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

(version for cohort-type studies)

**Version 19 September 2016**



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

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

## Specify the review question

|  |  |
| --- | --- |
| Participants | People with end stage kidney disease who are eligible for kidney transplantation |
| Experimental intervention | Pre-emptive kidney transplantation (PET, transplantation before dialysis) |
| Comparator | Transplantation after a period of dialysis |
| Outcomes | All-cause mortality |

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

|  |
| --- |
|  |

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

|  |
| --- |
|  |

# 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 |  |
| Experimental intervention |  |
| Comparator |  |

## 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.

|  |
| --- |
| Mortality. |

## 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.

|  |
| --- |
| HR 0.46 (95% CI 0.27–0.80), P = 0.006 (Table 4). This is the adjusted hazard ratio for pre-emptive vs non-pre-emptive kidney transplantation. |

## 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 |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

\* 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 |
|  |  | Favour experimental / Favour comparator / No information |
|  |  | Favour experimental / Favour comparator / No information |
|  |  | Favour experimental / Favour comparator / No information |
|  |  | 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 |
|  |  | Favour experimental / Favour comparator / No information |
|  |  | Favour experimental / Favour comparator / No information |
|  |  | Favour experimental / Favour comparator / No information |
|  |  | 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** | **Elaboration** | **Response options** | **Description** |
| **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 | In rare situations, such as when studying harms that are very unlikely to be related to factors that influence treatment decisions, no confounding is expected and the study can be considered to be at low risk of bias due to confounding, equivalent to a fully randomized trial. There is no NI (No information) option for this signalling question. | Y / PY / PN / 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. | If participants could switch between intervention groups then associations between intervention and outcome may be biased by time-varying confounding. This occurs when prognostic factors influence switches between intended interventions. | 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) | If intervention switches are unrelated to the outcome, for example when the outcome is an unexpected harm, then time-varying confounding will not be present and only control for baseline confounding is required. | 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? | Appropriate methods to control for measured confounders include stratification, regression, matching, standardization, and inverse probability weighting. They may control for individual variables or for the estimated propensity score. Inverse probability weighting is based on a function of the propensity score. Each method depends on the assumption that there is no unmeasured or residual confounding. | 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? | Appropriate control of confounding requires that the variables adjusted for are valid and reliable measures of the confounding domains. For some topics, a list of valid and reliable measures of confounding domains will be specified in the review protocol but for others such a list may not be available. Study authors may cite references to support the use of a particular measure. If authors control for confounding variables with no indication of their validity or reliability pay attention to the subjectivity of the measure. Subjective measures (e.g. based on self-report) may have lower validity and reliability than objective measures such as lab findings. | 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? | Controlling for post-intervention variables that are affected by intervention is not appropriate. Controlling for mediating variables estimates the direct effect of intervention and may introduce bias. Controlling for common effects of intervention and outcome introduces bias. | 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? | Adjustment for time-varying confounding is necessary to estimate the effect of starting and adhering to intervention, in both randomized trials and NRSI. Appropriate methods include those based on inverse probability weighting. Standard regression models that include time-updated confounders may be problematic if time-varying confounding is present. | 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? | See 1.5 above. | NA / Y / PY / PN / N / NI |  |
|  | **Risk of bias judgement** | See Table 1 | Low / Moderate / Serious / Critical / NI |  |
| Optional: What is the predicted direction of bias due to confounding? | If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions. | Favours experimental / Favours comparator / Unpredictable |  |

Table 1: Reaching risk of bias judgements for bias due to confounding

|  |  |
| --- | --- |
| Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain) | No confounding expected. |
| Moderate risk of bias (the study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial) | (i) Confounding expected, all known important confounding domains appropriately measured and controlled for;  *and*  (ii) Reliability and validity of measurement of important domains were sufficient, such that we do not expect serious residual confounding. |
| Serious risk of bias (the study has some important problems) | (i) At least one known important domain was not appropriately measured, or not controlled for;  *or*  (ii) Reliability or validity of measurement of an important domain was low enough that we expect serious residual confounding. |
| Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention) | (i) Confounding inherently not controllable  *or*  (ii) The use of negative controls strongly suggests unmeasured confounding. |
| No information on which to base a judgement about risk of bias for this domain | No information on whether confounding might be present. |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Signalling questions** | **Elaboration** | **Response Options** | **Description** |
| **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 | This domain is concerned only with selection into the study based on participant characteristics observed *after* the start of intervention. Selection based on characteristics observed *before* the start of intervention can be addressed by controlling for imbalances between experimental intervention and comparator groups in baseline characteristics that are prognostic for the outcome (baseline confounding). | 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? | Selection bias occurs when selection is related to an effect of either intervention or a cause of intervention **and** an effect of either the outcome or a cause of the outcome. Therefore, the result is at risk of selection bias if selection into the study is related to both the intervention and the outcome. | NA / Y / PY / PN / N / NI  NA / Y / PY / PN / N / NI |  |
| 2.4. Do start of follow-up and start of intervention coincide for most participants? | If participants are not followed from the start of the intervention then a period of follow up has been excluded, and individuals who experienced the outcome soon after intervention will be missing from analyses. This problem may occur when prevalent, rather than new (incident), users of the intervention are included in analyses. | 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? | It is in principle possible to correct for selection biases, for example by using inverse probability weights to create a pseudo-population in which the selection bias has been removed, or by modelling the distributions of the missing participants or follow up times and outcome events and including them using missing data methodology. However such methods are rarely used and the answer to this question will usually be “No”. | NA / Y / PY / PN / N / NI |  |
| **Risk of bias judgement** | See Table 2. | Low / Moderate / Serious / Critical / NI |  |
| Optional: What is the predicted direction of bias due to selection of participants into the study? | If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions. | Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable |  |

Table 2: Reaching risk of bias judgements in selection of participants into the study

|  |  |
| --- | --- |
| Low risk of bias (the study is comparable to a well-performed randomized trial with regard to this domain) | (i) All participants who would have been eligible for the target trial were included in the study;  *and*  (ii) For each participant, start of follow up and start of intervention coincided. |
| Moderate risk of bias (the study is sound for a non-randomized study with regard to this domain but cannot be considered comparable to a well-performed randomized trial) | (i) Selection into the study may have been related to intervention and outcome;  *and*  The authors used appropriate methods to adjust for the selection bias;  *or*  (ii) Start of follow up and start of intervention do not coincide for all participants;  *and*  (a) the proportion of participants for which this was the case was too low to induce important bias;  *or*  (b) the authors used appropriate methods to adjust for the selection bias;  *or*  (c) the review authors are confident that the rate (hazard) ratio for the effect of intervention remains constant over time. |
| Serious risk of bias (the study has some important problems) | (i) Selection into the study was related (but not very strongly) to intervention and outcome;  *and*  This could not be adjusted for in analyses;  *or*  (ii) Start of follow up and start of intervention do not coincide;  *and*  A potentially important amount of follow-up time is missing from analyses;  *and*  The rate ratio is not constant over time. |
| Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention) | (i) Selection into the study was very strongly related to intervention and outcome;  *and*  This could not be adjusted for in analyses;  *or*  (ii) A substantial amount of follow-up time is likely to be missing from analyses;  *and*  The rate ratio is not constant over time. |
| No information on which to base a judgement about risk of bias for this domain | No information is reported about selection of participants into the study or whether start of follow up and start of intervention coincide. |