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Risk-of-bias assessment using RoB2 was useful but challenging and resource-intensive: observations from a systematic review

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Abstract

Objective

To report our experience using Version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB2).

Study design and setting

Two reviewers independently applied RoB2 to results of interest in a large systematic review of complex interventions and reached consensus. We recorded time taken, and noted and discussed our difficulties using the tool, and the resolutions we adopted. We explored time taken with regression analysis and summarised our experience of implementing the tool.

Results

We assessed risk of bias in 860 results of interest in 113 studies. Staff resource averaged 358 minutes per study (SD 183). Number of results (β=22) and reports (β=14) per study and experience of the team (β=-6) significantly affected assessment time. To implement the tool consistently we developed cut-points for missingness and considerations of balance regarding missingness, assumed some concerns with intervention deviations unless otherwise prevented or investigated, some concerns with measurements from unblinded self-reporting participants, and judged low risk of selection for certain dichotomous outcomes despite the absence of an analysis plan.

Conclusion

The RoB2 tool and guidance are useful but resource-intensive and challenging to implement. Critical appraisal tools and reporting guidelines should detail risk-of-bias implementation. Improved guidance focussing on implementation could assist reviewers.

Keywords

RoB2; risk of bias; process duration; research methods; certainty assessment; systematic reviews

Running title

Risk-of-bias assessment using RoB2 was useful but challenging and resource-intensive

Word count

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What is New?

Key findings

It took 5h 58m of staff time to assess risk of bias per study on average using version 2 of the Cochrane tool for assessing risk-of-bias in randomised trials (RoB2) in a systematic review of community-based complex interventions.

Variation in time per study was largely explained by models including the number of results of interest, the experience of the reviewers with use of the RoB2 tool, and, for individual assessments, number of reports.

Despite the extensive guidance we had difficulty implementing aspects of most domains.

What this adds to what is known

This is the first research to identify the impact of number of results of interest and number of reports on the time taken to assess RoB2, and adds to a limited body of published evidence about how reviewers have implemented the RoB2 tool.

What is the implication, what should change now

Improved guidance is needed to further assist review authors in implementing the RoB2 tool and to encourage reporting details of their approach to implementation.

1 Introduction

Systematic reviews that synthesise evidence of the effectiveness of interventions are a cornerstone of clinical guidelines and evidence-based medicine. Evaluating risk of bias is an essential element of systematic reviews and one step towards establishing the degree of confidence or certainty in the synthesis [1, 2]. Methods for evaluating risk of bias have evolved from study quality checklists to an increasing focus on factors that affect the internal validity of the results of studies. In 2008 the Cochrane Collaboration published a tool to evaluate risk of bias in randomised controlled trials (RCTs) which became the standard for such assessments [3-5].

Version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB2) was published in 2019 [6, 7]. This revised version, developed through an expert consensus process, introduced substantial changes. For example, each relevant result of a study was now assessed instead of the study as a whole and an overall judgement was to be reached. There was some restructuring of the domains of bias in response to theoretical developments. Additionally, a series of signalling questions (SQs) and accompanying algorithm were provided for each domain to try to improve reviewers' agreement [8].

RoB2 has been widely cited in the three years since its publication (over 8000 citations according to Google Scholar) suggesting widespread uptake. A recent meta-epidemiological study identified 196 completed systematic reviews that applied RoB2 [9]. Two studies have estimated the time taken to apply RoB2, finding it demanding with problematic reliability, and recommending development of operational criteria specific to the review to improve implementation [10, 11].

We used RoB2 to assess risk of bias in a large, robust systematic review with network meta-analysis. This article reports our experiences, including details to help reviewers planning to use RoB2, how we operationalised aspects of it, and recommendations for those maintaining and developing the tool.

2 Methods

2.1 Overarching systematic review

We undertook a systematic review and network meta-analysis of community-based complex interventions to sustain independence in older people. The review followed standard procedures, was prospectively registered on PROSPERO (CRD42019162195) and the protocol published [12].

