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** | Mak WW, Tong AC, Yip SY, Lui WW, Chio FH, Chan AT, Wong CC (2018). Efficacy and Moderation of Mobile App–Based Programs for Mindfulness-Based Training, Self-Compassion Training, and Cognitive Behavioral Psychoeducation on Mental Health: Randomized Controlled Noninferiority Trial. JMIR Ment Health, 5(4), e60. doi: 10.2196/mental.8597 |   **Study design**   |  |  | | --- | --- | | X | 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: | Mindfulness-based program & Self-compassion program | Comparator: | Cognitive behavioral psychoeducation |  |  |  | | --- | --- | | **Specify which outcome is being assessed for risk of bias** | Mental well-being (WHO-5 item Well-Being Index) |  |  |  | | --- | --- | | **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. | Table 3, journal article, Intention To Treat (ITT) mental well-being outcome at pre, post and follow-up |   **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  X 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?** | “Randomization took place when participants activated their user account in the email that was sent immediately to their email address after they provided informed consent on the study website. A simple randomization to 1 of the 3 conditions was performed by the computer system automatically. Participants were informed about their assigned condition after they had completed the pretraining questionnaire when they logged into the app or website” (Journal article, p.5). | Y  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?** | Y  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?** | See figure 1. Group sizes, table 1. Baseline characteristics and table 2. Baseline characteristics of outcome measures.  “Demographics and baseline psychological attributes of the participants are shown in Tables 1 and 2. Overall, they had a mean age of 33.64 (SD 12.08), with the majority being female (72.88%, 1575/2161), and 79.59% (1720/2161) received or were receiving tertiary education (undergraduate or above).” (Journal article, p.6).  Rationale:  Although no statistical analysis appears to have been performed on the differences in baseline characteristics, visual inspection show no baseline differences that suggest a problem with the randomization process, apart from the group sizes which are 795, 748, and 739 following randomisation. However, we consider this to be possible with chance. | 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** |  | Low |
| Optional: What is the predicted direction of bias arising from the randomization process? |  | NA |

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 Despite providing study information, participants were all asked to download the same app and automatically received access to their part of the intervention delivered through the same app.  2.2 No, the intervention was delivered digitally.  Supporting evidence (Journal article, p.4):  “Individuals who were interested in the study could download the mobile app hrough Apple Store or Google play or visit the website where informed consent was sought through the built-in consent form in the app or website. Apart from the inclusion criteria, **details of the study aims, length of the program, involvement of the participants, and randomization of participants to interventions were also described.** …The Living With Heart (LWH) mobile app was developed, and it contained 3 training programs mentioned above. It runs on iOS and Android platform. A Web-browser version was also developed so that it can be accessed through various devices including mobile phones, tablets, and desktop computers. It was made available on Google Play and Apple Store, along with the website, since March 2015 after functional tests were conducted. The mobile app (and website) is fully automated and includes common features.  In addition to the above-mentioned common features, all 3 conditions consisted of 28 daily sessions, which were divided into 4 weekly modules. The course contents were released weekly, and all 7 sessions of that particular week are available to the user on the first day of that week. Users were encouraged to read the content at their own pace with suggested home practices every week”. | PN |
| **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?** |  | 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?** | “The mean completion rate of the 28 sessions (4 modules) of all participants (including completers and noncompleters) was 31.95% (SD 34.94), approximately 9 out of 28 days. The mean completion rate for MBP was 29.48% (SD 34.23), 32.15% (SD 34.72) for SCP, and 34.08% (SD 34.13) for CBP. The 3 conditions differ significantly on the overall progress, F2=3.272, P=.04.Follow-up test showed that the progress was significantly greater in CBP than in MBP (P=.03).” | PY |
| **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?** | PP and ITT analysis were conducted. Additional moderators were also investigated:  “Results revealed that the proposed moderators did not moderate the effect of intervention efficacy in terms of WBI. The moderation of discomfort with emotions (F4=0.60, P=.66) and ambiguity tolerance (F4=1.40, P=.23) were not significant”. | PN |
| **Risk-of-bias judgement** |  | High |
| Optional: What is the predicted direction of bias due to deviations from intended interventions? |  | Towards null |

