

# Utah Review: Clinical Studies: AMSTAR-2

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|-----------------------------------------------------------------|----------------|
| 1. PICO Components in Research Questions and Inclusion Criteria | No             |
| <b>2. Protocol and Deviations</b>                               | No             |
| 3. Study Design Selection                                       | Yes            |
| <b>4. Literature Search Strategy</b>                            | No             |
| 5. Study Selection in Duplicate                                 | Yes            |
| 6. Data Extraction in Duplicate                                 | No             |
| <b>7. Excluded Studies</b>                                      | Partial Yes    |
| 8. Description of Included Studies                              | Partial Yes    |
| <b>9. Assessed study-level ROB</b>                              | Partial Yes    |
| 10. Funding Sources of Included Studies                         | No             |
| <b>11. Meta-Analysis Methods</b>                                | Not applicable |
| 12. Impact of RoB on Meta-Analysis                              | Not applicable |
| <b>13. RoB Consideration in Interpretation</b>                  | No             |
| 14. Heterogeneity Explanation                                   | No             |
| <b>15. Publication Bias</b>                                     | No             |
| 16. Conflicts of Interest                                       | Yes            |

Critical domains are marked in **bold**.

Overall confidence in the systematic review:

**Critically low** (*lowest possible rating outcome*)

Rationale:

There are weaknesses in all but one critical domain (2, 4, 7, 11, 13, 15)

| AMSTAR-2 Item                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Utah Report                                                                                                                                                                                                                                                                                                                                                                                                                                     |
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| <p>1. PICO Components in Research Questions and Inclusion Criteria</p> <p>Did the research questions and inclusion criteria include the components of PICO?</p> <ul style="list-style-type: none"> <li>• Population</li> <li>• Intervention</li> <li>• Comparator group</li> <li>• Outcome</li> <li>• Timeframe for follow-up (optional/recommended)</li> </ul>                                                                                                                                                                                                                                                                            | <p>No</p> <p><i>The review does not present a clearly structured PICO-formulated research question. Key elements—Population, Intervention, Comparator, and Outcome—are not explicitly and systematically defined. Separate research questions should have been specified for puberty blockers (PBs) and cross-sex hormones (CSH).</i></p>                                                                                                       |
| <p>2. Protocol and Deviations</p> <p>Was there an explicit statement that review methods were established prior to the review, and were deviations justified?</p> <p>For Partial Yes (must include all):</p> <ul style="list-style-type: none"> <li>• Review question(s)</li> <li>• Search strategy</li> <li>• Inclusion/exclusion criteria</li> <li>• Risk of bias assessment</li> </ul> <p>For Yes (all of the above, plus):</p> <ul style="list-style-type: none"> <li>• Protocol registered</li> <li>• Meta-analysis/synthesis plan</li> <li>• Plan for investigating heterogeneity</li> <li>• Justification for deviations</li> </ul> | <p>No</p> <p><i>No protocol was identified. There are no clearly specified inclusion and exclusion criteria defining eligible study types. No pre-specified plan for evidence synthesis or quality of evidence assessment is described. The report also deviated from its stated approach in several areas, including data extraction, risk of bias assessment, and evidence synthesis, without justification.</i></p>                          |
| <p>3. Study Design Selection</p> <p>Did the authors explain their selection of study designs?</p> <ul style="list-style-type: none"> <li>• Explanation for including only RCTs</li> <li>• OR only NRSI</li> <li>• OR both RCTs and NRSI</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                         | <p>Yes</p>                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <p>4. Literature Search Strategy</p> <p>Was a comprehensive search strategy used?</p> <p>For Partial Yes (all required):</p> <ul style="list-style-type: none"> <li>• Searched ≥2 databases</li> <li>• Provided keywords/search strategy</li> <li>• Justified publication restrictions</li> </ul> <p>For Yes (all of the above, plus):</p> <ul style="list-style-type: none"> <li>• Searched reference lists</li> </ul>                                                                                                                                                                                                                    | <p>No</p> <p><i>Grey literature was not searched. The review did not search the websites of relevant public health authorities (e.g., NICE/NHS) for recent reviews or high-quality studies, and no justification was provided for this omission. The search was also outdated (conducted in March and June 2023, with ClinicalTrials.gov searched in September 2023), with no indication that more recent publications were considered.</i></p> |

| AMSTAR-2 Item                                                                                                                                                                                                                                                                                            | Utah Report                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
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| <ul style="list-style-type: none"> <li>Searched trial/study registries</li> <li>Consulted content experts</li> <li>Searched grey literature</li> <li>Search conducted within 24 months of review completion</li> </ul>                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <p>5. Study Selection in Duplicate<br/>Was study selection performed in duplicate?</p> <ul style="list-style-type: none"> <li>Two reviewers independently selected studies and reached consensus</li> <li>OR sample reviewed with <math>\geq 80\%</math> agreement, remainder by one reviewer</li> </ul> | Yes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <p>6. Data Extraction in Duplicate<br/>Was data extraction performed in duplicate?</p> <ul style="list-style-type: none"> <li>Two reviewers reached consensus</li> <li>OR sample reviewed with <math>\geq 80\%</math> agreement, remainder by one reviewer</li> </ul>                                    | <p>No</p> <p><i>Dual screening and resolution of discrepancies reduces bias risk. This review did not properly extract information from primary studies. The authors reported: "We included all eligible case reports and case series if they addressed the population and interventions of interest. Initially we had planned to extract data for all descriptive study designs, including case reports that contained a statement about IRB (or other ethics board) review and approval/exemption, or specified that informed consent was obtained from study subjects ... However, due to time constraints and the number of relevant publications, only longitudinal, pre-post descriptive studies underwent data collection." Only 90 studies were extracted for research or publication in Part I and 17 studies in Part II.</i></p> |
| <p>7. Excluded Studies<br/>Did authors provide and justify a list of excluded studies?</p> <ul style="list-style-type: none"> <li>List of full-text excluded studies</li> <li>Justification for each exclusion</li> </ul>                                                                                | <p>Partial Yes</p> <p><i>Appendix I.C lists excluded studies by criterion. However, in Part I the authors refer to 134 primary clinical studies at one point and 230 at another, without clarification. It is unclear whether the 230 studies correspond to the 219 studies described in Tables I.8–I.11, Table I.G, and the bibliography. Of these primary included studies, only 90 underwent both data extraction and risk of bias assessment following full-text screening.</i></p>                                                                                                                                                                                                                                                                                                                                                    |

