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

**Location**: GoTo Meeting

**Date and time**: 26 March 2020, 16:00-17:00 (GMT)

**Recorded**: Yes link to recording (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: Julian Higgins (Bias methods Group)** Tess Moore (Systematic Review Methodology Editor)

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

# **Minutes1. Update from last Web Clinic (No Update)**

RevMan Web (Not on this webclinic)

## **2. FAQs about RoB2**

## **2.1 Domain 2:**

**Question 1:** How do we deal with Naïve per protocol analyses when considering effect of adherence?

**Answer 1:** This is not an appropriate analysis to estimate the per protocol effect. It removes the benefit of randomisation since it removes people from one or more arms on the basis of characteristics (e.g. adherence) that are likely to be related to prognosis. The answer to SQ2.6 would then be N

**Question 2:** Is there a nice simple, plain language explanation of the difference between 'effect of assignment' and 'effect of adherence'? Or some good examples of when you would use each one?

**Answer 2:** This is tricky – we have tried to simplify, describe a rationale and to provide examples.

”Effect of assignment” or “Intention to treat” or “ITT effect”: The RoB2 default is for “Effect of assignment”. Most review authors should be looking at “Effect of assignment”.

* 1. Most systematic reviews will be interested in the ‘Effect of assignment’ This is also known as the ITT or ‘Intention to treat’ effect. This is what most RCTS are setting out to assess.
	2. The aim of ITT analysis in clinical trials is to determine the effect of the intervention as delivered in the real world.
	3. Within the clinical trial – for ITT analysis - every participant randomised should be in the primary analysis. Patients who drop out, switch treatments, or take a different treatment should all be included. And they should be included within the group to which they were originally randomised.
	4. The participants are analysed according to their original assignment even if they change treatment. The aim is to keep the groups as complete as possible. Trialists may call this the “Full analysis set”.
		1. Participants may be excluded from the analysis set if outcome data were not available. However, this problem is addressed in the domain ‘Bias due to missing outcome data’
		2. The reason this is important in systematic reviews - is that we want to provide evidence from the real world on how effective an intervention is. And if people are assigned the intervention, and drop out – switch treatments, etc – that is all part of how effective the treatment is. E.g some people will forget to take their pills, or may stop going to therapy sessions if they start feeling better. These are all legitimate ‘effects’ of the intervention as delivered.

”Effect of adherence” or “per protocol effect” (usually of interest to patients – but not normally of interest to reviewers). A good example is screening.

* + 1. The aim of a per-protocol analysis in a clinical trial is to find the treatment effect under optimum conditions. If a participant took the intervention exactly as directed – what would the potential benefits/ harms be?
		2. For this analysis some participants need to be thought about carefully:
			1. Any major protocol deviations (i.e people not taking the intervention or following the intervention as it should be’
			2. Non-availability of measurements from the primary endpoint
			3. They didn’t get enough of the intervention (again this would be a deviation from intended)
		3. Unfortunately, the methods that are needed to address these problems are complex. The solution is not simply to drop participants from the data set.

Examples

* + 1. If you were preparing a review “Effects of topical intervention for Eczema in children” than you would most likely be interested in effect of assignment. Does the intervention work as prescribed to people to give to their children? For a given RCT of Experimental cream vs placebo cream - you would include all the participants – no matter what happened during the treatment. And overall the effect size found in the analysis would be that of participants in a real clinical situation (as much as is possible in an RCT). It would include, in intervention and control arms, all the people who stopped applying the cream, applied it less regularly than was prescribed, those who were moved to a more intensive treatment etc.
		2. If you were preparing a review of prostate cancer screening – you might want to assess both effects. The effect of assignment – to see how well screening works in reducing mortality were you to roll out a screening service in your country. This is because we know that not all men asked to attend screening would attend.
		3. In addition to this you would also want to assess “Effect of adhering to the intervention”. This is because you would want to be able to answer for individuals that actually do attend screening what is the effect of screening on them of attending screening. We know that those people who do not attend for screening are likely to be systematically different to those to take up screening. For example, they might be more likely to be obese, more likely to be older and therefore might be more at risk of prostate cancer. So, it would be inappropriate just to remove them from the data set, since we then do not compare similar groups.
		4. This is described in the Introduction to RoB2 Webinar by Luke McGuinness. [Link to Evidence Synthesis Ireland Webinar](https://evidencesynthesisireland.ie/rob2-0/): <https://evidencesynthesisireland.ie/rob2-0/>

Question 3: Is there an example review for “Effect of adherence”?

Answer 3: No, not at the moment. Some author teams have used it for looking at adverse effects of intervention – looking at what really happens if people take the drug? But we wouldn’t encourage people to necessarily to do this. Looking at the effect of assignment is not for novice teams. Most should use Effect of assignment.