Briefly, the methods of relevance to our use of RoB2 were as follows.

Following a comprehensive search, we included randomised controlled trials (RCTs) or cluster-RCTs that measured outcomes at least 24 weeks after baseline. Participants were older people living at home (≥ 65 years). Eligible interventions were community-based complex interventions targeted at the individual, focused on sustaining independence. Eligible comparators were usual care, "placebo" or attention control, or a different complex intervention which met our criteria.

Two researchers independently screened records (title and abstract), assessed eligibility, and extracted data.

Our outcomes of interest comprised six dichotomous outcomes and seven continuous outcomes. Each comparison between two trial arms (e.g. experimental and control interventions) for an outcome of interest at a particular timepoint for which an effect estimate was reported or could be calculated is referred to henceforth as a *result of interest*. Results of interest were extracted for three timeframes.

2.2 Risk-of-bias assessment using RoB2

Two reviewers independently assessed risk of bias (RoB) in each result of interest from each included study, using version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB2) [6-8]. We were interested in the effect of assignment to the intervention ('intention-to-treat' effect). Disagreements were resolved by consensus between the reviewers or through discussion with the Programme Management Group (PMG) which included expert clinicians, trialists and statisticians.

For individually randomised studies, we assessed risk of bias in five domains: (1) the randomization process; (2) deviations from intended interventions; (3) missing outcome data; (4) measurement of the outcome; and (5) selection of the reported result. Domain 1 was assessed at the study level and the other domains were assessed at the result level. Cluster-RCTs, were assessed similarly, except with two domains of allocation bias in place of domain 1: (1a) the randomization process, and (1b) identification or recruitment of participants [13].

For each domain, we made a judgement of high risk of bias, low risk of bias, or some concerns. We used the SQs and algorithm and considered whether to override the algorithm result, recording our reasons and supporting evidence. We reached an overall judgement at least as severe as the most severe domain risk.

Reviewers who conducted RoB2 assessments read the guidance and watched the Cochrane RoB2: Learning Live webinars [8, 13, 14]. Two reviewers had previous experience of using the original Cochrane risk-of-bias tool (TC, NL) and three were new to assessing risk of bias (CB, MJ, MP).

2.3 Evaluation of RoB2 usage

We recorded details of the time taken per study to conduct assessments (per reviewer) and reach consensus. We discussed and noted our difficulties with using the tool, and the resolutions we adopted.

We produced graphs, summary statistics, and conducted multivariable linear regression to explore whether time taken to assess risk of bias for a study (per individual, per consensus meeting, overall) was influenced by:

- the number of results to be assessed (increasing time);
- experience using RoB2 (decreasing time);
- number of reports per study (increasing time).

Additionally, we anticipated variability between individual reviewers and so included this as a categorical variable for regressions of individual assessment time.

In these analyses we only included studies with time data for two individual assessments. We calculated resource used in person-hours, and full-time equivalent (FTE) as one person working 7.5 hours per day, five days per week, with 33 days leave per year (including public holidays): 142.3 hours per month.

We summarised our approach and reasoning to RoB2 implementation.

3 Results

3.1 Overarching systematic review

Our literature searches produced 40,112 records after deduplication. We included 129 studies consisting of 496 reports, of which 113 reported results of interest (see Appendix A). Among these studies there were 860 results of interest for which we assessed risk of bias,[1] ranging from 1 to 33 per study (median 6).

3.2 RoB2 Assessments

In every result of interest we judged there to be at least some concerns about overall risk of bias (28%), with 72% at high risk of bias. A description of risk of bias by domain is provided in Appendix B.

[1] 34 were unsuitable for inclusion, 826 results are presented in Appendix B.

3.3 RoB2 assessment process time

Mean time per study to conduct an individual assessment (per reviewer) was 127 minutes (2h 7m; SD 67) and 54 minutes (SD 43) for the consensus meeting (see Table 1). We had complete timing data for 99 studies; overall these included 35,472 minutes of worktime (591.2 person-hours or 2.1 months of 2 x FTE work) including each individual assessment and two people in a consensus meeting (5h 58m per study, 47m per result).

