Supplementary Material

Inhaled therapies targeting prostacyclin pathway in pulmonary hypertension due to COPD: systematic review

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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** | Boeck L, Tamm M, Grendelmeier P, Stolz D (2012) Acute Effects of Aerosolized Iloprost in COPD Related Pulmonary Hypertension - A Randomized Controlled Crossover Trial. PLoS ONE 7(12): e52248. doi:10.1371/journal.pone.0052248 |

**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**

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| Experimental: | Aerosolized Iloprost | Comparator: | placebo |

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| **Specify which outcome is being assessed for risk of bias** | six-minute walking distance, dyspnoea, and Peak oxygen consumption |

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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. | Figure 2 and table 3 |

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

|  |  |
| --- | --- |
| X | 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)**X Journal article(s) with results of the trialX Trial protocolX 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?** | Formulas for inhalation were randomized by an automated computer-generated randomization scheme and assigned to specific study days.. | 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?** | It is not clear | NI |
| **Risk-of-bias judgement** | Low risk of bias in terms of randomization process | Low  |
| Optional: What is the predicted direction of bias arising from the randomization process? | NA | 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?** | It is crossover study | Y |
| **S.2 If N/PN/NI to S.1: Were period effects accounted for in the analysis?** |  | NA/Y/PY/PN/N/NI |
| **S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?** | Yes | Y |
| **Risk-of-bias judgement** | Low risk in terms of bias arising from period and carryover effects | Low  |
| Optional: What is the predicted direction of bias arising from period and carryover effects? | NA | 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?** | The patient as well as the study personnel, who administered the inhalation and performed all tests, was blinded to the medication allocation. A nurse and a physician, responsible for preparation of the medication, were the only persons aware of the randomization code during the trial. They were not involved in other study functions | N  |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during each period of the trial?** | N  |
| **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?** |  | NA / Y / PY / PN / N / NI |
| **2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?** |  | NA / Y / PY / PN / N / NI |
| **2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?**  |  | NA / Y / PY / PN / N / NI |
| **2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?** | Power was calculated using the 6MWT distance before and after treatment as the primary outcome variable.  | Y  |
| **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?** |  | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** |  | Low  |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? | NA | 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?** | The patient as well as the study personnel, who administered the inhalation and performed all tests, was blinded to the medication allocation. A nurse and a physician, responsible for preparation of the medication, were the only persons aware of the randomization code during the trial. They were not involved in other study functions. | N  |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during each period of the trial?** | N  |
| **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?** | Nothing has been mentioned regarding this | N  |
| **2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants’ outcomes?** | Nothing has been mentioned regarding this | N  |
| **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 | Low  |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? | NA | 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?** | Yes: Data were available for primary outcome for all participants randomized | Y  |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** |  | NA / Y / PY / PN / N |
| **3.3 If N/PN to 3.2 Could missingness in the outcome depend on its true value?** |  | NA / Y / PY / PN / N / NI |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | NA / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** | Low | Low  |
| Optional: What is the predicted direction of bias due to missing outcome data? | NA | 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?** | Exercise capacity (primary outcome) was assessed using 6MWT which is considered as appropriate method. | N  |
| **4.2 Could measurement or ascertainment of the outcome have differed between interventions within each sequence?** | No differences were noticed  | N  |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** |  | NA / Y / PY / PN / N / NI |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?** |  | NA / Y / PY / PN / N / NI |
| **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 / Y / PY / PN / N / NI |
| **Risk-of-bias judgement** | Low risk of bias | Low  |
| Optional: What is the predicted direction of bias in measurement of the outcome? | NA | 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?** | None | Y  |
| **Is the numerical result being assessed likely to have been selected, on the basis of the results, from...** | None |  |
| **5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?** | None | N |
| **5.3 ... multiple eligible analyses of the data?** | None | N  |
| **5.4 Is a result based on data from both periods sought, but unavailable on the basis of carryover having been identified?** | None | N  |
| **Risk-of-bias judgement** | Low | Low  |
| Optional: What is the predicted direction of bias due to selection of the reported result? | NA | NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

