SWAR 22: Evaluating baseline imbalances in randomised trials included in a systematic review assessing numerical formats for communicating risk

Objective of this SWAR
To compare the outcome of risk of bias assessments of randomised trials included in a systematic review using the Cochrane RoB 1 tool with and without evaluations of baseline imbalances on (1) the classification for risk of selection bias as low, unclear or high, and (2) the overall certainty of evidence in the primary outcome of the systematic review (very low, low, moderate or high).

Study area: Study Identification
Sample type: Studies
Estimated funding level needed: Unfunded

Background
Randomized trials, and the systematic reviews they contribute to, are considered to provide the most valid assessment of the causal effect of healthcare interventions. However, flaws in the design, conduct and analysis of trials may render their findings unreliable. Therefore, evaluating the risk of bias in randomised trials is a pivotal step in the process of conducting systematic reviews. The most widely used tool for assessing the risk of bias in randomised trials is the original Cochrane Risk of Bias (RoB) tool [1]. This incorporates seven items in six bias domains, with selection bias being the only domain divided into two items - random sequence generation and allocation sequence concealment. The RoB tool was updated to become RoB 2 and one of the main changes involves the assessment of selection bias [2]. In the earlier version (RoB 1), selection bias was evaluated based on the methods employed to generate the randomisation sequence and to conceal this sequence during the randomisation process. Once evaluated, the risk of selection bias is categorised as high, unclear or low.

Issues with the randomisation precipitate selection bias, leading to baseline differences in groups being compared. Hence, another key indicator of selection bias is the baseline imbalances of attributes known to hold prognostic significance. This could hint at the likelihood of improper conduct or even failure to implement true randomisation.

Although RoB 1 does allow for the assessment of baseline imbalances under the "other biases" domain, this evaluation is not included in all systematic reviews. Moreover, even when included, the assessment of baseline imbalances does not automatically influence the assignment of the risk of selection bias to the studies included in the review.

In the updated tool (RoB 2), the first domain – “bias arising from the randomisation process” – encompasses not only the assessment of random sequence generation and concealment methods, but also the evaluation of baseline imbalances with evidence of baseline imbalance suggesting possible problems with the randomization process. These include substantial differences in group sizes relative to the intended allocation ratio; a higher number of statistically significant differences in baseline characteristics between intervention groups than would be expected by chance; imbalance in key prognostic factors, or baseline measures of outcome variables that are unlikely to be due to chance; and a high number of overly similar baseline characteristics that is not compatible with chance.

Therefore, the addition of baseline imbalance evaluations to the assessment of selection bias in randomised trials using the RoB 1 tool might help clarify what would otherwise be an unclear risk of bias, allowing reclassification to low risk of bias or to high risk of bias [3]. For instance, even if the allocation sequence was random and concealed, significant baseline imbalances could prevent a study from being assigned a low risk for selection bias, a situation that would not arise if only RoB 1 was used. Similarly, if allocation concealment details are missing (hence an unclear risk of bias using RoB 1), but baseline imbalances indicate a problem, the risk of selection bias could be classified as high.

The RoB 2 tool is considered a difficult and challenging tool, even for raters with expertise in systematic reviews [4], and this may have a negative effect on its wide adoption. Many systematic

reviews have not yet adopted it [5], and adherence has been low even among Cochrane reviews and protocols [6]. As a result, many systematic reviews may be neglecting baseline imbalances in the assessment of selection bias in their included randomised trials by not considering this when, for example, they use the RoB 1 tool.

We will therefore carry out a Study Within A Review (SWAR) to examine the effect of supplementing the use of RoB 1 with an evaluation of baseline imbalances when assessing the risk of selection bias for randomised trials included in the host systematic review “The effects of presenting diagnostic accuracy and intervention efficacy statistics in different numerical formats: a systematic review”.

Interventions and comparators
Intervention 1: Assessment of the risk of selection bias of randomised trials included in a systematic review using the Cochrane RoB 1 tool (domains to be assessed: random sequence generation and allocation sequence concealment).
Intervention 2: Assessment of the risk of selection bias of randomised trials included in the systematic review using the Cochrane RoB 2 tool (domains to be assessed: random sequence generation, allocation sequence concealment, and baseline imbalances).

Index Type: Full Review

Method for allocating to intervention or comparator
Non-Random

Outcome measures
Primary: Proportion of randomised trials for which the risk of selection bias, as assessed by the RoB 1 tool, changes (either downgraded or upgraded) after incorporating the assessment of baseline imbalances as suggested by the RoB 2 tool.
Secondary: (1) Changes to the certainty of evidence in the primary outcome of the systematic review based on classification for risk of selection bias when baseline imbalance evaluations are included; and (2) reasons for changing the classifications of selection bias and certainty of evidence.

Analysis plans
Included randomised trials will be assessed for baseline imbalances by two reviewers independently using the methods suggested by the RoB 2 tool as follows:
- Substantial differences between intervention group sizes, compared with the intended allocation ratio;
- A substantial excess of statistically significant differences in baseline characteristics between intervention groups, beyond that expected by chance;
- Imbalance in key prognostic factors, or baseline measures of outcome variables, that are unlikely to be due to chance;
- Excessive similarity in baseline characteristics that is not compatible with chance.

Possible problems in implementing this SWAR
The RoB 2 tool is considered a difficult and challenging tool, even for raters with expertise in systematic reviews. Moreover, there is currently no standard method to assess excessive similarity in baseline characteristics that is not compatible with chance.

References
1. Higgins JPT Altman DDG, Sterne JAC on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011.
2. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
3. Corbett MS, Higgins JP, Woolacott NF. Assessing baseline imbalance in randomised trials: implications for the Cochrane risk of bias tool. Research Synthesis Methods 2014;5(1):79-85.

4. Minozzi S, Cinquini M, Gianola S, et al. The revised Cochrane risk of bias tool for randomized trials (RoB 2) showed low interrater reliability and challenges in its application. Journal of Clinical Epidemiology 2020;126:37-44.
5. Minozzi S, Gonzalez-Lorenzo M, Cinquini M, et al. Adherence of systematic reviews to Cochrane RoB2 guidance was frequently poor: a meta epidemiological study. Journal of Clinical Epidemiology 2022;152:47-55.
6. Martimbianco ALC, Sa KMM, Santos GM, et al. Most Cochrane systematic reviews and protocols did not adhere to the Cochrane's risk of bias 2.0 tool. Revista da Associacao Medica Brasileira (1992) 2023;69(3):469-72.

Publications or presentations of this SWAR design

Examples of the implementation of this SWAR

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Date of idea: 20/JUN/2023
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