

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

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|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| <b>1. Did the research questions and inclusion criteria for the review include the components of PICO?</b>                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                |
| For Yes:<br><input checked="" type="checkbox"/> Population<br><input checked="" type="checkbox"/> Intervention<br><input checked="" type="checkbox"/> Comparator group<br><input checked="" type="checkbox"/> Outcome                                                                                                                                                                       | Optional (recommended)<br><input type="checkbox"/> Timeframe for follow-up                                                                                                                                                                                                                                                                                                                                                                                  | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No                                         |
| <b>2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?</b>                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                |
| For Partial Yes:<br>The authors state that they had a written protocol or guide that included ALL the following:<br><br><input type="checkbox"/> review question(s)<br><input type="checkbox"/> a search strategy<br><input type="checkbox"/> inclusion/exclusion criteria<br><input type="checkbox"/> a risk of bias assessment                                                            | For Yes:<br>As for partial yes, plus the protocol should be registered and should also have specified:<br><br><input type="checkbox"/> a meta-analysis/synthesis plan, if appropriate, <i>and</i><br><input type="checkbox"/> a plan for investigating causes of heterogeneity<br><input type="checkbox"/> justification for any deviations from the protocol                                                                                               | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> Partial Yes<br><input type="checkbox"/> No |
| <b>3. Did the review authors explain their selection of the study designs for inclusion in the review?</b>                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                |
| For Yes, the review should satisfy ONE of the following:<br><input type="checkbox"/> <i>Explanation for including only RCTs</i><br><input type="checkbox"/> <i>OR Explanation for including only NRSI</i><br><input type="checkbox"/> <i>OR Explanation for including both RCTs and NRSI</i>                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                |
| <b>4. Did the review authors use a comprehensive literature search strategy?</b>                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                |
| For Partial Yes (all the following):<br><br><input type="checkbox"/> searched at least 2 databases (relevant to research question)<br><input type="checkbox"/> provided key word and/or search strategy<br><input type="checkbox"/> justified publication restrictions (e.g. language)                                                                                                      | For Yes, should also have (all the following):<br><br><input type="checkbox"/> searched the reference lists / bibliographies of included studies<br><input type="checkbox"/> searched trial/study registries<br><input type="checkbox"/> included/consulted content experts in the field<br><input type="checkbox"/> where relevant, searched for grey literature<br><input type="checkbox"/> conducted search within 24 months of completion of the review | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> Partial Yes<br><input type="checkbox"/> No |
| <b>5. Did the review authors perform study selection in duplicate?</b>                                                                                                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                |
| For Yes, either ONE of the following:<br><input type="checkbox"/> at least two reviewers independently agreed on selection of eligible studies and achieved consensus on which studies to include<br><input type="checkbox"/> OR two reviewers selected a sample of eligible studies <u>and</u> achieved good agreement (at least 80 percent), with the remainder selected by one reviewer. |                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                |

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|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>6. Did the review authors perform data extraction in duplicate?</b>                                                                                                                                                                                     |                                                                                                                               |                                                                                                                                                               |
| For Yes, either ONE of the following:                                                                                                                                                                                                                      |                                                                                                                               |                                                                                                                                                               |
| <input type="checkbox"/> at least two reviewers achieved consensus on which data to extract from included studies                                                                                                                                          | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No                                                        |                                                                                                                                                               |
| <input type="checkbox"/> OR two reviewers extracted data from a sample of eligible studies <u>and</u> achieved good agreement (at least 80 percent), with the remainder extracted by one reviewer.                                                         |                                                                                                                               |                                                                                                                                                               |
| <b>7. Did the review authors provide a list of excluded studies and justify the exclusions?</b>                                                                                                                                                            |                                                                                                                               |                                                                                                                                                               |
| For Partial Yes:                                                                                                                                                                                                                                           |                                                                                                                               |                                                                                                                                                               |
| <input type="checkbox"/> provided a list of all potentially relevant studies that were read in full-text form but excluded from the review                                                                                                                 | For Yes, must also have:                                                                                                      | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> Partial Yes<br><input type="checkbox"/> No                                                |
| <input type="checkbox"/> Justified the exclusion from the review of each potentially relevant study                                                                                                                                                        |                                                                                                                               |                                                                                                                                                               |
| <b>8. Did the review authors describe the included studies in adequate detail?</b>                                                                                                                                                                         |                                                                                                                               |                                                                                                                                                               |
| For Partial Yes (ALL the following):                                                                                                                                                                                                                       |                                                                                                                               |                                                                                                                                                               |
| <input type="checkbox"/> described populations<br><input type="checkbox"/> described interventions<br><input type="checkbox"/> described comparators<br><input type="checkbox"/> described outcomes<br><input type="checkbox"/> described research designs | For Yes, should also have ALL the following:                                                                                  | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> Partial Yes<br><input type="checkbox"/> No                                                |
| <input type="checkbox"/> described population in detail                                                                                                                                                                                                    | <input type="checkbox"/> described intervention in detail (including doses where relevant)                                    |                                                                                                                                                               |
| <input type="checkbox"/> described population in detail (including doses where relevant)                                                                                                                                                                   | <input type="checkbox"/> described comparator in detail (including doses where relevant)                                      |                                                                                                                                                               |
| <input type="checkbox"/> described study's setting                                                                                                                                                                                                         | <input type="checkbox"/> timeframe for follow-up                                                                              |                                                                                                                                                               |
| <b>9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?</b>                                                                                                 |                                                                                                                               |                                                                                                                                                               |
| <b>RCTs</b>                                                                                                                                                                                                                                                |                                                                                                                               |                                                                                                                                                               |
| For Partial Yes, must have assessed RoB from                                                                                                                                                                                                               |                                                                                                                               |                                                                                                                                                               |
| <input type="checkbox"/> unconcealed allocation, <i>and</i><br><input type="checkbox"/> lack of blinding of patients and assessors when assessing outcomes (unnecessary for objective outcomes such as all-cause mortality)                                | For Yes, must also have assessed RoB from:                                                                                    | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> Partial Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> Includes only NRSI |
| <input type="checkbox"/> allocation sequence that was not truly random, <i>and</i>                                                                                                                                                                         | <input type="checkbox"/> selection of the reported result from among multiple measurements or analyses of a specified outcome |                                                                                                                                                               |
| <b>NRSI</b>                                                                                                                                                                                                                                                |                                                                                                                               |                                                                                                                                                               |
| For Partial Yes, must have assessed RoB:                                                                                                                                                                                                                   |                                                                                                                               |                                                                                                                                                               |
| <input type="checkbox"/> from confounding, <i>and</i><br><input type="checkbox"/> from selection bias                                                                                                                                                      | For Yes, must also have assessed RoB:                                                                                         | <input type="checkbox"/> Yes<br><input type="checkbox"/> Partial Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> Includes only RCTs            |
| <input type="checkbox"/> methods used to ascertain exposures and outcomes, <i>and</i>                                                                                                                                                                      | <input type="checkbox"/> selection of the reported result from among multiple measurements or analyses of a specified outcome |                                                                                                                                                               |
| <b>10. Did the review authors report on the sources of funding for the studies included in the review?</b>                                                                                                                                                 |                                                                                                                               |                                                                                                                                                               |
| For Yes                                                                                                                                                                                                                                                    |                                                                                                                               |                                                                                                                                                               |
| <input type="checkbox"/> Must have reported on the sources of funding for individual studies included in the review. Note: Reporting that the reviewers looked for this information but it was not reported by study authors also qualifies                | <input type="checkbox"/> Yes<br><input checked="" type="checkbox"/> No                                                        |                                                                                                                                                               |