Overall risk of bias

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



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The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**



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# ROBINS-I tool (Stage I): At protocol stage

## Title of the study: The safety and tolerability of inhaled treprostinil in patients with pulmonary hypertension and chronic obstructive pulmonary disease

## Specify the review question

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| --- | --- |
| Participants | Patients with Pulmonary Hypertension and Chronic Obstructive Pulmonary Disease |
| Experimental intervention | inhaled Treprostinil sodium |
| Comparator | Baseline  |
| Outcomes | Primary aim was to explore the impact of inhaled Treprostinil sodium inhalation on gas exchange when used in PH with COPD patients by measuring ABG at both the beginning and end of study. Secondary aims included the effects of inhaled Treprostinil sodium on COPD-related quality of life, 6MWT, PFT, WHO FC, and the modified Borg dyspnea score at the end of the 6MWT |

## List the confounding domains relevant to all or most studies

|  |
| --- |
| Smoking, age, gender, and body mass index  |

## List co-interventions that could be different between intervention groups and that could impact on outcomes

|  |
| --- |
| Drugs that target nitric oxide, endothelin pathway and other pulmonary vasodilators  |

# ROBINS-I tool (Stage II): For each study

## Specify a target randomized trial specific to the study

|  |  |
| --- | --- |
| Design | Individually randomized / Cluster randomized / Matched (e.g. cross-over) |
| Participants | Patients with Pulmonary Hypertension and Chronic Obstructive Pulmonary Disease |
| Experimental intervention | inhaled treprostinil sodium |
| Comparator | Baseline  |

## Is your aim for this study…?

|  |  |
| --- | --- |
| □ | to assess the effect of *assignment to* intervention |
| □ | to assess the effect of *starting and adhering to* intervention |

## Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

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| --- |
| gas exchange, quality of life, 6MWT, PFT, WHO FC, and the modified Borg dyspnea score |

## 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.

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| Figures 1 and 2: Tables 2 and 3 |

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

#### “Important” confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. “Validity” refers to whether the confounding variable or variables fully measure the domain, while “reliability” refers to the precision of the measurement (more measurement error means less reliability).

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| **(i) Confounding domains listed in the review protocol** |
| Confounding domain | Measured variable(s)  | Is there evidence that controlling for this variable was unnecessary?\* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Smoking status | gas exchange, quality of life, 6MWT, PFT, WHO FC, and the modified Borg dyspnea score | Yes: This is before and after study design. The effect of the intervention was compared with baseline. In addition, it is assumed that most patients with COPD are either smokers or ex-smokers  | Yes / No / No information | Favour experimental / Favour comparator / No information |
| body mass index | gas exchange, quality of life, 6MWT, PFT, WHO FC, and the modified Borg dyspnea score | Yes: This is before and after study design. The effect of the intervention was compared with baseline  |  |  |
| Age and gender | gas exchange, quality of life, 6MWT, PFT, WHO FC, and the modified Borg dyspnea score | Yes: This is before and after study design. The effect of the intervention was compared with baseline  |  |  |

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| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** |
| Confounding domain | Measured variable(s)  | Is there evidence that controlling for this variable was unnecessary?\* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
|  |  |  | Yes / No / No information | Favour experimental / Favour comparator / No information |
| Same as above |  |

\* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii)

relevant to the setting of this particular study, or which the study authors identified as important.

#### “Important” co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.

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| **(i) Co-interventions listed in the review protocol** |
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Drugs that target nitric oxide pathway | Yes: it was not administered | Favour experimental / Favour comparator / No information |
| Drugs that target endothelin pathway  | Yes: it was not administered | Favour experimental / Favour comparator / No information |
| Other pulmonary vasodilators  | Yes: it was not administered | Favour experimental / Favour comparator / No information |

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| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** |
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Same as above | Favour experimental / Favour comparator / No information |