Table 1. Descriptive data for time taken to conduct risk of bias assessments and consensus meetings.

	Individual assessments*	Consensus meetings†	Resource for overall process‡
Studies with complete data (n)	106§	105‖	99¶
Results of interest per study	7.4 (5.7) [1 to 33]	7.8 (6.0) [1 to 33]	7.6 (5.8) [1 to 33]
Reports per study	3.8 (2.8) [1 to 12]	3.9 (2.8) [1 to 12]	3.9 (2.8) [1 to 12]
Time per study (mins)	127 (67) [32 to 421]	54 (43) [6 to 271]	358 (183) [98 to 976]
Time per result of interest (mins)#	17	6.9	47

Data are presented as mean (SD) [min to max] unless otherwise stated.

* Studies with timing data for two complete individual assessments only. Times are presented per reviewer so total resource use is double.

† Studies with timing data for consensus meetings (following two independent individual assessments). Times are presented for the meeting in which two reviewers were present so total resource use is double.

‡ Studies with timing data for two complete individual assessments and a consensus meeting. Times are presented for total resource use counting both reviewers.

§ Seven studies missing: four with missing timing data for at least one reviewer, and three with more than two reviewers involved in the assessment.

‖ Eight studies with missing timing data for the consensus meeting.

¶ Fourteen studies not analysable for the overall process. Of the 106 studies with timing data for (only) two complete individual assessments, seven did not have timing data for the consensus meeting.

\# Only means are presented as times were recorded per study.

3.3.1 Factors influencing process time

Graphs and results of regression analyses are presented in Appendix C. The number of results of interest per study affected time to conduct individual assessments and consensus meetings, adding 22 minutes per result (95% confidence interval (CI) 18 to 26) to overall worktime. Number of reports affected time to conduct individual assessments but not the consensus meetings, adding 14 minutes per report (95% CI 6 to 22) to overall worktime. Experience reduced time taken to conduct individual assessments and consensus meetings. Additionally, there was substantial variation between individual reviewers.

Thirty-two studies were assessed by two experienced reviewers who had each previously assessed at least 25 studies in this review using RoB2. For these studies, overall worktime was 5 hours 15 minutes per study or 44 minutes per result on average. Regression analysis estimated this to be 178 minutes per study (2h 58m; 95% CI 139 to 218) plus 19 minutes per result (95% CI 15 to 24) (adjusted R^2 .73).

3.4 Challenges implementing RoB2

Although the guidance for RoB2 is extensive, reviewers found certain aspects of the guidance to be lacking specificity sufficient to operationalise it.

3.4.1 Deviations from the intended interventions

We were uncertain what evidence should be considered sufficient to indicate there were 'probably no' deviations from the intended intervention that arose because of the trial context (SQ 2.3). This signalling question often decided the judgement for the domain because we were unable to answer that both participants and personnel were unaware of their allocation for any of these complex intervention studies (SQ 2.1 and 2.2). The guidance provided an example of trial enrolment and randomisation potentially leading control participants to feel in need and unlucky and thus seek other interventions they would not have otherwise. This seemed like a risk that was always plausible although, perhaps, often unlikely, and one that was very difficult for trialists to investigate.

We answered 'probably no' for four studies: three where authors had specifically investigated control group behaviours and found no concerns; and one where we considered the stepped-wedge design would make such deviation unlikely. We answered 'no information' for most studies, answering 'probably yes' for nine studies with evidence of contamination.

3.4.2 Missing outcome data

We found several difficulties in implementing the guidance regarding assessment of missing outcome data. Firstly, standardising assessment of 'nearly all' data being available (SQ 3.1). We operationalised this as at most 5% of participants missing as a proportion of: the number allocated for continuous outcomes; or, recorded cases for binary outcomes (e.g. 1 person missing if 20 people died regardless of sample size).