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?** | “Figure 2 shows the number of participants who stayed in the program after each module. Numbers indicated that the majority of attrition was noted in the first week. Specifically, 69.0% (485/703) of participants in the MBP, 65.7% (463/705) in the SCP, and 66.4% (500/753) in the CBP stopped using the app after 7 days” (p.9 and figure 2). | N  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?** | Analysis show evidence that there was no bias in missing outcome data: “To investigate the potential causes of attrition, we compared the baseline attributes between participants who dropped-out (N=1653) with those who remained (N=508) at postprogram. Participants who stayed in the program (mean 34.75 SD 12.76) were significantly older than those who left (mean 33.3 SD 11.84), t794.29=2.27, P=.02. They also differed in terms of education level, χ 2 6=14.23, P=.03, with more people obtaining postgraduate education in the dropout group.  No significant difference was found in all outcome measures and potential moderators at baseline.” (journal paper, p.9, attrition analysis).  ITT and PP show no different results either. | Y  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** | Despite the high dropout rate, there’s evidence that this did not bias the result and therefore a low overall bias. | 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?** | Rationale: A standardised validated questionnaire has been used to measure mental well-being.  Supporting information: “ Mental Well-Being The World Health Organization 5-item Well-Being Index (WBI) [51] was used to measure mental well-being. Participants were asked to indicate how they had been feeling over the past 2 weeks on a 6-point Likert scale from 0 (never) to 5 (all of the time). In this study, its Cronbach alpha was .90 at baseline, .92 at postprogram, and .93 at 3-month follow-up.” (Journal paper, p.5). | 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?** | All groups receive the same standardised automatically administered measures. However, there is no information whether the trained supporters were aware of the intervention received by participants: “Participants filled in the pre-, post-, and follow-up assessments online via the website or mobile app. Trained supporters contacted the participants via a phone call and short message service text messages once after the end of the program and at 3-month follow-up to encourage the completion of postprogram and follow-up evaluations.” | PN  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?** | Participants were not aware of what intervention they received as they were single blinded, see: <http://www.chictr.org.cn/hvshowproject.aspx?id=6220>  Supporting evidence: “Apart from the inclusion criteria, **details of the study aims, length of the program, involvement of the participants, and randomization of participants to interventions were also described.** For safety, participants are reminded that the mobile app is not equivalent to a psychological treatment. They were reminded to seek professional support at any occurrence of suicidality or other medical issues. Information on help-seeking resources was provided. They were also informed that the study was conducted by the Department of Psychology at The Chinese University of Hong Kong. Individuals who agreed to participate proceeded to registration after giving informed consent by clicking the I agree button. From there, an activation link was sent to the participants, and they were randomly assigned to 1 of the 3 conditions.”  Specific information on the trial will have been provided which will have allowed the participants to identify what kind of intervention they received. | 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?** | See: <http://www.chictr.org.cn/hvshowproject.aspx?id=6220> . Although all results produced are in line with the pre-specified plan, there’s no pre-specified analysis plan. | 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?** | The WHO-5 well-being outcome and all timepoints (pre, post and follow-up) have been predetermined in the prospective registration of the study, see: <http://www.chictr.org.cn/hvshowproject.aspx?id=6220> . | Y  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?** | “To examine and compare the efficacy between SCP, MBP, and CBP, both intention-to-treat (ITT) and per-protocol (PP) analysis were performed on the 2 primary outcome variables, that is, mental well-being and psychological distress, as well as the secondary outcome variables, that is, mindful awareness and self-compassion. For both analyses, a series of linear mixed model (LMM) analyses were conducted. Model for each outcome variable consisted of the time effect, condition effect, and the interaction effect of time by condition. First-order autoregressive covariance matrix was used. When the main effect of time or condition was significant, follow-up tests were conducted to compare the outcomes in postprogram and follow-up with the preprogram, and results were adjusted with Bonferroni correction.” | 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? | Due to non-adherence of intervention. | Towards null |



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