## 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.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Signalling questions** | **Response options** | **Response options** |
| **Bias due to confounding** |
|  | 1.1 Is there potential for confounding of the effect of intervention in this study?**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | N. No: This is before and after study design. The effect of the intervention was compared with baseline. | N |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: |  |  |
| 1.2. Was the analysis based on splitting participants’ follow up time according to intervention received?**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3. |  | NA / Y / PY / PN / N / NI |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)  |  | NA / Y / PY / PN / N / NI |

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| --- | --- |
|  | **Questions relating to baseline confounding only** |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? |  | NA / Y / PY / PN / N / NI |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? |  | NA / Y / PY / PN / N / NI |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? |  | NA / Y / PY / PN / N / NI |
|  | **Questions relating to baseline and time-varying confounding** |  |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? |  | NA / Y / PY / PN / N / NI |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? |  | NA / Y / PY / PN / N / NI |
|  | **Risk of bias judgement** |  | Low  |
| Optional: What is the predicted direction of bias due to confounding? |  | Favours experimental / Favours comparator / Unpredictable |

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| **Bias in selection of participants into the study** |
|  | 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?**If N/PN to 2.1:** go to 2.4 | N. NO: The selection was based on the confirmed diagnosis of pulmonary hypertension before the start of the study.  | N  |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention?2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? |  | NA / Y / PY / PN / N / NINA / Y / PY / PN / N / NI |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | Y. Yes, start of follow-up and start of administration of iloprost coincide for all patients | Y  |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? |  | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** |  | Low  |
| Optional: What is the predicted direction of bias due to selection of participants into the study? |  | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

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| **Bias in classification of interventions**  |
|  | 3.1 Were intervention groups clearly defined?  | NI. Only one group (before and after study design)  | NI |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | PY. Again, this is before and after study design. However, before the start of the study intervention is clearly defined.  | PY  |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | PN | PN  |
| **Risk of bias judgement** |  | Low  |
| Optional: What is the predicted direction of bias due to classification of interventions? |  | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

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| **Bias due to deviations from intended interventions** |
|  | **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** |  |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | PN | PN  |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? |  | NA / Y / PY / PN / N / NI |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** |  |
| 4.3. Were important co-interventions balanced across intervention groups? |  | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? |  | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? |  | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? |  | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** |  | Low  |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? |  | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

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| **Bias due to missing data** |
|  | 5.1 Were outcome data available for all, or nearly all, participants? | PY. outcome data are available for nearly all | PY  |
| 5.2 Were participants excluded due to missing data on intervention status? | N. No patients were excluded due to data missing | N  |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | N | N  |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? |  | NA / Y / PY / PN / N / NI |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? |  | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** |  | Low  |
| Optional: What is the predicted direction of bias due to missing data? |  | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

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| **Bias in measurement of outcomes**  |
|  | 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | PN: This is unlikely: some of the measurements were taken invasively | PN  |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | NI | NI |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | Y | Y  |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | N | N  |
| **Risk of bias judgement** |  | Low  |
| Optional: What is the predicted direction of bias due to measurement of outcomes? |  | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

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| **Bias in selection of the reported result** |
|  | Is the reported effect estimate likely to be selected, on the basis of the results, from... | PN |  |
| 7.1. ... multiple outcome *measurements* within the outcome domain?  |  | PN  |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? | PN | PN  |
| 7.3 ... different *subgroups*? | PY | PY |
| **Risk of bias judgement** |  | Medium  |
| Optional: What is the predicted direction of bias due to selection of the reported result? | Unpredictable | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

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



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The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**



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# ROBINS-I tool (Stage I): At protocol stage

## hemodynamic and gas exchange effects of inhaled iloprost in patients with COPD and pulmonary hypertension

## Specify the review question

|  |  |
| --- | --- |
| Participants | Patients with Pulmonary Hypertension and Chronic Obstructive Pulmonary Disease |
| Experimental intervention | Iloprost |
| Comparator | Baseline  |
| Outcomes | Primary outcome: Hemodynamic index (PVR, PAWP, mPAP, RAP, CIx, CO and MAP): Secondary outcomes: Gas exchange (PaO2, PaCO2, SaO2, DA-a O2 and Qs/Qt). |

