Revised Cochrane risk-of-bias tool for randomized crossover trials

TEMPLATE FOR COMPLETION

**Version of 18 March 2021**

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| **Study details**   |  |  | | --- | --- | | **Reference** | Tjepkema-Cloostermans 2016 |   **Study design**   |  |  | | --- | --- | | □ | Individually-randomized parallel-group trial | | □ | Cluster-randomized parallel-group trial | | X | Individually randomized cross-over (or other matched) trial |   **For the purposes of this assessment, the interventions being compared are defined as**   |  |  |  |  | | --- | --- | --- | --- | | Experimental: | Burst SCS | Comparator: | sham |  |  |  | | --- | --- | | **Specify which outcome is being assessed for risk of bias** | Pain, continuous, short term |  |  |  | | --- | --- | | **Specify the numerical result being assessed.** In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed. | -2 (-15.90, 11.90) |   **Is the review team’s aim for this result…?**   |  |  | | --- | --- | | 🞪 | to assess the effect of *assignment to intervention* (the ‘intention-to-treat’ effect) | | □ | to assess the effect of *adhering to intervention* (the ‘per-protocol’ effect) |   **If the aim is to assess the effect of *adhering to intervention***, select the deviations from intended intervention that should be addressed (at least one must be checked):  □ occurrence of non-protocol interventions  □ failures in implementing the intervention that could have affected the outcome  □ non-adherence to their assigned intervention by trial participants  **Which of the following sources were obtained to help inform the risk-of-bias assessment? (tick as many as apply)**  🞪 Journal article(s) with results of the trial  □ Trial protocol  □ Statistical analysis plan (SAP)  🞪 Non-commercial trial registry record (e.g. ClinicalTrials.gov record)  □ Company-owned trial registry record (e.g. GSK Clinical Study Register record)  □ “Grey literature” (e.g. unpublished thesis)  □ Conference abstract(s) about the trial  □ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)  □ Research ethics application  □ Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)  □ Personal communication with trialist  □ Personal communication with the sponsor |

## Risk of bias assessment

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

**Domain 1a: Risk of bias arising from the randomization process**

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| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **1.1 Was the allocation sequence random?** | No information of method provided beyond the word "randomized" | NI |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | NI |
| **1.3 Did baseline differences between intervention groups at the start of the first period suggest a problem with the randomization process?** | No baseline data presented by condition or phase | NI |
| **Risk-of-bias judgement** |  | Some concerns |
| Optional: What is the predicted direction of bias arising from the randomization process? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

**Domain S: Risk of bias arising from period and carryover effects**

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| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **S.1 Was the number of participants allocated to each of the two sequences equal or nearly equal?** | Information not provided | NI |
| **S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?** | “The results are checked for period effects as a period affect was found in a previous study evaluating high frequency stimulation (8). The period effect is evaluated by comparing the difference in VAS scores for pain during high and low amplitude burst stimulation (VAS high burst2VAS low burst) from patients who first receive low amplitude burst stimulation (group A) with the scores from patients from who first receive high amplitude burst stimulation (group B). This comparison is done by using a Mann–Whitney U test. The potential period effect on patient’s preference was evaluated by using a  Chi-squared test. If there is no statistically significant difference  between both groups in the difference in VAS score and patient’s  preference, it is assumed that there is no period effect, and all patients  are grouped for further analysis regardless of their study arm(A or B).”  Note: statistical significance not an optimal threshold for ruling out potential period effects | PY |
| **S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?** | No real washout period as tonic SCS used as washout | N |
| **Risk-of-bias judgement** |  | High |
| Optional: What is the predicted direction of bias arising from period and carryover effects? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

**Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)**

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| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **2.1. Were participants aware of their assigned intervention during each period of the trial?** | While burst stimulation is likely subperceptual there was no formal evaluation of blinding success.  No mention of clinical/ study personnel blinding. | PY |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during each period of the trial?** | PY |
| **2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?** | No information reported | NI |
| **2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?** |  | NA |
| **2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?** |  | NA |
| **2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?** | Not clear if there were deviations or how managed in the analysis | NI |
| **2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?** |  | NI |
| **Risk-of-bias judgement** | Potential for adequate blinding as stimulation subthreshold but this was not formally evaluated. | Some concerns |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

**Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)**

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| **Signalling questions** | **Comments** | **Response options** |
| **2.1. Were participants aware of their assigned intervention during each period of the trial?** |  | Y / PY / PN / N / NI |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during each period of the trial?** | Y / PY / PN / N / NI |
| **2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced between interventions?** |  | NA / Y / PY / PN / N / NI |
| **2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?** |  | NA / Y / PY / PN / N / NI |
| **2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants’ outcomes?** |  | NA / Y / PY / PN / N / NI |
| **2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?** |  | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low / High / Some concerns |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

**Domain 3: Risk of bias due to missing outcome data**

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| **Signalling questions** | **Comments** | **Response options** |
| **3.1 Were data for this outcome available for all, or nearly all, participants randomized?** | 1 participant withdrew post randomisation | Y |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** |  | NA |
| **3.3 If N/PN to 3.2 Could missingness in the outcome depend on its true value?** |  | NA |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | NA |
| **Risk-of-bias judgement** |  | Low |
| Optional: What is the predicted direction of bias due to missing outcome data? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

**Domain 4: Risk of bias in measurement of the outcome**

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| **Signalling questions** | **Comments** | **Response options** |
| **4.1 Was the method of measuring the outcome inappropriate?** | Pain measured using validated scales | N |
| **4.2 Could measurement or ascertainment of the outcome have differed between interventions within each sequence?** | No reason to think it did. | PN |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** | While burst stimulation likely subperceptual there is no formal evaluation of blinding success | PY |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?** | Subjective self-reported outcome. But as burst stimulation is likely subperceptual there is a good chance that blinding may have been successful. No discussion of clinician blinding. | Y |
| **4.5 If Y/PY/NI to 4.4:** **Is it likely that assessment of the outcome was influenced by knowledge of intervention received?** | PN |
| **Risk-of-bias judgement** |  | Some concerns |
| Optional: What is the predicted direction of bias in measurement of the outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

**Domain 5: Risk of bias in selection of the reported result**

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| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?** | No protocol or SAP available | NI |
| **Is the numerical result being assessed likely to have been selected, on the basis of the results, from...** |  |  |
| **5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?** | Outcomes consistent with registry record BUT Trial registry reports VAS is primary outcome but published report demonstrates potential for selection "During all phases of the study, patients were requested to fill in a pain diary, including as VAS scores (on a scale of 0–100) for pain in their back, legs, and feet separately. The average VAS scores for pain during the last three days of each stimulation period (tonic at baseline, low amplitude burst, and high amplitude burst) were used to assess the pain score for that period, thereby the score of the most affected body part, defined as the body part with the highest VAS score at baseline during tonic stimulation, was used." | PY |
| **5.3 ... multiple eligible analyses of the data?** | No SAP or protocol available | NI |
| **5.4 Is a result based on data from both periods sought, but unavailable on the basis of carryover having been identified?** |  | N |
| **Risk-of-bias judgement** |  | Some concerns |
| Optional: What is the predicted direction of bias due to selection of the reported result? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Overall risk of bias

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| --- | --- | --- |
| **Risk-of-bias judgement** |  | High |
| Optional: What is the overall predicted direction of bias for this outcome? |  | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |



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