No adjustments for missing data
	3.3	PY	Reasons for drop out include withdrawal of consent (6/9), adverse events (2/9) and protocol deviation (1/9)
	3.4	PY	Drop out was higher in the homeopathy group (6/9) compared to placebo (3/9). Health status was among the reasons for drop out
		High	**High concerns due to missing data and reasons for drop out relating to health status**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double-blind study
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	Y	Pre-specified analysis plan available
	5.2	PY	Evidence of selective reporting of outcomes as only 3 of 8 domains for quality of life were reported
	5.3	PN	Primary outcome data were subjected to ITT and per-protocol analysis. For secondary outcomes, per-protocol analysis was used
		Some concerns	**Some concerns due to evidence of selective reporting**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Klein-Laansma 2018**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated random numbers by a third party
	1.2	Y	Allocation concealed until disclosure, after the intake interview
	1.3	PN	Some baseline imbalances noted. Not likely due to the randomisation process
		Low	**Some baseline imbalances but not likely due to the randomisation process**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	Y	Allocation was disclosed to participants after the intake interview
	2.2	Y	Allocation was disclosed to researchers after the intake interview
	2.3	PN	Only deviations reported were non-completion by some participants. Not considered to be due to the trial context.
	2.4	NA	
	2.5	NA	
	2.6	PY	Both ITT and per-protocol analysis was performed
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	14/60 participants had missing data
	3.2	N	ITT and per protocol analysis used
	3.3	PY	Reasons for drop out included not randomised to preferred group (4/14), too much burden (3/14), person reasons (2/14), lost to follow up (2/14), pregnancy (2/14). 1/14 excluded from analysis due to incomplete data
	3.4	PY	Not specified if drop out reasons related to health status. Drop-out was higher in the control group (10/14) compared to the homeopathy group (4/14)
		Some concerns	**Some concerns due to missing data**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	Y	Participants were the outcome assessors (self-reported outcomes measures). Participants aware of treatment allocation
	4.4	Y	Assessment of the outcome could have been influenced by knowledge of treatment
	4.5	PN	Knowledge of intervention could bias self-reported outcomes, but there is no evidence to suggest that this is likely
		Some concerns	**Some concerns that knowledge of intervention could bias outcome measures**
Bias in selection of the reported result	5.1	PN	Paper makes reference in text to a study protocol, however details and access to protocol not provided
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	PN	Both ITT and per-protocol analysis was performed
		Some concerns	**Some concerns as pre-specified analysis plan not available to view**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

* see risk-of-bias tool at www.riskofbias.info for signalling questions and guidance.

Study ID		**Singh 2020**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated random numbers (simple random sampling method)
	1.2	PY	No specific information on allocation concealment. Researchers aware of allocations, participants were blinded
	1.3	NI	No information. Assumed no significant difference as balanced by randomisation.
		Low	**Baseline characteristics not provided, presumed balanced due to randomisation process**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Participants blinded to treatment allocation
	2.2	Y	Single blinded study (only the participants were blinded to treatment allocation)
	2.3	PN	Only deviation reported was non-completion by one participant. Not considered to be due to the trial context
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis conducted
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	PY	1/65 participants had missing data
	3.2	N	ITT analysis conducted
	3.3	PY	1 participant in the placebo group dropped out due to mild improvement in pain
	3.4	PY	1 participant in the placebo group dropped out due to mild improvement in pain
		Low	
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Participants were the outcome assessors (self-reported measure), and were not aware of treatment allocation
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	PN	Reference to a study protocol was made, pre-specified analysis plan not available to view
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements
		Some concerns	**Some concerns as pre-specified analysis plan not available to view**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

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Study ID		**Yakir 2019**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated random numbers
	1.2	Y	Codes concealed until after termination of study
	1.3	N	No significant baseline differences noted
		Low	**Allocation sequence was random and concealed. No significant baseline differences noted**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Participants blinded to treatment allocation
	2.2	N	Double-blind study
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	PY	Both ITT and per-protocol analysis was performed
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	9/105 participants had missing data
	3.2	N	ITT and per protocol analysis used
	3.3	PY	Reasons for drop out included not taking the prescribed treatment (2/9), pregnancy (3/9) and lost to follow up (4/9). Reasons for not taking medicine and lost to follow up not provided
	3.4	PN	Not specified if reasons for drop out provided may have related to health status. Drop-out was higher in the homeopathy group (6/9) compared to the placebo group (3/9)
		Some concerns	**Some concerns due to missing data and reasons for participant drop-out**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcome measurements consistent between groups
	4.3	N	Double-blind study
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	PN	Reference to a study protocol was made, pre-specified analysis plan not available to view
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	PN	Both ITT and per-protocol analysis was performed
		Some concerns	**Some concerns as pre-specified analysis plan not available to view**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

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Study ID		**McKendrick 1999**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Statistician computer-generated randomisation sequence
	1.2	Y	Sequence concealed from the trialists
	1.3	N	Baseline characteristics are comparable between groups
		Low	**Randomisation sequence was truly random, allocation sequence concealed and any baseline difference likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo controlled
	2.2	N	Only the dispensing pharmacist and statistician were aware of the code
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis was specified. Participants who did not return post-treatment questionnaires were excluded. mITT was used
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	Data from 17/103 participants was missing at follow up
	3.2	N	No analysis presented to assess the effect of missing data
	3.3	NI	No reasons for missingness were provided
	3.4	PN	No reasons for missingness were provided. The amount of missing data was balanced between groups
		Some concerns	**Some concerns due to the amount of missing data and lack of reasons provided**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcomes were measured in the same way between the intervention and control groups
	4.3	N	Double blind trial
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	Y	Authors report that data analysis was conducted by a statistician blinded to group assignment until after the initial analysis was complete. Protocol not available, however the study was registered.
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	N	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Low	
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable

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Study ID		**Bell 2004**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated random numbers
	1.2	Y	Only the methodologist had access to the sequence
	1.3	PN	Some baseline imbalances were noted but not considered likely to be due to randomisation
		Low	**Some baseline imbalances not considered due to randomisation**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo-controlled
	2.2	N	No, only the methodologist had access to the sequence
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis specified. mITT used.
	2.7	NA	
		Low	
Bias due to missing outcome data	3.1	N	9/62 (14.5%) participants had missing data
	3.2	N	No adjustment for drop out was reported. It was reported that baseline characteristics did not differ between completers and those who dropped out.
	3.3	PN	Primary reasons for drop out were time and travel demands of the study.
	3.4	NA	
		Some concerns	**Some concerns due to missing data, with no analysis assessing the impact**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcomes were measured in the same way between the intervention and control groups
	4.3	N	Double blind trial
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan
	5.2	PN	There is some evidence of selective reporting of outcomes based on multiple eligible measures or domains (POMS and FACIT outcome measures)
	5.3	PN	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		High	**Some concerns due to lack of pre-specified analysis plan an missing outcome data**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

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Study ID		**Fisher 1988**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	PY	Described as randomised, but details not specified
	1.2	Y	Homeopathic doctor, clinical metrologist and patient blinded to allocation sequence
	1.3	NI	Baseline information not provided
		Some concerns	**Some concerns due to lack of randomisation details and no baseline characteristics provided**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	N	Placebo-controlled
	2.2	N	Homeopathic doctors and clinical metrologist were blinded
	2.3	NA	
	2.4	NA	
	2.5	NA	
	2.6	NI	Presumed ITT used however the number of participants analysed was not reported.
	2.7	NI	
		Some concerns	**Some concerns due to lack explanation of analysis used**
Bias due to missing outcome data	3.1	NI	Number of participants analysed was not provided. Not specified if there was any missing data
	3.2	NI	
	3.3	NA	
	3.4	NA	
		High	
Bias in measurement of the outcome	4.1	PN	Validated outcome measures used
	4.2	PN	Outcomes were likely measured in the same way between the intervention and control groups
	4.3	N	Double blind trial
	4.4	NA	
	4.5	NA	
		Low	
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	PY	Transformation of continuous to binary outcomes, unclear whether pre-specified or clinically meaningful
		High	**High concerns due to lack of pre-specified analysis plan and transformation of outcome data**
Overall risk of bias		**High**	The study has plausible bias that seriously weakens confidence in the results.

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Study ID		**Relton 2009**	
	SQ *	**Judgement**	**Comments**
Bias arising from the randomisation process	1.1	Y	Computer generated random numbers by independent statistician
	1.2	Y	Randomisation performed by independent statistician, delivered to patients in an opaque sealed envelope
	1.3	N	No significant differences in baseline characteristics between groups
		Low	**Randomisation sequence was truly random, allocation sequence concealed and any baseline difference likely due to chance**
Bias due to deviations from intended interventions (effect of assignment to intervention [ITT])	2.1	Y	Participants not blinded to treatment allocation
	2.2	Y	Clinicians not blinded to treatment allocation
	2.3	PN	Only deviations reported were non-completion by some participants. Not considered to be due to the trial context.
	2.4	NA	
	2.5	NA	
	2.6	Y	ITT analysis specified
	2.7	NA	
		Low	**Any deviations from intended intervention reflect usual practice and method for analysis is appropriate.**
Bias due to missing outcome data	3.1	N	11/47 participants had missing data
	3.2	PN	Presented both completers analysis and ITT using last observation carried forward.
	3.3	NI	Reasons for drop out not reported for 10/11 participants (1 participant emigrated).
	3.4	PN	Drop out is higher in the usual care group, likely due to the non-blinded nature of the study. Not considered likely to be due to the true value of the outcome.
		Some concerns	**Some concerns due to missing data**
Bias in measurement of the outcome	4.1	N	Validated outcome measures used
	4.2	N	Outcomes were likely measured in the same way between the intervention and control groups
	4.3	PY	Outcome assessors were not blinded to treatment allocations with the exception of the outcome 'tender point count,' which was conducted by an independent assessor
	4.4	Y	Knowledge of intervention could have influenced self-reported outcome measures
	4.5	PN	Knowledge of intervention could bias self-reported outcomes, but there is no evidence to suggest that this is likely
		Some concerns	**Some concerns that knowledge of intervention could bias outcome measures**
Bias in selection of the reported result	5.1	N	No pre-specified analysis plan
	5.2	N	No evidence of selection of results based on multiple eligible outcome measurements with the outcome domain
	5.3	PN	All eligible reported results for the outcome domain appear to correspond to all intended outcome measurements.
		Some concerns	**Some concerns due to lack of pre-specified analysis plan**
Overall risk of bias		**Some concerns**	The study has plausible bias that raises some doubt about the results.

Y=yes; PY=partial yes; N=no; PN=partial no; NI=no information; NA=not applicable
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