**Question 4 :** If the ITT analysis (for an RCT) is NOT presented as the primary analysis but is buried in the back of a supplement or other paper – is it a problem?

**Answer 4**: No – its fine as long as you find it somewhere.

**Question 5:** In the review we are working on. For our outcome of adverse effects the trilalists have reported adverse effects using only a per protocol analysis. How do we deal with this?

**Answer 5:** We would apply the signalling w questions in the usual way. That means if your ROB2 is set to “Effect of Assignment” (as advised for most reviews) then you will find that when you get to assessing the analysis for this outcome (Signalling question 2.6) it will come out as ‘High risk of bias’ because the trialists have used a per-protocol analysis.

**Question 6:** For one of the studies that we have analysed the RoB, there was a large proportion of clients in both the intervention and control groups who were excluded from the analysis in the study, as they did not receive the intended intervention. Therefore, we have answered PY in relation to 2.4 in the Effect of Adhering to intervention (Signalling Q: Could failures in implementing the intervention have affected the outcome?) However, we have also answered Y for 3.1 (Signalling Q: Were data for this outcome available for all, or nearly all, participants randomized?) for the same reason. It seems a little unfair to penalise the study in 2 domains for the same reason.  What would your advice be in this situation?

**Answer 6:** People may be missing from the analysis for two reasons, and they are dealt with in different parts of the tool – so there should be no double counting of reasons. The first reason is exclusions by the trial investigators. This is often done, for example, to exclude people who did not receive the intervention when doing a naïve per-protocol analysis. These exclusions are addressed in Domain 2 (question 2.4). The second reason is when there were outcome data should have been included but were missing (e.g. due to drop out or missed clinic visits). These missing data are addressed in Domain 3 (question 3.1). Your example fits squarely in the first of these alternatives.

## **2.2 Domain 3:**

**Question 7**. How do we think about missing data for per protocol analyses?

**Answer 7**. By per-protocol analysis Do you mean “Assessing the effect of adhering to the intervention” if so then:

Failure to include all participants in the analysis for “Assessing the effect of adhering to the intervention” is covered in two domains:

1. Trial participants who were excluded by the trial investigators, for example because they did not adhere to assignment are dealt with in Domain 2. “Deviations from intended interventions”. There are signalling questions specific to “Effects of adherence to intervention” for Domain2. These are patients who switched treatment arm etc. See signalling questions 2.5 and 2.6. See section 5 of the guidance tool.
2. For Domain 3 “Bias due to missing data” the signalling questions are the same whether we are assessing the “Effects of assignment to intervention” or “Effects of adherence to intervention”. This is because the “Circumstances in which missing data lead to bias are similar regardless of the effect of interest” (Section 6.1.2 Detailed Guidance.

Section 6.1.2 of the detailed guidance describes how we assess bias due to missing data when estimating the effect of adhering to the intervention. However, it is advisable to read All of the detailed guidance in section 6 to help fully understand this domain.

The guiding principle for Domain 3 is to consider “in order to estimate the effect I am interested in estimating (adherence or assignment) what data would I want to have AND are any missing in the analyses the trialists have presented?

For a per-protocol analyses e.g. an instrumental variable analysis is that it needs ALL the participants who were randomised in the trial. So, in order to estimate the per protocol effects – you need to check to see if there are any data missing from the analysis – as the trialists have presented it?

**Question 8.** SQ 3.2. Is there evidence that the result was not biased by missing outcome data?

In the guidance is stated that: “ 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.”

For non-statisticians can be difficult to understand and recognize adequate analyses and sensitivity analysis. We’d like to have a detailed and clear list (also for non-statisticians) of 1) analysis methods that correct for bias and 2) types of sensitivity analyses adequate to show that there is no relation between missingness in the outcomes and its true value?

**Answer 8.** It is not helpful to focus on methods per se. The important thing is to ensure that the sensitivity analysis entertains the full plausible range of outcomes that the missing participants could have experienced. This will always require judgement. There is no list of “analysis methods that correct for bias”, since we cannot know if the analyses conducted will achieve this. There are a few that in general will not correct for bias (like last observation carried forward, and most multiple imputation approaches).

The trick is not to worry too much about the ‘high falutin” stats methods used by the trialists – rather to focus on phrases like ‘we assumed that’ to see what assumptions they have made about people who were missing… you have to be sure that they have looked at the sort of outcomes people might have had – if they weren’t missing.

That is something you can look at with your content judgement

And that's something that you can use with your content judgement, without needing, to understand the statistics. Because they should tell you what assumptions they made about those people in a way that means something to you, even if you don't understand statistical methods that are used on top of those.