SQ 3.2 asks "Is there evidence that the result was not biased by missing outcome data?" [8]. We judged there was insufficient evidence, even when study authors had conducted multiple imputation with multiple measured variables to correct for bias. Our outcomes of interest were so distal it was unlikely *all* relevant variables were included in such models (we were uncertain whether this could ever be a plausible assumption).

For almost all results where some data was missing it was plausible that missingness *could* have depended on the true value of the outcome (SQ 3.3). This was because outcomes were health outcomes and reasons for missingness typically included mortality, care home admission or withdrawal. SQ 3.4 delineates between a judgement of some concerns and high risk. It asks whether it is *likely* missingness depended on the true value of the missing result; the elaboration indicates we should answer '(probably) yes' if "Reported reasons for missing outcome data provide evidence that missingness in the outcome depends on its true value" [8]. Therefore, when we first applied the tool we invariably answered 'probably yes' to SQ 3.4 based on our reason for SQ 3.3. Almost all results were therefore judged high risk. It seemed inappropriate and at odds with the preceding guidance that we would judge a high risk of bias due to missingness when losses were relatively small and balanced in numbers and reasons; for example, for a continuous outcome where 5.1% of participants had died in both arms.

To decide between a judgement of some concerns and high risk we first considered whether more than 45% of participants/cases were missing overall, regardless of how balanced, as an arbitrary upper limit. Secondly, we considered whether differences in total numbers or reasons missing differed by our threshold values of 5%, or if insufficient detail regarding reasons was given. In any of these cases we would make a judgement of high risk. For remaining results where between 5% and 45% of participants/cases were missing overall we sought increasing balance in the numbers and reasons of missingness to judge the result some concerns only.

We decided against answering 'no information' to SQ 3.4 (which would have resulted in a judgement of high risk) in the common situation where numbers and reasons for losses were presented by group for a trial overall but not for each specific result of interest, although we were uncertain this was how we were supposed to interpret the guidance.

3.4.3 Measurement of the outcome

For participant-reported outcomes (PROs) ("involving judgement"), we had to judge the likelihood that knowledge of the intervention influenced assessment (high risk) or not (some concerns) (SQ 4.5). Based on the guidance we considered the degree of participant judgement for each outcome, whether certain interventions (e.g. alternative medicine) or closely related outcomes (e.g. ADL training for ADL outcomes) should indicate high risk, and whether studies with active comparators should only be rated 'some concerns' despite some of these features. We were concerned that such judgements were predicated on assumptions rather than evidence, risking our own biases influencing the assessment. In the absence of stronger empirical evidence regarding the factors influencing risk of bias for PROs, we decided that knowledge of the intervention could influence

assessment but that this was unlikely (some concerns in the absence of other problems). Our reasoning was that unblinded observers were a greater risk than unblinded self-reporting participants, many of the interventions may not be recognised as departures from usual care by participants, and measurements would often be temporally distant from intervention receipt. We were able to judge this domain low risk for some PRO results for which we concluded that the participants were probably unaware of the intervention received, usually in cluster trials.

3.4.4 Selection of the reported result

Domain five considers selective reporting of results. To reach a judgement of low risk, the algorithm requires the result of interest to have been analysed in accordance with a pre-specified analysis plan. Such plans are rarely available. When a dichotomous outcome that could only be measured in one way (e.g. mortality) was reported as the number of participants, we considered that this was equivalent to a situation where we gathered and reanalysed individual patient data, and therefore judged the risk as low, regardless of a pre-specified plan.

4 Discussion

This article detailed the substantial resource taken to conduct RoB2 assessments in a systematic review (358 mins/study) and estimated that multiple results and study reports increased time per study, while experience reduced time taken. We have detailed the way we operationalised guidance for missing outcome data, deviations due to trial context, knowledge of the intervention influencing assessment, and selection of the reported result. Overall, we found the signalling questions and algorithms helpful. However, sections of the guidance seemed unnecessarily discursive and theoretical with insufficient practical advice for interpreting the SQs. We also found the wording for some SQs misleading. Additionally, completing the SQs and the supporting free-text boxes for each SQ and each result in each study was time-consuming.

