**Meeting title**: RoB 2 Pilot Web Clinic

**Location**: GoTo Meeting

**Date and time**: 27 February 2020, 09:00-10:00 (GMT)

**Recorded**: Yes [link to recording](https://transcripts.gotomeeting.com/#/s/79a49f419cc90fb5c22ab98d0835450b7ac2036cfec94e5875c68e0421a02492) (all past recordings are available [here](https://www.dropbox.com/sh/boc6gh44jh4q3fb/AAAGiNSZHXNf_t8KVo0rhLRxa?dl=0))

**Chair:** Kerry Dwan, Methods Support Unit Lead and Statistical Editor

**Other organisers:** Ella Flemyng (Methods Implementation Coordinator), Rebecka Hall (RevMan Product Owner), Tess Moore (Systematic Review Methodology Editor)

**Notes**: Tess Moore (Systematic Review Methodology Editor)

# **Minutes1. Update from last Web Clinic**

RevMan Web

1.1 The guidance for reporting RoB2 recommends that authors don’t need to use domain names as subheadings when they write up RoB2. But in RevMan Web (for users of RoB2) the risk of bias section had included these as fixed headings. As of today, in RevMan Web, these domain name subheadings (Under the ‘Risk of bias in included studies’ heading) are removed. This is to match the guidance on write up of RoB2.

1.2 In RevMan 5 it is possible, within the analyses, to switch off and on studies in a meta-analysis but this functionality was not available in RevMan Web. From this afternoon this this functionality will be available in RevMan Web.

## **2. FAQs about RoB2**

## **2.1 Domain 2:**

**Question 1:** For signalling question 2.1 What do we do for a trial that states only “Double blind” if all else looks ok (identical drugs etc)? Do we give them the benefit of the doubt?

**Answer 1**: We ask users to look at the trial and assess if they think blinding has been carried out reasonably well or not and to make a decision based on that (PY/PN). See response to Question 2 below.

**Question 2:** We are interested in how participants/ trial personnel knowing what treatment they were on - affects bias? We keep getting ‘Low’ risk of bias - despite knowing that participants (and or personnel) in the trials we are looking at can tell what treatment they are receiving. This is very different to how we would have judged trials using ROB 1.

**Answer 2:** In RoB2 the bias around blinding of participants was completely overhauled compared to earlier versions. Answers to this question will differ according to whether you were interested in “Effect of assignment” or “Effect of adherence”. Participants knowing which the intervention they received does not in itself lead to bias. The key to this is how the answers to your questions lead you through the algorithm, and how you answer other key questions for this domain. In short if there are no other issues with implementation of the intervention then a judgement of ‘Low risk of bias’ will be reported for this domain even if the study is unblinded. For more information please see Section 5.1.3 in the detailed guidance.

If you are considering effect of assignment:

If you follow through the algorithm for this (See Figure 2 of the detailed guidance).

If participants (personnel) are aware of their intervention (Answer Y/PY to signalling question 2.1 and 2.2) But there are no deviations that have arisen because of the trial context (Answer N/PN to signalling question 2.3) Then this domain will be at ‘Low risk of bias’.

For more information please visit Section 5.1.3 in the detailed guidance.

If you are considering effect of adherence:

If you follow through the algorithm for this (See Figure3 of the detailed guidance).

If participants (personnel) are aware of their intervention (Answer Y/PY to signalling question 2.1 and 2.2): And a) any variations in interventions (that would not be expected in a trial), are balanced between groups (signalling question 2.3); b) No additional failures of implementation were found that are likely to affect the outcome (signalling question 2.4); And finally c) that the analysis was appropriate (Signalling questions 2.5) this domain will be at ‘Low risk of bias’.

**Response 2 Tess Moore:** Recent paper in the BMJ on effect of blinding on effect sizes. The META/Blind study. <https://www.bmj.com/content/368/bmj.m229>

**Question 3:** Can you please provide example of what was a ‘non protocol’ deviation from interventions are?

**Answer 3:** Some of these are provided in in Section 5.1.2.1 Section 5.1.2.2 and Box 5 of the detailed guidance:

For ‘Assignment to the intervention’ we would be looking for variations in practice that come about because the participants are in a trial. As an example, if as a result of the recruitment process - the participants assigned to placebo or no intervention, went on to take the intervention, then that would be a protocol violation. E.g. in a trial of debt advice versus no intervention for improving financial and general circumstances. The intervention was a debt advice phone line that was nationally available to all citizens in that country. During the informed consent process all participants were made aware of the national debt advice helpline and many participants (10%) in the control group sought help from the debt advice helpline (Pleasance & Balmer 2007 doi.org/10.1111/j.1740-1461.2007.00102.x). More examples are available in Section 5.1.2.1 of the guidance and in Box 5 of the detailed guidance.