## List the confounding domains relevant to all or most studies

|  |
| --- |
| Smoking, age, gender, and body mass index  |

## List co-interventions that could be different between intervention groups and that could impact on outcomes

|  |
| --- |
| Drugs that target nitric oxide, endothelin pathway and other pulmonary vasodilators  |

# ROBINS-I tool (Stage II): For each study

## Specify a target randomized trial specific to the study

|  |  |
| --- | --- |
| Design | Individually randomized / Cluster randomized / Matched (e.g. cross-over) |
| Participants | Patients with Pulmonary Hypertension and Chronic Obstructive Pulmonary Disease |
| Experimental intervention | Iloprost |
| Comparator | Baseline  |

## Is your aim for this study…?

|  |  |
| --- | --- |
| □ | to assess the effect of *assignment to* intervention |
| □ | to assess the effect of *starting and adhering to* intervention |

## Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

|  |
| --- |
| Primary outcome: Hemodynamic index (PVR, PAWP, mPAP, RAP, CIx, CO and MAP): Secondary outcomes: Gas exchange (PaO2, PaCO2, SaO2, DA-a O2 and Qs/Qt). |

## 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.

|  |
| --- |
| Figures 1-3: tables 2 and 3 |

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

#### “Important” confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. “Validity” refers to whether the confounding variable or variables fully measure the domain, while “reliability” refers to the precision of the measurement (more measurement error means less reliability).

|  |
| --- |
| **(i) Confounding domains listed in the review protocol** |
| Confounding domain | Measured variable(s)  | Is there evidence that controlling for this variable was unnecessary?\* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
| Smoking status | Hemodynamic index and Gas exchange | Yes: This is before and after study design. The effect of the intervention was compared with baseline. In addition, it is assumed that most patients with COPD are either smokers or ex-smokers  | Yes / No / No information | Favour experimental / Favour comparator / No information |
| body mass index | Hemodynamic index and Gas exchange | Yes: This is before and after study design. The effect of the intervention was compared with baseline  |  |  |
| Age and gender | Hemodynamic index and Gas exchange |  |  |  |

|  |
| --- |
| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** |
| Confounding domain | Measured variable(s)  | Is there evidence that controlling for this variable was unnecessary?\* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
|  |  |  | Yes / No / No information | Favour experimental / Favour comparator / No information |
|  |  |  |  |  |
|  |  |  |  |  |

\* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

#### “Important” co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.

|  |
| --- |
| **(i) Co-interventions listed in the review protocol** |
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Drugs that target nitric oxide pathway | Yes: it was not administered | Favour experimental / Favour comparator / No information |
| Drugs that target endothelin pathway  | Yes: it was not administered | Favour experimental / Favour comparator / No information |
| Other pulmonary vasodilators  | Yes: it was not administered | Favour experimental / Favour comparator / No information |

|  |
| --- |
| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** |
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Same as above | Favour experimental / Favour comparator / No information |

## 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.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Signalling questions** | **Description** | **Response options** |
| **Bias due to confounding** |
|  | 1.1 Is there potential for confounding of the effect of intervention in this study?**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | No: This is before and after study design. The effect of the intervention was compared with baseline. | N |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: |  |  |
| 1.2. Was the analysis based on splitting participants’ follow up time according to intervention received?**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3. |  | NA / Y / PY / PN / N / NI |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)  |  | NA / Y / PY / PN / N / NI |

|  |  |
| --- | --- |
|  | **Questions relating to baseline confounding only** |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? |  | NA / Y / PY / PN / N / NI |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? |  | NA / Y / PY / PN / N / NI |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? |  | NA / Y / PY / PN / N / NI |
|  | **Questions relating to baseline and time-varying confounding** |  |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? |  | NA / Y / PY / PN / N / NI |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? |  | NA / Y / PY / PN / N / NI |
|  | **Risk of bias judgement** |  | Low  |
| Optional: What is the predicted direction of bias due to confounding? |  | Favours experimental / Favours comparator / Unpredictable |