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| <p>8. Description of Included Studies</p> <p>Were included studies described in adequate detail?</p> <p>For Partial Yes (all required):</p> <ul style="list-style-type: none"> <li>• Populations</li> <li>• Interventions</li> <li>• Comparators</li> <li>• Outcomes</li> <li>• Research designs</li> </ul> <p>For Yes (all of the above, plus):</p> <ul style="list-style-type: none"> <li>• Detailed population</li> <li>• Detailed intervention/comparator (incl. doses)</li> <li>• Study setting</li> <li>• Follow-up timeframe</li> </ul>                                                                                                                                      | <p>Partial Yes</p> <p><i>The review extensively redacts information that is already publicly available in the original publications, including study locations, years, and patient characteristics.</i></p>                                                                                                                                                   |
| <p>9. Risk of Bias (RoB) Assessment</p> <p>Was a satisfactory RoB technique used?</p> <p>For RCTs:</p> <p>Partial Yes:</p> <ul style="list-style-type: none"> <li>• Unconcealed allocation</li> <li>• Lack of blinding (if relevant)</li> </ul> <p>Yes (all of the above, plus):</p> <ul style="list-style-type: none"> <li>• Non-random allocation</li> <li>• Selective reporting</li> </ul> <p>For NRSI:</p> <p>Partial Yes:</p> <ul style="list-style-type: none"> <li>• Confounding</li> <li>• Selection bias</li> </ul> <p>Yes (all of the above, plus):</p> <ul style="list-style-type: none"> <li>• Exposure/outcome ascertainment</li> <li>• Selective reporting</li> </ul> | <p>Partial Yes</p> <p><i>For primary studies, the authors used the Newcastle-Ottawa Scale for cohort, case-control, and cross-sectional studies, and the NIH Quality Assessment Tool for Before-After studies. There are clear mistakes in the risk of bias assessments, and the review appears more lenient than a rigorous appraisal would warrant.</i></p> |
| <p>10. Funding Sources of Included Studies</p> <p>Did authors report funding sources for included studies?</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <p>No</p> <p><i>Funding not reported</i></p>                                                                                                                                                                                                                                                                                                                  |

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| <p><b>11. Meta-Analysis Methods</b><br/> If meta-analysis was performed, were appropriate methods used?<br/> For RCTs:</p> <ul style="list-style-type: none"> <li>• Justified combining data</li> <li>• Used appropriate weighting</li> <li>• djusted for heterogeneity</li> </ul> <p>For NRSI:</p> <ul style="list-style-type: none"> <li>• Justified combining data</li> <li>• Used appropriate weighting</li> <li>• Adjusted for confounding</li> <li>• Reported separate estimates for RCTs and NRSI</li> </ul> | <p><b>Not applicable</b><br/> No meta-analysis conducted</p>                              |
| <p><b>12. RoB Consideration in Interpretation</b><br/> Was the impact of RoB on meta-analysis assessed?</p> <ul style="list-style-type: none"> <li>• Included only low RoB RCTs</li> <li>• OR analyzed impact of RoB on summary estimates</li> </ul>                                                                                                                                                                                                                                                                | <p><b>Not applicable</b><br/> <i>No meta-analysis conducted</i></p>                       |
| <p><b>13. RoB Consideration in Interpretation</b><br/> Did authors account for RoB in interpreting results?</p> <ul style="list-style-type: none"> <li>• Included only low RoB RCTs</li> <li>• OR discussed impact of RoB</li> </ul>                                                                                                                                                                                                                                                                                | <p><b>No</b><br/> <i>Risk of bias not considered in any way in evidence synthesis</i></p> |
| <p><b>14. Heterogeneity Explanation</b><br/> Was heterogeneity explained and discussed?</p> <ul style="list-style-type: none"> <li>• No significant heterogeneity</li> <li>• OR investigated and discussed sources of heterogeneity</li> </ul>                                                                                                                                                                                                                                                                      | <p><b>No</b><br/> <i>Heterogeneity not considered</i></p>                                 |
| <p><b>15. Publication Bias</b><br/> Was publication bias assessed and discussed?</p> <ul style="list-style-type: none"> <li>• Graphical/statistical tests performed</li> <li>• Discussed likelihood and impact</li> </ul>                                                                                                                                                                                                                                                                                           | <p><b>No</b><br/> <i>Publication bias not assessed or discussed</i></p>                   |
| <p><b>16. Conflicts of Interest</b><br/> Did authors report potential conflicts of interest?</p> <ul style="list-style-type: none"> <li>• No competing interests reported</li> <li>• OR funding sources and conflict management described</li> </ul>                                                                                                                                                                                                                                                                | <p><b>Yes</b></p>                                                                         |