It can be helpful for those reviewers most familiar with the subject area to think through what might constitute potential deviations and to list these in the systematic review protocol.

For reviewers considering the question ‘Adherence to the intervention’: There are more variations in intended intervention that are concerning with regards to bias than for ‘Assignment to the intervention’. The is because we are interested in both those that arose because of the trial process (as we are for adherence) AND all the others that happen not because of the trial process. These are based around participants stopping taking the intervention. But, the reason why participants stop taking the intervention is key. For example: If participants were bored with their intervention, and stopped taking it, or stopped attending - this **would not** be considered a non-protocol violation. However, participants withdrawing from the interventions due to adverse events or side effects - would be a protocol violation. There is more examples and more information on this in section 5.1.2.2 and in Box 5 of the detailed guidance.

It can be helpful for those reviewers most familiar with the subject area to think through what might constitute potential deviations and to list these in the systematic review protocol.

**Question 3.1: Rachel Richardson** We ran a trial a few years ago in which we randomised people to three interventions 1: CBT online free for users and 2) CBT paid for and 3) no intervention. A lot of the people in the ‘no intervention’ arm of the trial sought out the free intervention because they could and they found out about it as part of the trial. How does this affect the risk of bias? In the real world people would do this they seek out additional help? Would you rate it as high risk of bias or would it depend on whether it was adherence or assignment?

**Response 3.1 Julian Higgins:** It depends on the reasons they sought the free intervention. In the real-world people will look for free advice to solve their medical problems - and that is not a problem (a risk of bias) in itself. It *is* a problem (risk of bias) if they are told about the free intervention - as part of the trial recruitment process - in a way that they wouldn’t ordinarily know about it - were they just in a real world setting.

**Question 3.2 Julian Higgins:** May I ask a question to this group. If people are struggling with this trial context issue we, the developers, were thinking of splitting it into two questions: One about whether the so-called recruitment and engagement activities and the consent process led to participants behaving differently than they would in the real world. and 2) whether people implementing the interventions somehow undermined the trial comparisons. We were wondering whether you think that would be a useful modification to make?

**Response 3.2 Kerry Dwan :** At present many of the people on the call are not yet using the tool, and many reviews are at the Protocol stage so they are working on data extraction.

Ella Flemyng: We can include this question in our next email out to pilot groups to seek answers?

**Question 3.3 Silvia Minozzi:** Could Julian write down a preliminary version of the two questions, we could see if they are useful in our context (pilot review)

**Response 3.3 Julian Higgins:** The wording of the questions would take some work and consideration to get right – so it is not possible to draft them quickly.

## **Question 3.4 Fi Stewart**: With reference to the second question (does knowing what treatment trial participants were on affect bias?). I wanted to clarify, is this referring to people in the trial not being blinded but it could still be low risk of bias because the outcome is objective (e.g. mortality)?

**Response 3.4 Julian Higgins:** In this domain (Domain 2) blinding is not related to the outcome it is about how people behave during the trial, whether they seek other interventions, whether they take medicine as prescribed, or do what they are meant to do. Many useful trials are open label/ pragmatic trials because we are only interested in concealed trials when we are interested in the ability of the active ingredient to effect change.

**Question 3.5. Celest Naude:** So, we have a trial in which participants are randomised to a specific diet and they know which diet they are getting. We have evidence that participants didn’t like the diet. We know this from their diet record keeping etc. Is this something we need to consider when making a judgement of risk of bias for this domain?

**Response 3.5 Julian Higgins:** If you are assessing *Assignment to intervention* then no - absolutely not. It does not matter at all if people choose to not use their diet and go off to do something else - because you are assessing the effects of being *assigned* to the diet. People are free to choose what they want to do within the trial. *But* if you are assessing *adherence to the diet* then it really matters. But we generally recommend that people don’t assess *adhering to the intervention’* unless they really know what they are doing and want to answer that question.

**Question 4.**, SQ 2.3: in the guidance “trial context” is defined as: “*We use the term trial context to refer to effects of recruitment and engagement activities on trial participants and when trial personnel (carers or people delivering the interventions) undermine the implementation of the trial protocol in ways that would not happen outside the trial”*

**Answer Question 4:** Please see the answer to **Question 3** above, and subsequent questions which covers this question.

**2.2 Domain 3:**

**Question 5:** I saw in the signalling question explanation for question 3.1 the question “For continuous outcomes, availability of data from 95% of the participants will often be sufficient”, how close to this threshold should I consider for missing data? E.g if there are 93 or 94% available?

