Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

TEMPLATE FOR COMPLETION

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne  
on behalf of the RoB2 Development Group

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| **Study details**   |  |  | | --- | --- | | **Reference** | Di Consiglio, M., Fabrizi, G., Conversi, D., La Torre, G., Pascucci, T., Lombardo, C., Violani, C. & Couyoumdjian, A. (2021). Effectiveness of NoiBene: A Web-based programme to promote psychological well-being and prevent psychological distress in university students. Appl Psychol Health Well-Being, 13, 317-340. https://doi.org/10.1111/aphw.12251 |   **Study design**   |  |  | | --- | --- | | £ | Individually-randomized parallel-group trial | | £ | Cluster-randomized parallel-group trial | | £ | Individually randomized cross-over (or other matched) trial |   **For the purposes of this assessment, the interventions being compared are defined as**   |  |  |  |  | | --- | --- | --- | --- | | Experimental: | NoiBene intervention | Comparator: | Active psychoeducation control group |  |  |  | | --- | --- | | **Specify which outcome is being assessed for risk of bias** | Psychological well-being: Italian PWB containing 84 items. |  |  |  | | --- | --- | | **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. | Pre and post-intervention measures of PWB for the experimental NoiBene and Active psychoeducation control group. |   **Is the review team’s aim for this result…?**   |  |  | | --- | --- | | £ | to assess the effect of *assignment to intervention* (the ‘intention-to-treat’ effect) | | X | 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):  X occurrence of non-protocol interventions  £ failures in implementing the intervention that could have affected the outcome  X 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 trial + Supplementary materials  £ 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 1: Risk of bias arising from the randomization process**

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| **Signalling questions** | **Comments** | **Response options** |
| **1.1 Was the allocation sequence random?** | “Otherwise, the participant would be randomly assigned to the experimental or control condition.”  2.2 This depends entirely on how the randomisation took place and therefore we can’t answer this with certainty. Participants were interviewed, following which they were randomised. If randomisation was done by the interviewer there’s high risk for bias, however, if this was done digitally there’s a low risk of bias. | NI  Answer ‘Yes’ if a random component was used in the sequence generation process. Examples include computer-generated random numbers.  Answer ‘No’ if no random element was used in generating the allocation sequence or the sequence is predictable.  Answer ‘No information’ if the only information about randomization methods is a statement that the study is randomized. |
| **1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?** | NI  Answer ‘Yes’ if the trial used any form of remote or centrally administered method to allocate interventions to participants, where the process of allocation is controlled by internet-based randomization service providers.  Answer ‘No’ if there is reason to suspect that the enrolling investigator or the participant had knowledge of the forthcoming allocation. |
| **1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?** | There is no analysis of demographic characteristics or prognostic factor differences between groups at baseline. Visual inspection of supplementary materials table S2 indicates some differences, which relatively consistently indicate lower well-being/distress scores in the control compared to the intervention group. However, these are minor differences and could be considered to occur by chance. Especially considering the sample size of 24 (12 in each condition). | PN  Answer ‘Yes’ if there are imbalances that indicate problems with the randomization process, including:  (1) substantial differences between intervention group sizes, compared with the intended allocation ratio; or  (2) a substantial excess in statistically significant differences in baseline characteristics between intervention groups, beyond that expected by chance; or  (3) imbalance in one or more key prognostic factors, or baseline measures of outcome variables, that is very unlikely to be due to chance and for which the between-group difference is big enough to result in bias in the intervention effect estimate. |
| **Risk-of-bias judgement** |  | Some concerns |
| Optional: What is the predicted direction of bias arising from the randomization process? |  | 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 the trial?** | 2.1 Intervention information was introduced to all study participants at the start of the study.  “NoiBene was introduced to participants as a programme to promote psychological well-being and, more specifically, to promote emotional awareness, commitment to personal values, assertive and empathic communication, planning and goal setting.”  2.2 Fully automated digital delivery. | Y |
| **2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?** | N |
| **2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?** | There is no information regarding whether participants engaged in any non-protocol interventions. | NI |
| **2.4. [If applicable:] Were there failures in implementing the intervention that could have affected the outcome?** |  | NA |
| **2.5. [If applicable:] Was there non-adherence to the assigned intervention regimen that could have affected participants’ outcomes?** | All participants remained in and completed their allocated condition (see figure 1). | PN |
| **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?** | “A series of ANOVAs were run on PWB, DERS, TAS-20 and SIB scores as a function of the factor between condition and the factor within Time. In the case of a significant Time × Condition interaction, the post hoc analyses were conducted with the Bonferroni test.” | PN |
| **Risk-of-bias judgement** |  | High |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? |  | Unpredictable |

