2. Modified Cochrane Risk of Bias Tool

Cochrane Risk of Bias Tool

Selection Bias

1. Was the allocation sequence adequately generated (e.g., rand number table, computer-generated randomization)

There is a LOW RISK OF BIAS if the investigators describe a random component in the sequence generation process such as: referring to a random number table, using a computer random number generator, coin tossing, shuffling cards or envelopes, throwing dice, drawing of lots. There is a HIGH RISK OF BIAS if the investigators describe a non-random component in the sequence generation process, such as: sequence generated by odd or even date of birth, date (or day) of admission, hospital or clinic record number; or allocation by judgement of the clinician, preference of the participant, results of a laboratory test or a series of tests, or availability of the intervention. IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.

- [ ] Low risk (yes)
- [ ] High risk (no)
- [ ] Unclear

**Clear Response**

High risk notes

2. Was ALLOCATION adequately concealed (prior to assignment)?

There is a LOW RISK OF BIAS if the participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomization); sequentially numbered drug containers of identical appearance; or sequentially numbered, opaque, sealed envelopes. There is a HIGH RISK OF BIAS if participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; or other explicitly uncontrolled procedures. IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.

- [ ] Low risk
3. Were PARTICIPANTS or THE HEALTH CARE PROVIDER who administered the intervention adequately BLINDED?

There is a LOW RISK OF BIAS if blinding of participants was ensured and it was unlikely that the blinding could have been broken; or if there was no blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding.

4. Were OUTCOME ASSESSORS adequately BLINDED?
There is LOW RISK OF BIAS if the blinding of the outcome assessment was ensured and it was unlikely that the blinding could have been broken; or if there was no or incomplete blinding, but the outcome is unlikely to be influenced by lack of blinding (i.e., lab tests—lipids—inherently low risk of bias, but not blood pressure).

- Low risk
- High risk
- Unclear

Clear Response

High risk notes

Attrition bias

5. Incomplete outcome data (ATTRITION BIAS) due to amount, nature or handling of incomplete outcome data

There is a LOW RISK OF BIAS if there were no missing outcome data; reasons for missing outcome data were unlikely to be related to the true outcome; missing outcome data were balanced in numbers, with similar reasons for missing data across groups (**The percentage of withdrawals and drop-outs should not exceed 20% for short-term follow-up [<1 year] and 30% for long-term follow-up [>1 year]**). IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.

- Low risk
- High risk
- Unclear

Clear Response

High risk notes
Reporting bias

6. Is there evidence of SELECTIVE OUTCOME REPORTING bias?

Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported? The authors can refer to a published protocol or to another study. Select high risk if they list outcomes for which they report no data, do not refer to another article for that outcome, or don’t mention a published (posted) protocol, OR if they say they used something like the WOMAC but report only the outcome for, say, pain or function.

- Low risk
- High risk
- Unclear

Clear Response

Notes

Other bias

7. INTENTION-TO-TREAT analysis? (Yes/No)

YES if they state ITT and methods used were actually ITT, or **all** participants were analyzed in the group to which they were allocated by randomization (no cross-over). IF NO ITT, EXPLAIN IN NOTES.

- Yes
- No
- Unclear

Clear Response

Notes
8. Group SIMILARITY AT BASELINE (**GENERAL**)

There is LOW RISK OF BIAS if groups are similar at baseline for demographic and other factors (e.g., BMI, baseline pain). Also LOW risk of bias if any baseline differences were adjusted for in all relevant analyses. IF HIGH RISK OF BIAS, EXPLAIN IN NOTES.

- Low risk
- High risk
- Unclear

Clear Response
Notes

9. Was there incomplete adherence/COMPLIANCE with interventions across groups?

There is LOW RISK OF BIAS if compliance with the interventions was acceptable (>=80% across intervention duration), based on the reported actual compliance compared to protocol or increased biomarker levels were reported during or at the end of the intervention. There is HIGH RISK OF BIAS if compliance was low (<80%). There is UNCLEAR RISK OF BIAS if these data were not reported.

- Low risk
- High risk
- Unclear

Clear Response
Notes
10. Additional Bias: Did authors report a power calculation and did they achieve adequate n?

- [ ] Yes
- [ ] No