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** | Perruchoud 2013 |   **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: | HF-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. | -0.90, (-9.16, 7.35) |   **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record)  □ Company-owned trial registry record (e.g. GSK Clinical Study Register record)  □ “Grey literature” (e.g. unpublished thesis)  □ Conference abstract(s) about the trial  □ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)  □ Research ethics application  □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?** | "Subjects were randomized at baseline to receive either HFSCS or no stimulation (sham) using a central randomization service." | 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 group or condition | 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 reported | NI |
| **S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?** | “Pain VAS and EQ-5D index values were analyzed using a conventional within-subjects model, accounting for the “period effect” and utilizing the baseline scores before each treatment (visits 2 and 4) in an analysis of covariance model (regarded as the most efficient  model).” | Y |
| **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)**

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| --- | --- | --- |
| **Signalling questions** | **Comments** | **Response options** |
| **2.1. Were participants aware of their assigned intervention during each period of the trial?** | "A major priority of this study was to ensure proper blinding as the paresthesia-free stimulation (HFSCS) would, for the first time ever, allow a comparison with true sham conditions, i.e., the absence of stimulation. We took every precaution to conceal the nature of the treatment applied and research teams were split into two groups of blinded and unblinded personnel with no crossover, and only personnel blinded to the therapy collected outcome data from the patients. In patients with rechargeable devices, we have programmed the IPG to have a current leakage in the sham period to mirror the current usage during HFSCS period. This maintained the requirement for identical recharging times whether sham or HFSCS was delivered. Results show that blinding was successful as four out of eight patients responding favorably to sham treatment at visit 3 indicated that they thought they were on sham and the other four that they had received HFSCS”  “teams were divided into unblinded clinical care teams who did the programming and instructed the patients and the blinded observers who collected the study outcome measures with no input into the patient care” | PN |
| **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?** | Per protocol analysis. | N |
| **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** |  | 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)**

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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?** | 5/38 (13%) excluded post randomisation. all appear to have had device issues | N |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** | Per protocol analysis without sensitivity analysis | N |
| **3.3 If N/PN to 3.2 Could missingness in the outcome depend on its true value?** | All exclusions appear to have been due to device issues | Y |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | PY |
| **Risk-of-bias judgement** | High | High |
| 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?** | Validated scale used | N |
| **4.2 Could measurement or ascertainment of the outcome have differed between interventions within each sequence?** | Assessors blinded (participants and staff). Formal assessment of blinding suggests success | N |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** | Assessors blinded (participants and staff) | N |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?** |  | NA |
| **4.5 If Y/PY/NI to 4.4:** **Is it likely that assessment of the outcome was influenced by knowledge of intervention received?** | NA |
| **Risk-of-bias judgement** |  | Low |
| 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 | PN |
| **5.3 ... multiple eligible analyses of the data?** | No SAP 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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