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

TEMPLATE FOR COMPLETION

**Version of 18 March 2021**

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](http://creativecommons.org/licenses/by-nc-nd/4.0/).

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study details**

|  |  |
| --- | --- |
| **Reference** | Sokal 2020 |

**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: | Conventional 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. | -12.40 (-29.54, 4.74) |

**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**

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **1.1 Was the allocation sequence random?** | "Randomisation was performed by drawing notes with the name of the modality or treatment arm (i.e., LF tonic, 1kHz, clustered tonic, sham) by an independent examiner. At the next meeting (after two weeks), the selection of notes with names of modalities was modified by the notes that were previously chosen."Note: Method prone to bias and concealment processes not really clear. | PN  |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | PN |
| **1.3 Did baseline differences between intervention groups at the start of the first period suggest a problem with the randomization process?** | Baseline data not presented by phase/ condition | NI |
| **Risk-of-bias judgement** |  | High  |
| 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**

|  |  |  |
| --- | --- | --- |
| **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 reported | NI |
| **S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?** | No clear accounting for period effects | PN |
| **S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?** | No washout period employed | PN |
| **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)**

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **2.1. Were participants aware of their assigned intervention during each period of the trial?** | Conventional stimulation is suprathreshold and the resulting sensations prevent proper blinding compared to sham. | 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?** |  | 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?** | No clear information on deviations and how analysed | 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** | ? could go some concerns here – don’t appear to be any exclusions | High |
| 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)**

|  |  |  |
| --- | --- | --- |
| **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**

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **3.1 Were data for this outcome available for all, or nearly all, participants randomized?** |  No post randomisation exclusions reported | 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**

|  |  |  |
| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **4.1 Was the method of measuring the outcome inappropriate?** | Pain measured using recognised scales | PN  |
| **4.2 Could measurement or ascertainment of the outcome have differed between interventions within each sequence?** | No reason to think this. | PN  |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** | Conventional stimulation likely suprathreshold and not blinded, no formal evaluation of blinding | 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 and an unblinded comparison | 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?** | PY  |
| **Risk-of-bias judgement** |  | High  |
| 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**

|  |  |  |
| --- | --- | --- |
| **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 published protocol or SAP. Registry documents suggest 1 year follow up which does not make sense in the context of this study. | 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?** |  | NI |
| **5.3 ... multiple eligible analyses of the data?** |  | 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

|  |  |  |
| --- | --- | --- |
| **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 |



This work is licensed under a [Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License](http://creativecommons.org/licenses/by-nc-nd/4.0/).