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

TEMPLATE FOR COMPLETION

**Version of 18 March 2021**

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| **Study details**

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| **Reference** | Kriek 2017 |

**Study design**

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| □ | 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**

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| Experimental: | HF- SCS | Comparator: | sham |

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| **Specify which outcome is being assessed for risk of bias** | Pain Intensity, continuous, short term |

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| **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. | -20.80 (-40.99, -0.61) |

**Is the review team’s aim for this result…?**

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| 🞪 | 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record)□ Company-owned trial registry record (e.g. GSK Clinical Study Register record)□ “Grey literature” (e.g. unpublished thesis)□ Conference abstract(s) about the trial□ Regulatory document (e.g. Clinical Study Report, Drug Approval Package)□ Research ethics application□ Grant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 was performed with a computer based program at the beginning of the trial and no blocks were used since this is not viable in our study design. In our study design all patients in the crossover will be subjected to all five stimulation modalities in random order, resulting in 5! (120) different orders in which the stimulation modalities can be programmed. Only 48 (the required sample size) of these 120 potential different orders are selected at random by the computer to be used. The specific order of the programming for an individual patient is revealed to the local SCS programmer only during each of the five crossover periods. " | Y  |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | Y  |
| **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 condition or phase. | 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?** | Limited information but likely equal. | NI |
| **S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?** | No report of period effects accounted for | PN |
| **S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?** | Washout period employed. NB: Only 2 days duration. "However, the significantly increased NRS pain scores found during the washout periods indicate that there was no carryover effect in terms of lingering pain reduction or a metaplasticity (priming-like) effect." NO ACTUAL DATA | 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?** | HF stimulation likely subperceptual but no formal evaluation of blinding conducted | 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?** | 4 participants discontinued cross-over, 2 due to lead dislocation, 1 by request due to pain increase and one as moved away. Not clearly beyond what might be expected in practice but not reported by phase | 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 employed with 12% post randomisation exclusions | 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?** |  | PY  |
| **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?** |  4 (12%) discontinued and excluded from the analysis | N |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** | No information as to which phases/ conditions the withdrawals occurred | N |
| **3.3 If N/PN to 3.2 Could missingness in the outcome depend on its true value?** | 4 participants discontinued cross-over, 2 due to lead dislocation, 1 by request due to pain increase and one as moved away. | Y  |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | Y  |
| **Risk-of-bias judgement** |  | 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 validated scales | N  |
| **4.2 Could measurement or ascertainment of the outcome have differed between interventions within each sequence?** |  | 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 stimulation likely subperceptual no formal evaluation of blinding was reported. | PY  |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?** | As stimulation subthreshold there is potential for successful blinding but it was not formally evaluated | PY |
| **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 SAP but outcomes and analysis seem consistent with published protocol | PY  |
| **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?** |  | PN  |
| **5.3 ... multiple eligible analyses of the data?** |  | PN |
| **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** |  | Low  |
| 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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