|  |
| --- |
| **Bias in selection of participants into the study** |
|  | 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?**If N/PN to 2.1:** go to 2.4 | No. The selection was based on the confirmed diagnosis of pulmonary hypertension before the start of the study.  | N  |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention?2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? |  | NA / Y / PY / PN / N / NINA / Y / PY / PN / N / NI |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | Yes, start of follow-up and start of administration of iloprost coincide for all patients | Y  |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? |  | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** |  | Low  |
| Optional: What is the predicted direction of bias due to selection of participants into the study? |  | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

|  |
| --- |
| **Bias in classification of interventions**  |
|  | 3.1 Were intervention groups clearly defined?  | NI. Only one group (before and after study design)  | NI |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | PY. Again, this is before and after study design. However, before the start of the study intervention is clearly defined.  | PY  |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | PN | PN  |
| **Risk of bias judgement** |  | Low  |
| Optional: What is the predicted direction of bias due to classification of interventions? |  | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

|  |
| --- |
| **Bias due to deviations from intended interventions** |
|  | **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** |  |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | PN | PN  |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? |  | NA / Y / PY / PN / N / NI |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** |  |
| 4.3. Were important co-interventions balanced across intervention groups? |  | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? |  | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? |  | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? |  | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** |  | Low  |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? |  | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

|  |
| --- |
| **Bias due to missing data** |
|  | 5.1 Were outcome data available for all, or nearly all, participants? | PY. outcome data are available for all | PY  |
| 5.2 Were participants excluded due to missing data on intervention status? | No. No patients were excluded. | N  |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | No | Y / PY / PN / N / NI |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? |  | NA / Y / PY / PN / N / NI |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? |  | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** |  | Low  |
| Optional: What is the predicted direction of bias due to missing data? |  | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

|  |
| --- |
| **Bias in measurement of outcomes**  |
|  | 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | PN: This is unlikely: Hemodynamic measurements were taken invasively  | PN  |
| 6.2 Were outcome assessors aware of the intervention received by study participants? |  | NI |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? |  | Y  |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? |  | N  |
| **Risk of bias judgement** |  | Low  |
| Optional: What is the predicted direction of bias due to measurement of outcomes? |  | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

|  |
| --- |
| **Bias in selection of the reported result** |
|  | Is the reported effect estimate likely to be selected, on the basis of the results, from... |  |  |
| 7.1. ... multiple outcome *measurements* within the outcome domain?  |  | PN  |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? |  | PN  |
| 7.3 ... different *subgroups*? |  | PN  |
| **Risk of bias judgement** |  | Low  |
| Optional: What is the predicted direction of bias due to selection of the reported result? |  | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

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



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The Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool

(version for cohort-type studies)

**Version 19 September 2016**



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# ROBINS-I tool (Stage I): At protocol stage

Iloprost Improves Gas Exchange and Exercise Tolerance in Patients with Pulmonary Hypertension and Chronic Obstructive Pulmonary Disease

## Specify the review question

|  |  |
| --- | --- |
| Participants | Patients with Pulmonary Hypertension and Chronic Obstructive Pulmonary Disease |
| Experimental intervention | Iloprost |
| Comparator | Baseline  |
| Outcomes | Primary outcome: Gas exchange (DA–a O2, VE/VO2), (VE/ VCO2)). Secondary outcome: Exercise capacity (6MWT ) and Lung function (spirometry and diffusion capacity) |

## List the confounding domains relevant to all or most studies

|  |
| --- |
| Smoking, age, gender, and body mass index  |

## List co-interventions that could be different between intervention groups and that could impact on outcomes

|  |
| --- |
| Drugs that target nitric oxide, endothelin pathway and other pulmonary vasodilators  |

# ROBINS-I tool (Stage II): For each study

## Specify a target randomized trial specific to the study

|  |  |
| --- | --- |
| Design | Individually randomized / Cluster randomized / Matched (e.g. cross-over) |
| Participants | Patients with Pulmonary Hypertension and Chronic Obstructive Pulmonary Disease |
| Experimental intervention | Iloprost |
| Comparator | Baseline  |

