Reviewer's report

Title: Incorporating Adjustments for Variability in Control Group Response Rates in Network Meta-Analysis: A Case Study of Biologics for Rheumatoid Arthritis

Version: 0 Date: 21 Jul 2019

Reviewer: Kristian Thorlund

Reviewer's report:

The manuscript represents a nice addition to the existing literature on meta-regression and baseline adjustments in network meta-analysis. The methods are adequate and the results are summarized and presented in a highly legible and interpretable format. I only have a few major comments which I expect will be easy for the authors to deal with.

While the methods, results and discussion sections are well written, the introduction is overly generic and does not make a case for performing the study. Conversely, the middle paragraphs in the discussion do all make very good cases for the study, so I would suggest taking some of those points and moving them up to the introduction while getting rid of the more generic NMA intro blurbs (i.e., drop the boring sentences like 'NMAs have become increasingly popular over the past decade..') . In particular, the case to be made is the meta-regression on baseline covariates doesn't work on an aggregate level, either because of 1) the ecological fallacy, which contrary to popular believe almost always biases towards the null; 2) because there typically aren't enough trials per comparison in the network to inform a reliable meta-regression. On that note, there also isn't much point in arguing for (or referencing) rare examples where meta-regression of baseline covariates (not control risk) made a difference from a statistical point of view, because referencing such rare cases gives a false and overly positive impression of its utility (again, use of baseline covariates, not control risks in meta-regression).

Though out the introduction, methods, and results, there is come repeated mentioning of adjustments being 'clinically important'. Please rephrase to something more moderate and accurate like having a potential impact on decision-making in an health technology assessment context (again, the wording in the discussion is very adequate).

When it comes to actual potential impact on interpretation of findings and decision-making in the HTA context, it is important that all metrics used in the manuscript are easy to interpret, and supported by some worked examples of how the adjustments may matter in the HTA context.
While the manuscript does have a very nice format for presenting results, there are two issues that could benefit from some simple revisions:

- A change in the beta-coefficient of -0.68 is observed, but what does this mean for medical decision-making, i.e. how does it impact reimbursement decisions based on health technology assessments that include NMAs)? One could easily start by transforming the beta-coefficient estimate from the reported log odds ratio scale to the odds ratio scale. This would make the interpretation much easier.

- With respect to the changes observed comparative treatment effects and SUCRAs from adjusting is obtained with respect to the average control risk, but there is no way of assessing that this is representative in the population for which the NMA is informing decision-making. To keep things relevant to the population the NMA is aiming to represent, wouldn't it be more informative to also look at adjustments to some preset control risks. The data set used in the manuscript is from a CADTH review, so why not look at control risks from either the entire Canadian populations or individual provinces of Canada? This is particularly relevant since the majority of trials in the network are either US or Euro centric.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

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