Domain 3: 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?** | All data was available, see figure 1. | Y  The appropriate study population for an analysis of the intention to treat effect is all randomized participants.“Nearly all” should be interpreted as that the number of participants with missing outcome data is sufficiently small that their outcomes, whatever they were, could have made no important difference to the estimated effect of intervention.For continuous outcomes, availability of data from 95% of the participants will often be sufficient. |
| **3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?** |  | NA  Evidence that the result was not biased by missing outcome data may come from: (1) analysis methods that correct for bias; or (2) sensitivity analyses showing that results are little changed under a range of plausible assumptions about the relationship between missingness in the outcome and its true value. However, imputing the outcome variable, either through methods such as ‘last-observation-carried-forward’ or via multiple imputation based only on intervention group, should not be assumed to correct for bias due to missing outcome data. |
| **3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?** |  | NA  If loss to follow up, or withdrawal from the study, could be related to participants’ health status, then it is possible thatmissingness in the outcome was influenced by its true value. However, if all missing outcome data occurred for documented reasons that are unrelated to the outcome then the risk of bias due to missing outcome data will be low (for example, failure of a measuring device or interruptions to routine data collection).In time-to-event analyses, participants censored during trial follow-up, for example because they withdrew from the study, should be regarded as having missing outcome data, even though some of their follow up is included in the analysis. Note that such participants may be shown as included in analyses in CONSORT flow diagrams. |
| **3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?** | NA  Reasons for answering ‘Yes’ are:  1.Differences between intervention groups in the proportions of missing outcome data.  2.Reported reasons for missing outcome data provide evidence that missingness in the outcome depends on its true value.  3.Reported reasons for missing outcome data differ between the intervention groups.  4.The circumstances of the trial make it likely that missingness in the outcome depends on its true value. For example, in trials of interventions to treat schizophrenia it is widely understood that continuing symptoms make drop out more likely.  Answer ‘No’ if the analysis accounted for participant characteristics that are likely to explain the relationship between missingness in the outcome and its true value. |
| **Risk-of-bias judgement** |  | Low |
| Optional: What is the predicted direction of bias due to missing outcome data? |  | NA |