## Is your aim for this study…?

|  |  |
| --- | --- |
| □ | to assess the effect of *assignment to* intervention |
| □ | to assess the effect of *starting and adhering to* intervention |

## Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the Summary of Findings table). Specify whether this is a proposed benefit or harm of intervention.

|  |
| --- |
| Primary outcome: Gas exchange (DA–a O2, VE/VO2), (VE/ VCO2)). Secondary outcome: Exercise capacity (6MWT ) and Lung function (spirometry and diffusion capacity) |

## 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.

|  |
| --- |
| Figures 1 and 2: tables 2 and 3 |

## Preliminary consideration of confounders

Complete a row for each important confounding domain (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as potentially important.

#### “Important” confounding domains are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. “Validity” refers to whether the confounding variable or variables fully measure the domain, while “reliability” refers to the precision of the measurement (more measurement error means less reliability).

|  |
| --- |
| **(i) Confounding domains listed in the review protocol** |
| Confounding domain | Measured variable(s)  | Is there evidence that controlling for this variable was unnecessary?\* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
|  |  |  | Yes / No / No information | Favour experimental / Favour comparator / No information |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

|  |
| --- |
| **(ii) Additional confounding domains relevant to the setting of this particular study, or which the study authors identified as important** |
| Confounding domain | Measured variable(s)  | Is there evidence that controlling for this variable was unnecessary?\* | Is the confounding domain measured validly and reliably by this variable (or these variables)? | OPTIONAL: Is failure to adjust for this variable (alone) expected to favour the experimental intervention or the comparator? |
|  |  |  | Yes / No / No information | Favour experimental / Favour comparator / No information |
| Same as above |

\* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

## Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

#### “Important” co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.

|  |
| --- |
| **(i) Co-interventions listed in the review protocol** |
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Drugs that target nitric oxide pathway | Yes: it was not administered | Favour experimental / Favour comparator / No information |
| Drugs that target endothelin pathway  | Yes: it was not administered | Favour experimental / Favour comparator / No information |
| Other pulmonary vasodilators  | Yes: it was not administered | Favour experimental / Favour comparator / No information |

|  |
| --- |
| **(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important** |
| Co-intervention | Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)? | Is presence of this co-intervention likely to favour outcomes in the experimental intervention or the comparator |
| Same as above | Favour experimental / Favour comparator / No information |

## 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.

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Signalling questions** | **Description** | **Response options** |
| **Bias due to confounding** |
|  | 1.1 Is there potential for confounding of the effect of intervention in this study?**If N/PN to 1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered | No | N |
| **If Y/PY to 1.1**: determine whether there is a need to assess time-varying confounding: |  |  |
| 1.2. Was the analysis based on splitting participants’ follow up time according to intervention received?**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3. |  | NA / Y / PY / PN / N / NI |
| 1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?**If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6)**If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)  |  | NA / Y / PY / PN / N / NI |

|  |  |
| --- | --- |
|  | **Questions relating to baseline confounding only** |
| 1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains? |  | NA / Y / PY / PN / N / NI |
| 1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? |  | NA / Y / PY / PN / N / NI |
| 1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention? |  | NA / Y / PY / PN / N / NI |
|  | **Questions relating to baseline and time-varying confounding** |  |
| 1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? |  | NA / Y / PY / PN / N / NI |
| 1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? |  | NA / Y / PY / PN / N / NI |
|  | **Risk of bias judgement** |  | Low / Moderate / Serious / Critical / NI |
| Optional: What is the predicted direction of bias due to confounding? |  | Favours experimental / Favours comparator / Unpredictable |

|  |
| --- |
| **Bias in selection of participants into the study** |
|  | 2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?**If N/PN to 2.1:** go to 2.4 | The selection was based on the confirmed diagnosis of pulmonary hypertension before the start of the study.  | Y / PY / PN / N / NI |
| 2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention?2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? |  | NA / Y / PY / PN / N / NINA / Y / PY / PN / N / NI |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | Yes, start of follow-up and start of administration of iloprost coincide for all patients | Y / PY / PN / N / NI |
| 2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases? |  | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** |  | Low / Moderate / Serious / Critical / NI |
| Optional: What is the predicted direction of bias due to selection of participants into the study? |  | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

