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** | Al-Kaisy 2018 |   **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: | SCS 3030 Hz | Comparator: | sham |  |  |  | | --- | --- | | **Specify which outcome is being assessed for risk of bias** | Pain intensity 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. | MD -2.60 (-24.92, 19.72) |   **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record)  □ Company-owned trial registry record (e.g. GSK Clinical Study Register record)  □ “Grey literature” (e.g. unpublished thesis)  🞪 Conference abstract(s) about the trial  □ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)  □ Research ethics application  □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?** | "randomization scheme was generated by the sponsor for the study that allocated subjects in a 1:1:1:1 fashion to each of the 4 different frequency/pulse width settings (sham, 1200 Hz @ 180 lsec, 3030 Hz @ 60 lsec, and 5882 Hz @ 30 lsec). There were a total of 24 unique sequences of those four frequency groups. The site received a box of envelopes, with each envelope containing a randomization sequence. Randomization sequences were assigned in sequential order until each unique sequence was distributed."  Note precise method of randomisation not reported. Randomisation sequences were assigned in sequential order until each unique sequence was distributed. | PY |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | PY |
| **1.3 Did baseline differences between intervention groups at the start of the first period suggest a problem with the randomization process?** | No baseline scores presented for primary outcome by group. | NI |
| **Risk-of-bias judgement** |  | Low |
| 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?** | “allocated subjects in a 1:1:1:1 fashion” | PY |
| **S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?** | "The treatment by period interaction term, carryover effect, was tested and removed from the final model as being not statistically significant." Question as to whether statistical significance is a good reason to exclude from the model. | PY |
| **S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?** | No washout period was employed. No formal analysis of carryover effects and baseline scores not presented for each stimulation condition. | 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?** | "All study subjects and all site personnel treating and administering questionnaires to subjects, including the principal investigator, were blinded to the order of the frequencies being tested and to the frequency being used to treat subjects during the long-term follow-up period. The efficacy of the blinding process was not formally tested. Two members of the local research team were unblinded to the frequencies being tested to perform the programming. These unblinded personnel were not involved in any other study procedures (including collecting outcome data). Two databases were used to store blinded and unblinded data separately."  No formal assessment of 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 clear evidence of deviations. | NI |
| **2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?** | No clear evidence of deviations. | NA |
| **2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?** | No clear evidence of deviations. | 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?** | 20% post randomisation exclusions and the crossover phase they occurred in not clear. | PY |
| **Risk-of-bias judgement** | High | 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?** | 6 (20%) of participants excluded post randomisation. “due to early discontinuations, deviations associated with randomization and programming affecting the ability to evaluate subjects’ data, and lack of device use”. | N |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** | Analysis excludes post randomisation exclusions | N |
| **3.3 If N/PN to 3.2 Could missingness in the outcome depend on its true value?** | “(due to early discontinuations, deviations associated with randomization and programming affecting the ability to evaluate subjects’ data, and lack of device use)”  Some of these are related to the intervention itself and thus likely related to the true value. | 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?** | Pain measured using recognised scales | N |
| **4.2 Could measurement or ascertainment of the outcome have differed between interventions within each sequence?** | No reason to think this. | N |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** | While assessors reported as blinded, no formal assessment 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 threats to adequate blinding in this condition. | 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** | As subthreshold and no recharging issues there is greater potential for successful blinding, though not formally evaluated | 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 match those in trial registry | PN |
| **5.3 ... multiple eligible analyses of the data?** | No indication of selectivity, though decision taken not to adjust for carryover effects on the basis of statistical significance. | NI |
| **5.4 Is a result based on data from both periods sought, but unavailable on the basis of carryover having been identified?** | Test for carryover included but removed from final model as not statistically significant; data from all phases amalgamated and reported” | PN |
| **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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