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?** | “Psychological Well-Being. To assess the level of psychological well-being we used the Psychological Well-Being Scale (PWB; Ryff & Keyes, 1995; Italian validation by Ruini et al., 2003), a self-report questionnaire used to assess the individual’s level of psychological well-being according to Ryff theory (1995). It encompasses six areas of psychological well-being: autonomy (i.e., self-regulation and independence), environmental mastery (i.e., a sense of competence to manage the environment), personal growth (i.e., a sense of improvement and expansion over time), positive relations with others (i.e., the ability to maintain trusting relationships with others), purpose in life (i.e., a belief in the meaning of one’s life), and self-acceptance (i.e., a positive attitude toward oneself and one’s past life). Scores range from 14 to 84, with high scores indicating better level of functioning. The original version showed Cronbach's alpha ranging from 0.83 to 0.91 for the six dimensions. In our sample, the Cronbach’s alpha ranged from 0.69 to 0.82 for the six dimensions (autonomy: 0.82; environmental mastery: 0.72; personal growth: 0.80; positive relations with others: 0.69; purpose in life: 0.81; self-acceptance: 0.82).” | N  Answer ‘Yes’ or ‘Probably yes’ if the method of measuring the outcome is inappropriate, for example because:  (1) it is unlikely to be sensitive to plausible intervention effects (e.g. important ranges of outcome values fall outside levels that are detectable using the measurement method); or  (2) the measurement instrument has been demonstrated to have poor validity. |
| **4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?** | Standardised questionnaire that was administered digitally automatically. | N  Comparable methods of outcome measurement (data collection) involve the same measurement methods and thresholds, used at comparable time points. Differences between intervention groups may arise because of ‘diagnostic detection bias’ in the context of passive collection of outcome data, or if an intervention involves additional visits to a healthcare provider, leading to additional opportunities for outcome events to be identified. |
| **4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?** | Outcome assessors (participants) were likely aware that they did or did not receive the intervention due to information provided about the study prior to the start of the study. | PY  Answer ‘No’ if outcome assessors were blinded to intervention status. For participant-reported outcomes, the outcome assessor is the study participant. |
| **4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?** |  | PY  Knowledge of the assigned intervention could influence participant-reported outcomes (such as level of pain), observer-reported outcomes involving some judgement, and intervention provider decision outcomes. They are unlikely to influence observer-reported outcomes that do not involve judgement, for example all-cause mortality. |
| **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  This question distinguishes between situations in which (i) knowledge of intervention status could have influenced outcome assessment but there is no reason to believe that it did (assessed as ‘Some concerns’) from those in which (ii) knowledge of intervention status was likely to influence outcome assessment (assessed as ‘High’). When there are strong levels of belief in either beneficial or harmful effects of the intervention, it is more likely that the outcome was influenced by knowledge of the intervention received. Examples may include patient-reported symptoms in trials of homeopathy, or assessments of recovery of function by a physiotherapist who delivered the intervention. |
| **Risk-of-bias judgement** |  | Some concerns |
| Optional: What is the predicted direction of bias in measurement of the outcome? |  | 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 pre-specified analysis plan or pre-registration could be found for the current study. | PN  If the researchers’ pre-specified intentions are available in sufficient detail, then planned outcome measurements and analyses can be compared with those presented in the published report(s). To avoid the possibility of selection of the reported result, finalization of the analysis intentions must precede availability of unblinded outcome data to the trial investigators. |
| **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?** | There is one well-validated scale that is mainly used for psychological well-being, based on the main theory of PWB. | PN  Answer ‘Yes’ or ‘Probably yes’ if:  There is clear evidence (usually through examination of a trial protocol or statistical analysis plan) that a domain was measured in multiple eligible ways, but data for only one or a subset of measures is fully reported (without justification), and the fully reported result is likely to have been selected on the basis of the results. Selection on the basis of the results can arise from a desire for findings to be newsworthy, sufficiently noteworthy to merit publication, or to confirm a prior hypothesis. For example, trialists who have a preconception, or vested interest in showing, that an experimental intervention is beneficial may be inclined to report outcome measurements selectively that are favourable to the experimental intervention.  Answer ‘No’ or ‘Probably no’ if:  There is clear evidence (usually through examination of a trial protocol or statistical analysis plan) that all eligible reported results for the outcome domain correspond to all intended outcome measurements.  Or  There is only one possible way in which the outcome domain can be measured (hence there is no opportunity to select from multiple measures).  or  Outcome measurements are inconsistent across different reports on the same trial, but the trialists have provided the reason for the inconsistency and it is not related to the nature of the results.  Answer ‘No information’ if:  Analysis intentions are not available, or the analysis intentions are not reported in sufficient detail to enable an assessment. |
| **5.3 ... multiple eligible analyses of the data?** |  | PN  There is clear evidence (usually through examination of a trial protocol or statistical analysis plan) that a measurement was analysed in multiple eligible ways, but data for only one or a subset of analyses is fully reported (without justification), and the fully reported result is likely to have been selected on the basis of the results. |
| **Risk-of-bias judgement** |  | Some concerns |
| Optional: What is the predicted direction of bias due to selection of the reported result? |  | 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? |  | Unpredictable |



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