|  |
| --- |
| **Bias in classification of interventions**  |
|  | 3.1 Were intervention groups clearly defined?  | NI. Only one group (before and after study design)  | Y / PY / PN / N / NI |
| 3.2 Was the information used to define intervention groups recorded at the start of the intervention? | PY. Again, this is before and after study design. However, before the start of the study intervention is clearly defined.  | Y / PY / PN / N / NI |
| 3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome? | PN | Y / PY / PN / N / NI |
| **Risk of bias judgement** |  | Low / Moderate / Serious / Critical / NI |
| Optional: What is the predicted direction of bias due to classification of interventions? |  | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

|  |
| --- |
| **Bias due to deviations from intended interventions** |
|  | **If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2** |  |
| 4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice? | PN | Y / PY / PN / N / NI |
| 4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome? |  | NA / Y / PY / PN / N / NI |
| **If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6** |  |
| 4.3. Were important co-interventions balanced across intervention groups? |  | Y / PY / PN / N / NI |
| 4.4. Was the intervention implemented successfully for most participants? |  | Y / PY / PN / N / NI |
| 4.5. Did study participants adhere to the assigned intervention regimen? |  | Y / PY / PN / N / NI |
| 4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention? |  | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** |  | Low / Moderate / Serious / Critical / NI |
| Optional: What is the predicted direction of bias due to deviations from the intended interventions? |  | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

|  |
| --- |
| **Bias due to missing data** |
|  | 5.1 Were outcome data available for all, or nearly all, participants? | Yes. outcome data are available for all | Y / PY / PN / N / NI |
| 5.2 Were participants excluded due to missing data on intervention status? | No. No patients were excluded. | Y / PY / PN / N / NI |
| 5.3 Were participants excluded due to missing data on other variables needed for the analysis? | No | Y / PY / PN / N / NI |
| 5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions? |  | NA / Y / PY / PN / N / NI |
| 5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data? |  | NA / Y / PY / PN / N / NI |
| **Risk of bias judgement** |  | Low / Moderate / Serious / Critical / NI |
| Optional: What is the predicted direction of bias due to missing data? |  | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

|  |
| --- |
| **Bias in measurement of outcomes**  |
|  | 6.1 Could the outcome measure have been influenced by knowledge of the intervention received? | PY | Y / PY / PN / N / NI |
| 6.2 Were outcome assessors aware of the intervention received by study participants? | PY | Y / PY / PN / N / NI |
| 6.3 Were the methods of outcome assessment comparable across intervention groups? | Y | Y / PY / PN / N / NI |
| 6.4 Were any systematic errors in measurement of the outcome related to intervention received? | N | Y / PY / PN / N / NI |
| **Risk of bias judgement** |  | Low / Moderate / Serious / Critical / NI |
| Optional: What is the predicted direction of bias due to measurement of outcomes? |  | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

|  |
| --- |
| **Bias in selection of the reported result** |
|  | Is the reported effect estimate likely to be selected, on the basis of the results, from... |  |  |
| 7.1. ... multiple outcome *measurements* within the outcome domain?  |  | Y / PY / PN / N / NI |
| 7.2 ... multiple *analyses* of the intervention-outcome relationship? |  | Y / PY / PN / N / NI |
| 7.3 ... different *subgroups*? |  | Y / PY / PN / N / NI |
| **Risk of bias judgement** |  | Low / Moderate / Serious / Critical / NI |
| Optional: What is the predicted direction of bias due to selection of the reported result? |  | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |

|  |
| --- |
| **Overall bias** |
|  | **Risk of bias judgement** |  | Low / Moderate / Serious / Critical / NI |
| Optional: What is the overall predicted direction of bias for this outcome? |  | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |



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