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**11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?**

**RCTs**

For Yes:

- |                                                                                                                                              |                                                     |
|----------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| <input type="checkbox"/> The authors justified combining the data in a meta-analysis                                                         | <input checked="" type="checkbox"/> Yes             |
| <input type="checkbox"/> AND they used an appropriate weighted technique to combine study results and adjusted for heterogeneity if present. | <input type="checkbox"/> No                         |
| <input type="checkbox"/> AND investigated the causes of any heterogeneity                                                                    | <input type="checkbox"/> No meta-analysis conducted |

**For NRSI**

For Yes:

- |                                                                                                                                                                                                                                           |                                                     |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| <input type="checkbox"/> The authors justified combining the data in a meta-analysis                                                                                                                                                      | <input type="checkbox"/> Yes                        |
| <input type="checkbox"/> AND they used an appropriate weighted technique to combine study results, adjusting for heterogeneity if present                                                                                                 | <input type="checkbox"/> No                         |
| <input type="checkbox"/> AND they statistically combined effect estimates from NRSI that were adjusted for confounding, rather than combining raw data, or justified combining raw data when adjusted effect estimates were not available | <input type="checkbox"/> No meta-analysis conducted |
| <input type="checkbox"/> AND they reported separate summary estimates for RCTs and NRSI separately when both were included in the review                                                                                                  |                                                     |

**12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?**

For Yes:

- |                                                                                                                                                                                                         |                                                     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| <input type="checkbox"/> included only low risk of bias RCTs                                                                                                                                            | <input type="checkbox"/> Yes                        |
| <input type="checkbox"/> OR, if the pooled estimate was based on RCTs and/or NRSI at variable RoB, the authors performed analyses to investigate possible impact of RoB on summary estimates of effect. | <input checked="" type="checkbox"/> No              |
|                                                                                                                                                                                                         | <input type="checkbox"/> No meta-analysis conducted |

**13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?**

For Yes:

- |                                                                                                                                                                   |                                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| <input type="checkbox"/> included only low risk of bias RCTs                                                                                                      | <input checked="" type="checkbox"/> Yes |
| <input type="checkbox"/> OR, if RCTs with moderate or high RoB, or NRSI were included the review provided a discussion of the likely impact of RoB on the results | <input type="checkbox"/> No             |

**14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?**

For Yes:

- |                                                                                                                                                                                                                         |                                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| <input type="checkbox"/> There was no significant heterogeneity in the results                                                                                                                                          |                                         |
| <input checked="" type="checkbox"/> OR if heterogeneity was present the authors performed an investigation of sources of any heterogeneity in the results and discussed the impact of this on the results of the review | <input checked="" type="checkbox"/> Yes |
|                                                                                                                                                                                                                         | <input type="checkbox"/> No             |

**15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?**

For Yes:

- |                                                                                                                                                                 |                                                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|
| <input type="checkbox"/> performed graphical or statistical tests for publication bias and discussed the likelihood and magnitude of impact of publication bias | <input checked="" type="checkbox"/> Yes             |
|                                                                                                                                                                 | <input type="checkbox"/> No                         |
|                                                                                                                                                                 | <input type="checkbox"/> No meta-analysis conducted |

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**16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?**

For Yes:

- ☐ The authors reported no competing interests OR
- ☐ The authors described their funding sources and how they managed potential conflicts of interest

☒ Yes  
☐ No

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