**Answer 5:** We do not want users to consider this example of 95% as a strict cut off. The potential impact of missing data upon the effect estimate will vary depending on the proportion of missing data, the type of outcome, and (for dichotomous outcomes) the risk of the event. There are conventions that a proportion of missing data of 5% or less is ‘small’ and that over 20% of missing data is ‘large’. However, we urge reviewers to read through all the guidance on missing data. To find out more about the amount of missing data please refer to section 6.1.3.2

Example: (See section 6.3.1.2) If more people die in the missing data group (20%) than the people for whom we have data (2%) the estimation of mortality rates can vary a lot. In this case - it can nearly double. (See Table 1 below)

Table 1 Example of effect of missing data on mortality (data from Section 6.3.1.2 of the Cochrane Handbook

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Proportion of missing data  | Number randomised (int)  | Data available for (int) | Number of deaths  | Mortality  |
| The people recruited  | 0%  | 1000 | 1000 |  |  |
| The outcome data available  | 10% | 1000 | 900 | 18 | 2% \*  |
| The missing data  |  |  | 100 | 20 | 20%  |
| Including this missing data  |  | 1000 | 1000 | 38 | 3.8% α |

\* Calculated as =(18/900) \* 100

α Mortality nearly doubles compare to what we see in the included data 3.8% vs 2%)

**Question 6:** For this domain, does the 95% threshold hold if the continuous outcome was dichotomised?

**Answer 6:** For signalling question 3.1 if continuous outcome data are dichotomised, it should be considered as dichotomous data. The place where dichotomised continuous outcome data are not treated as dichotomous data (see section 6.1.3 section 3) is for signalling question 3.3.

**2.3. Domain 4:**

**Question 7**: Signalling question 4.3 What do we do if it says ‘double blind’ but we don’t have any other information?

**Answer 7:** This question is concerned with whether outcome assessors could be aware of the intervention. If there is no other information, then either use ‘NI’ or assume they were aware of the assignment.

**2.4. Domain 5:**

**Question 8**. Please could you clarify what “before unblinded outcome data were available for analysis” means (Signalling Question 5.1)

**Question 9:**Signalling question5.1: *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?* Query: If the protocol is available only in clinical trial. gov or EudraCT, etc, the statistical plan is never reported. In this case the response to SQ 5.1 is always NI. Is it correct.?

**Answer 8 & 9.** See section 8.3.1 of the full guidance document: This states that analysis intentions may be documented in a range of clinical sources e.g. trial registry entry, trial protocol or the design paper. The statistical analysis plan (SAP) may provide the most details about whether a pre-specified plan was finalised before unblinded outcome data were available for analysis. But this may not be published. Prespecified plans can be compared to those that were described in the trial reports containing the results.

When assessing bias of this domain review authors MUST check the date stamp of all these documents (protocol, or statistical analysis plan, trial register), this is to ensure they were deposited

before trial data were released to the statistician to analyse (or before the end of the study). This is because some trials are registered retrospectively.

**Question 8.1 Silvia Minozzi:** for signalling question 5.1, the analysis plan is almost never reported in the protocol, so the answer to the SQ will be NI in the vast majority of cases, correct?

**Response 8.1 Julian Higgins:** If that's the case, then yes. However, these days I see quite a few protocols that provide sufficient details of the analysis to be confident about answering questions on the analysis.

**Question 8.2 Silvia Minozzi:** and, consequently, the answer to SQ 5.3 will be also be NI, because we have no analysis plan?

**Response 8.2 Julian Higgins:**

That may be the case - that there is NI and that is the only response to give. However we may easily have evidence that there was a problem in a trial, despite there being no analysis plan. Within the body of a trial report we might see inconsistency between the methods reported and the results presented that reveals selective reporting, and some people are quite blatant about it, they might state “We only presented statistically significant results”. If we see evidence of bias we should report it rather than stating NI. In addition, it might work the other way and you may be confident enough, despite not seeing an analysis plan, to be very sure that this particular group of trialists would have followed through their plan. However, if you want to make that judgement (that if there is no information for signalling question 5.1 and that all subsequent signalling questions for that domain are NI) , that's absolutely fine, use ‘Probably no’ just explain it and provide a reason.

For RoB2 we want the best judgements made not just, you know, taking everything entirely, literally, what we read. We want to try and read through it to get good judgement about risk of bias, which may not be brilliantly replicable, but I'd rather have the best judgements out there than 100% agreement between raters.

**Question 10:** Sig question 5.2 We have specified we are interested in the outcome ‘*30% reduction in spasticity*’ which is a distinct, well known, often used outcome in the Multiple sclerosis field. In the protocol for an RCT the trialists state they will collect data on ‘*30% reduction in spasticity’* And ‘*50% reduction in spasticity’* BUT in the write up of the review they present only on ‘*30% reduction in spasticity’.* How do we answerSignalling question 5.2? Was it selected from multiple eligible measurements?