Our results relate to one particularly challenging systematic review with network meta-analysis of pragmatic trials of complex interventions that required deliverer and participant involvement. Therefore, the time taken and some of our difficulties may not manifest for other reviews. However, the findings are from a real-world review without special support from the Cochrane Methods Support Unit. The order in which we reviewed studies was not randomly selected and so estimates of the effect of experience are limited in this regard. We did not attempt to clarify uncertainties regarding risk of bias with study authors, as recommended for domain 5 [8]; such action may have affected the time we took as well as our judgments. The approaches we took to implementing RoB2 were based on extensive reading of the guidance and discussion among the authors who comprise

experienced trialists and systematic reviewers. Nonetheless, they may not fit with the intentions of the tool authors, so we advise caution in following these approaches.

We are aware of only one other study that reports upon the implementation of the RoB2 tool in a systematic review: Minozzi et al. analysed the impact an implementation document had on times and inter-rater reliability of their RoB2 assessments in a review of cannabis and cannabinoids for people with multiple sclerosis [11]. The supplementary implementation document details their approach to similar challenges. Like Minozzi et al. we identified an improvement in speed over time, although to a lesser extent. We additionally estimated how number of results and reports per study affected time. Minozzi et al. implemented a 90% cut-point for judging nearly all data being available, while we implemented a 5% rule relating to missingness (SQ 3.1). More specific guidance from the RoB2 tool authors would help to develop consistency between review teams, in the absence of which reviewers are likely to develop their own cut-points. We decided that none of the analyses that attempted to correct for missing outcome data were sufficient to judge a low risk of bias whereas Minozzi et al. accepted these. For bias due to assessment of the outcome being influenced by knowledge of the intervention received we both decided that participant reported outcomes requiring judgement should be treated as some concerns rather than high risk, although their position was informed by relevant evidence.

We agree with Minozzi et al. [11] that review authors should develop guidance specific to their review to establish how to assess issues such as those described in this article and assure consistency across assessed results. Review authors can use our findings to plan the time it will take to assess risk of bias, although this may vary substantially. Review users should be aware that RoB2 implementation will affect judgement and thus certainty assessments.

Our findings suggest refined guidance from the tool developers is warranted, with a focus on operationalising the tool. We would welcome further specific examples directly related to the signalling questions, and more examples of 'judgement calls' rather than extremes. For example, the What Works Clearinghouse Standards Handbook provides boundaries for unacceptable risk of bias for combinations of overall and differential attrition under cautious and optimistic assumptions [15], the former being similar to our implementation for SQ 3.4. However, we recognise that it is important to limit the overall volume of guidance. Sometimes the theoretical background included factors that were not to be assessed; these and empirical evidence could be moved to an appendix. Reporting guidelines and critical appraisal tools should also include details of risk-of-bias implementation (e.g. PRISMA 2020 [16], AMSTAR2 [17]).

5 Conclusion

The RoB2 tool is a positive development from the original risk-of-bias tool, with the addition of signalling questions and an algorithm likely to improve consistency if carefully followed. Assessing individual results is useful for differentiating within-study risk of bias between outcomes and timepoints, particularly in domains such as missing outcome data. This combined with an overall risk-of-bias judgement assist in progressing to an assessment of the certainty of the evidence. Nonetheless, conducting assessments with RoB2 is a substantial and challenging undertaking. We recommend reporting guidelines and critical appraisal tools reflect this, requiring implementation details. Furthermore, the burden on reviewers should be reduced by improving the guidance with greater emphasis on the application of, and location of dividing lines for, each signalling question.

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Data availability

An anonymised version of the dataset upon which this article is based will be made available upon reasonable request to the author.

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