## **3.       Update on the status of the cluster and crossover trial extension:**

Until the extensions are ready, details should be ‘constructed’ from available materials as follows:

**Cluster RCTs: we have a firm recommendation**

Start with RoB 2 as it is

Refer to Section 23.1.2 in the Cochrane Handbook and Table 23.1.a of the [Cochrane Handbook](https://training.cochrane.org/handbook/current/chapter-23#_Ref529610397). These describe bias in cluster RCTs. They will help you to answer the questions, in addition to the main RoB 2 guidance.

To the domains of RoB2 add a domain: “Bias arising from the timing of identification and recruitment of participants”. For this domain use the signalling questions in the from Domain 1b of our [archived version](https://eur01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.riskofbias.info%2Fwelcome%2Frob-2-0-tool%2Farchive-rob-2-0-cluster-randomized-trials-2016&data=02%7C01%7Ckdwan%40cochrane.org%7C3570c2d9595047d44cb908d7bc459124%7Cb6c2e21e4db74533916398c1451c1caa%7C0%7C0%7C637184879288825340&sdata=bT6wZdqH28FjV%2BkhN8e6ublou3XJNsw4HXZ4vgGO73o%3D&reserved=0).

**Cross-over RCTs: Our current recommendation is this**

The following is our current recommendation ***please note that the eventual version for cross-over trials will look rather different.***

Start with RoB 2 as it is

Refer to Section 23.2.3 in the Cochrane Handbook and Table 23.2.a of the [Cochrane Handbook](https://training.cochrane.org/handbook/current/chapter-23#_Ref529610397). These describe bias in cross-over RCTs. They will help you to answer the questions, in addition to the main RoB 2 guidance.

* 1. For Domain 2 “Bias due to deviations from intended interventions” use the signalling questions in the from Domain 2 of our [archived version](https://eur01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fwww.riskofbias.info%2Fwelcome%2Frob-2-0-tool%2Farchive-rob-2-0-cluster-randomized-trials-2016&data=02%7C01%7Ckdwan%40cochrane.org%7C3570c2d9595047d44cb908d7bc459124%7Cb6c2e21e4db74533916398c1451c1caa%7C0%7C0%7C637184879288825340&sdata=bT6wZdqH28FjV%2BkhN8e6ublou3XJNsw4HXZ4vgGO73o%3D&reserved=0).
	2. For Domain 3 “Bias due to missing outcome data” use information in signalling question 3.2 of the [archived version](https://www.riskofbias.info/welcome/rob-2-0-tool/archive-rob-2-0-cross-over-trials-2016) to inform your answer to question 3.2 of the standard version.

***Please note:*** If you have intended from the OUTSET to ONLY use data from the first period of the cross-over – then you can use the standard version of RoB2 as it is. However, please be alert to the potential impact of selective reporting of first period of data only when carry over is detected by trialists. Omission of trials which do not report first period data may lead to bias at the meta-analysis level. For details and further explanation read section 23.2 of the Cochrane Handbook.

## **4. Feedback from an author on writing up RoB2**

Beth provided some feedback Beth feedback on writing up: Her review has 20 studies and 40 outcomes.

Beth started writing up before they got the guidance and have now scrapped their first draft. This took the form of a long descriptive summary, as you would do for RoB1. Their second draft focuses on generalisations and patterns across RoB2 and is more of a synthesis. There a have tended to be )for their review) few differences between RoB judgements for the different study outcomes. This has made it easier to summarise RoB findings. Yet they are highlighting patterns. E.g. if outcomes are scoring High RoB in a specific Domain or Domains they are summarising that.

They are also describing their sensitivity analyses.

Beth reported that they missed the ability to visualise the RoB2 assessments – in graphs and summary tables as this isn’t yet available in RevManWeb.

One suggestion for Beth and other teams, is to use RoBVis to generate tables/ graphs of RoB2 decisions, until this functionality is available in RevManWeb. This is the link to the [RoB2 webinar](https://evidencesynthesisireland.ie/rob2-0/)

## **5. Feedback from an author on implementing RoB2**

Beth: We found challenges ns being consistent with making judgements in RoB2.

Kerry: We are assessing ROB2 with Graziella for our review on Cannabis for MS. We also were finding consistency difficult. And the team have put together a document to help us approach the signalling question to the trials we are finding for this review.

Graziella: We found it necessary to decide how we can answer in the specific context of your review. And to add in a supplement how the authors decided to answer the signalling questions.

Julian: We have a strong view that all of the signalling questions and decisions should be in a supplementary file. On a data sharing website. Either the data repository sites available for your university site. Or a free scientific data sharing platform.

Kerry: Cochrane editorial advice is to ensure you have all the decision data stored on a data repository website where it is available to all.

## **6. Any other business:**

1. Recent updates to the RoB 2 Pilot Starter Pack.
2. Ella off sick at the moment
3. Link to Ireland Webinar
4. Next web clinic – Thursday 30 April, 09:00-10:00 (GMT).
5. Request from Ella Flemyng to all pilot review groups to drop us a brief email with the status of your review for our records.