Cochrane Scientific Committee

Recommendation statement/report

Date: July 2017

Relates to agenda item and meeting reference: 5i 18th May 2017

Priority: Medium

Open access/restricted: Open

Review of the development of the risk of bias tool for nonrandomised studies for interventions – ROBINS-I

Lead developers/investigators: Jonathan Sterne and Julian Higgins, Barney Reeves, Jelena Savović and Lucy Turner

Abstract:

Aim & objective

The ROBINS-I tool evaluates the risk of bias (RoB) in the results of nonrandomized studies of interventions (NRSI) that compare the health effects of two or more interventions.

This tool evaluates NRSI that are quantitative studies estimating the effectiveness (harm or benefit) of an intervention, which did not use randomization to allocate units (individuals or clusters of individuals) to comparison groups. These are typically observational studies and include cohort studies, case-control studies, controlled before-and-after studies, interrupted-time-series studies and controlled trials in which intervention groups are allocated using a method that falls short of full randomization (sometimes called “quasi-randomized” studies).

Methods for development

Expert consensus using working groups covering the domains of bias followed the seven principles for assessing risk bias (Higgins et al, 2011). The procedure included a survey of Cochrane Review Groups about current tools used and follow up interviews on a piloted version of the tool to ascertain interpretation and use of guidance. Dissemination activity led to further modifications and the current version.

Results/Development

The tool continues the domain approach used in the current Cochrane ‘Risk of bias’ tool adding three assessment domains specifically related to NRSI: bias due to confounding, bias in selection of participants into the study pre-intervention and bias in classification at intervention. Signalling questions to aid assessor judgements are a key feature, adopted from the QUADAS-2 tool (Whiting et al, 2011). Evaluation commences with considering the target trial. This hypothetical trial provides the assessor with a ‘model’ comparator of a pragmatic randomized trial without the features putting it at risk of bias.

Final product: The currently-published ROBINS-I tool (Word and Access versions) is designed for cohort-like designs, such as cohort studies, quasi-randomized trials and other concurrently controlled studies. Although applicable for case-control studies, cross-sectional studies, interrupted time series and controlled before-after studies further developments to signalling questions are underway. A substantial guidance document is available to support application.

References:

Higgins JPT, Altman DG, Goetzche P, et al. (2011)The Cochrane Collaboration's tool for assessing risk of bias in randomised trials *BMJ*; 343:d5928

Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, Leeflang MM, Sterne JA, Bossuyt PM. (2011) QUADAS-2 Group. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of Internal Medicine*; 18;155(8):529-36.

SUPPORTING DOCUMENTATION

Stern JAC, Herńan MA, Reeves BC, Savoić J, Berkman ND, Viswanathan M et al. (2016) ROBINS-I: a tool for assessing risk of bias in non-randomised studies of intervention; BMJ 2016; 355@i4919. http://dx.doi.org/10.1136/bmj.i4919

Access to tool documentation please see www.riskofbias.info

CSC RECOMMENDATION

[ ] ***Highly recommended***

[x] ***Recommended with provisions***
The ROBINS-I tool is recommended as the preferred tool for new reviews. It is not mandatory. The importance of competency to use the tool will be highlighted in guidance.

[ ] ***Optional/advisory (one among several options)***

[ ] ***Not recommended***

CSC STATEMENT

Summary statement

Jonathan Sterne elaborated the key features of the current version of the tool. This starts with specifying a hypothetical randomised trial based on PICO information drawn from the nonrandomised study. Key areas of bias that map onto key epidemiological terms are confounding, selection bias and misclassification bias, however, selective reporting bias does not have an epidemiological analogue and is dealt with separately. Risk judgements are *low, moderate, serious, critical* and *no information.* A nonrandomised study is most likely to make *moderate* at best. Web development is

underway and will permit question skipping. Versions adapted for case control, interrupted time series and before after designs are underway as certain aspects of each differ from the Cohort version. For example, for case control design confounding is the same, whereas selection bias differs because of the way the controls are selected.

CSC discussion focussed on implementation issues and acceptability amongst Co-eds. Opportunities for input into the development has enabled greater acceptance and led to a proposal to develop a triage approach whereby early identification of very low quality studies deemed to be critical, for example, could be removed from further assessment. However, it is not possible to radically simplify the tool and still conduct a proper assessment. Expertise in epidemiology is a key competency to undertake a review of nonrandomised studies. Further guidance to specify competence level needed is forthcoming. Some members were interested in some formal empirical testing of the tool. This is likely to occur over time when used in enough studies to warrant empirical research, permitting further improvements. Developments across similar risk of bias/quality assessment tools (DTA and Prognosis) stimulate feature changes such as the signalling questions, however, a suggestion was made to harmonise across all tools at some point.

The CSC agreed the ROBINS-I tool was the preferred tool to assess nonrandomised studies in Cochrane Reviews. It may be mandated at a later point after further evaluation and development. The development of the web version will assist with implementation. Further guidance will cover required competency of the author team. In addition, a triage tool will identify those studies at serious risk of bias and therefore further evaluation of all domains will not be required. So, there is a clear expectation that review authors where possible should use this tool. In some cases, it may seem appropriate to use another tool, such as the currently recommended Newcastle Ottawa Scale.

Credibility & validity

The tool starting from first principles has undergone iterative development following expert review and pilot testing. Further evaluation will take place during implementation that may lead to future empirical work.

Limitations/caveats

Strong level of competency required in epidemiology to use the tool.

Areas of concern/uncertainty

None noted

Impact on Cochrane

Tool is complicated to complete and needs a level of expertise. It is also time consuming to complete. However, this might be mitigated by the development of the triage tool. Training and

support could be high based on the number of reviews likely to include nonrandomised studies, which may increase due to stakeholder requirements.

Cochrane resources needed

Separate software (not RevMan) is in development. Publication of 'Risk of bias' tables and integration into GRADE will need further consideration.

Implementation

CSC members are not responsible for managing implementation of these recommendations which will require an implementation plan to ensure co-ordination for a smooth introduction. This will include launch, timescales and roll out strategy. Therefore, this statement does not signify immediate implementation.