Will the ROB-ME checklist prevent omission bias in meta-analyses?

Freemantle N [1], Irs A.[2]

[1]Comprehensive Clinical Trials Unit, Institute of Clinical Trials and Methodology, University College London, London WC1V 6LJ, UK

[2]Estonian State Agency of Medicines (Ravimiamet), Tartu, Estonia

Correspondence to: N Freemantle nicholas.freemantle@ucl.ac.uk

The checklist industry has produced another output, the ROB-ME instrument for assessing risk of bias due to missing evidence in pairwise meta-analyses, nestling between ROB-MEN for network meta-analyses and RoB 2 for assessing bias in the reporting of trials (doi:10.1136/bmj-2023-076754).[1] Selective reporting of study results is a well known source of bias in meta-analyses, and ROB-ME is the first structured approach for assessing the risk of bias that arises when entire studies, or particular results within studies, are missing from a meta-analysis because of the P value, magnitude, or direction of the study results.

The tool intends to help researchers select and define the meta-analyses to be assessed, identify the trials that might have missing results, and crucially consider the potential for missing studies across the review. In ideal circumstances when a meta-analysis includes all trials that have been conducted on a question, the results are an unbiased best estimate of treatment effect. Well conducted trials on the same topic differ on the basis of the play of chance (the mechanism by which treatment was allocated between participants), and it is obvious that if we select only those trials with results that (by chance) are more positive, the result of the meta-analysis (a weighted average of the individual trial results) is also inappropriately positively biased.

The objectives of the tool are clear and important, but will ROB-ME help? Such instruments are quite difficult to assess as they cannot be validated in the conventional manner, since the bias they identify is difficult to tease out because it is unmeasurable and obfuscated (a latency). We are not aware of what we have not included, nor the consequences of not including it. This situation is similar to the reduction in the overall death rate among young men during the SARS-CoV-2 pandemic (although the direction of effect is opposite). We did not explicitly experience the benefit (an unmeasurable latency) because we did not know who would have died had restrictions in activity not been in place. Of course, the loss of a young person would have been felt very strongly by family and friends had the counterfactual state of no restrictions been in place.

One potential form of validation is to consider whether a known exemplar of bias with substantial consequences would have been identified through the use of the tool. Probably the most notable of such examples in recent years was the EXCEL trial, where the publication of the main results in 2016[2] failed to report one of the outcomes prespecified in the trial protocol[3 4]; just the kind of biased reporting that ROB-ME is intended to mitigate.

EXCEL compared coronary artery bypass grafts with percutaneous coronary intervention using everolimus eluting stents in patients with left main coronary artery disease.[2] The protocol specified that myocardial infarction would be assessed both with the investigators' own measure based on elevated blood enzyme levels (with or without supporting signs from electrocardiography or imaging), and also with the conventional universal definition of myocardial infarction.[5]

The trial was published in 2016 with three years of follow-up and a finding of non-inferiority on the primary outcome (the composite of death, investigators measure of myocardial infarction, and stroke).[2] The findings went on to inform treatment for patients with this condition and justified strong recommendations for percutaneous coronary intervention using everolimus eluting stents.[6] Given the markedly less invasive nature of percutaneous coronary intervention with everolimus eluting stents than with open heart surgery, it was poised to become the preferred treatment strategy.

No one spotted that the authors had failed to report the prespecified universal definition myocardial infarction measure. A whistleblower released the trial dataset in SAS format to the BBC that had been created in 2016, which included all of the outcomes reported in the 2016 publication[2] plus the complete universal definition of myocardial infarction component measures. The authors initially denied that they had collected the data, and it was only in 2020 that they finally reported these results under intense pressure from various sources, including the *New England Journal of Medicine* and their own institutions.

Analysis with the universal definition described a substantial disadvantage for percutaneous coronary intervention using everolimus eluting stents, which predicted the findings of differences in overall mortality favouring coronary artery bypass grafts, which became apparent from four years' follow-up onwards. Support for the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines was withdrawn by EACTS, and ESC/EACTS recently reviewed the guidelines with a markedly lower class recommendation for stents in left main coronary artery disease than for coronary artery bypass surgery, resetting coronary artery bypass surgery as the preferred option.[7]

We all missed this omission from the publication, and it took a whistleblower to identify it. ROB-ME might not have helped because it directs researchers to look for gaps in the reporting of outcomes (eg, identifying which of the trials did not publish a myocardial infarction outcome), when EXCEL did publish its own definition outcome. RoB 2 might have helped to identify the omission, and correctly points reviewers to available sources such as trials registers to identify the prospective trial plan. A regulatory process would have helped as is routine for the European Medicines Agency or US Food and Drugs Administration to assess the study outcomes in a clinical study report against the protocol, and journals frequently require copublication of the protocol and statistical analysis plan (both were present in 2016 when EXCEL was first published). However, many trials, including EXCEL, are conducted to inform treatment outside of a regulatory process, and it is notable how the message can become more important than the science in these circumstances. Guideline developers, reviewers, and readers should exercise their duty of care towards those whose treatment will be influenced by their work through exercising similar due diligence. While certainly a helpful structure for assessing bias, such checklists and instruments can only supplement thoughtful, thorough, and painstaking assessment.

1. MJ, Sterne JAC, Boutron I, et al. ROB-ME: a tool for assessing risk of bias due to missing evidence in systematic reviews with meta-analysis. BMJ 2023;383:e076754. doi:10.1136/bmj-2023-076754.
2. Stone GW, Sabik JF, Serruys PW, et al; EXCEL Trial Investigators. Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease. N Engl J Med 2016;375:2223-35. PubMed doi:10.1056/NEJMoa1610227
3. YouTube. European guidelines on heart disease under review - BBC Newsnight. 2019. https://www.youtube.com/watch?v=_vGfJKMbpp8.
4. YouTube. Key death data from EXCEL trial of stents and heart surgery held back - BBC Newsnight. 2020. https://www.youtube.com/watch?v=lxWwyVCcrEs.
5. Stone GW, Sabik JF, Serruys PW, et al; EXCEL Trial Investigators. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. N Engl J Med 2016;375:2223-35. doi:10.1056/NEJMoa1610227. PubMed
6. Neumann F-J, Sousa-Uva M, Ahlsson A, et al; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40:87-165. PubMed doi:10.1093/eurheartj/ehy394

7. Byrne RA, Fremes S, Capodanno D, et al. 2022 Joint ESC/EACTS review of the 2018 guideline recommendations on the revascularization of left main coronary artery disease in patients at low surgical risk and anatomy suitable for PCI or CABG. Eur Heart J 2023;44:4310-20. doi:10.1093/eurheartj/ehad476. PubMed