**Answer 10:** For this question you would answer ‘No or Probably no’. That is because the outcome of interest for you (as specified in the systematic review protocol is ‘*30% reduction in spasticity’.* And the trialists have provided this data. However, if you had wanted‘*50% reduction in spasticity’.* Then the answer to signalling question 5.2 would be ‘Yes’*.* The key to answering this question is consideration of what you have specified in your systematic review protocol as your outcome of interest. This is covered in the ‘Elaboration’ for question 5.2 in Box 11 of the detailed guidance

**Question 10.a Rachel Richardson:** Can you please Clarify Question 10. So in the, in the protocol for the trial that we're considering they mentioned that they are looking for two different and outcomes regarding reduction in spasticity, but you said that we wouldn't then count that as selecting from multiple eligible measurements because we're only interested in the 30% reduction outcome?

**Response 10.a Kerry Dwan:** In the protocol for the review. The reviewers are looking for only one outcome. The more specific and detailed you are in the Protocol the less the chances of risk of bias. Kerry shares screen and talks through the Table 2 (below) demonstrating the balance between the reviewers’ specification of outcome.

**Question 10.b Rachel Richardson**: So, if that was the case, that they hadn't reported a 50% reduction in spasticity you would still have concerns, wouldn't you? about why haven't they reported that result in their paper? So, would that be a concern that you would discuss in the publication bias section? I am asking because we have changed how we assess trials (comparing the way we did it for RoB1 and how we are doing it now for RoB2) in terms of discussing missing outcomes and the like.

**Response 10.b Kerry Dwan:** For this review we were originally concerned about this until we sought clarification. But this outcome “50% reduction in spasticity” was not pre-specified for our review and so the lack of reporting is not a bias. If the 50% reduction in spasticity was an outcome we were interested in for our review, we would discuss the lack of reporting under publication bias and use the new RoBME tool.

**Response 10.b Julian Higgins:** This goes back to this distinction between quality and bias, which we (reviewers) are used to in terms of tools to assess trials for systematic reviews. But now we are considering just bias. For bias we need to consider what are the results that we want and what are the results that we're taking and using, and what should we believe? If we get what we want, (what we prespecified in our protocol) then we don't need to worry, and that's what this table (see Table 2 below) tries to portray. And so, for the RoB2 tool, it's about being much more targeted as reviewers in specifying what results/outcomes we want and assessing only that. We're interested in *specific* results, we are interested in bias in *only* those results and the fact that maybe the trialists have done some things that are less than ideal, like not reporting a sample size calculation or not reporting some of the results that we're not interested in, yes that is interesting, but not actually important for the results of our review, and not bias.

**Question 10.c Silvia Minozzi:** Does this apply to different follow up time. E.g. if you as reviewers you were interested in “Follow-up time 12 months” but the trialists only report at Follow up of 10 months. Would we consider this as High risk of bias?

**Response 10.c Julian Higgins:** Yes, this is correct.

Table 2: Assessing selective outcome reporting bias/ Missing Evidence

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Systematic Reviewer wants (a priori)** | **Trial analyses** | **Trial reports** | **Reviewer uses** | **Is there a risk of bias?** |
| **Any measure of depression** | HAM-D (P=0.01), Beck (P=0.1), mHAM-D (P=0.2) | HAM-D | HAM-D | Yes |
| **HAM-D only** | HAM-D (P=0.01), Beck (P=0.1), mHAM-D (P=0.2) | HAM-D | HAM-D | No |
| **Beck only** | HAM-D (P=0.01), Beck (P=0.1), mHAM-D (P=0.2) | HAM-D | nothing | RoB 2 not applicable (bias in M-A)\* |
| **HAM-D if available, then Beck, then mHAM-D** | HAM-D (P=0.01), Beck (P=0.1), mHAM-D (P=0.2) | HAM-D | HAM-D | No |
| **Beck if available, then HAM-D, then mHAM-D** | HAM-D (P=0.01), Beck (P=0.1), mHAM-D (P=0.2) | HAM-D | HAM-D | Yes |

Table from Julian Higgins.

\* This is covered in the RoBME tool a tool to assess for missing evidence

**Question 11:** For the trials which provide IPD, this analysis is being done by the systematic review team, rather than the trialists. We therefore find ourselves judging our own analysis and transparency which may be an issue. We have an SAP which is published, and we use that to guide selection of relevant outcome variables/data for analysis. We wonder whether there are any suggestions for us to consider when making domain 5 judgements on an IPD dataset?

**Answer 11.** If reviewers have the IPD then Domain 5 will be low risk of bias. As long as nearly the trialists nor the reviewers are selectively reporting the data and the trialists give the reviewers everything they ask for there will be no risk of bias.

**3. Any other business**

3.1 Recent updates to the RoB 2 Pilot Starter Pack. None. But FAQs from the webclinic are planned to be updated.

3.2 Next web clinic – Thursday 26 March, 16:00-17:00 (GMT).

3.2 Request from Ella Flemyng to all pilot review groups to drop us a brief email with the status of your review for our records.