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: 11 Jul 2019

Reviewer: Devon Boyne

Reviewer's report:

One of the biggest and most common threats to the internal validity of a network meta-analysis (NMA) is heterogeneity in the distribution of effect modifiers. In this article, the authors present a case study in which they present methods that can be used to detect and adjust for heterogeneity and highlight the importance of performing such adjustments using a large evidence base generated by a health technology assessment agency. The paper is well-written and the statistical analysis is sound. Given the growing number of NMAs published in the literature and their importance in health technology assessment, this case study will be of interest to the readers of this journal and to the broader NMA community.

With respect to the statistical analysis, I have one relatively minor suggestion that could help to enhance the discussion of the results. While the authors do an excellent job of presenting the results from the unadjusted and adjusted NMA in league tables and a forest plot, it is difficult to assess the impact of the adjustment overall given the large number treatment comparisons. To address this issue, I would to propose that the following be estimated for each treatment comparison within the network:

1) The percent change in the magnitude of the odds ratio, i.e., (|ORadj - ORunadj|) / ORunadj.

2) The percent change in the relative precision (i.e., the ratio of the upper 95% Cr limit to the lower limit) or perhaps the percent change in the absolute width of the 95% CrI

Once estimated, the authors could summarize the distribution of these values. For example, "After adjustment, the magnitude of the ORs changed by X% on average (min change = x, max change = x, etc.)." In addition, the authors could report the proportion of treatment comparisons where the OR changed by, for example, 15% or more (a ~10-20% change in the magnitude of the OR can be considered meaningful) as well as the proportion of treatment comparisons where the unadjusted and adjusted analyses were discordant regarding whether or not the 95% CrI included the null value or a region of practical equivalence (ROPE).
These additional metrics could be incorporated within the abstract and discussion. For example, I was a bit confused about the beta estimate and 95% credible interval presented in the abstract until I read the manuscript. Replacing it with something like "the magnitude of the ORs changed by X% on average after adjustment" may be more easily understood by a broader audience. Similarly in the discussion where you point out, "… demonstrating a bias against interventions which report higher ACR 50 response rates in the control group…", you could quantify that statement by reporting the mean % change in the OR among comparisons where the control group response rate was high vs. low (or plot the relationship between response rate and the percent change in the OR).

Aside from the additional analyses above, I had a few minor suggestions regarding the manuscript draft:

Intro:

- You could mention that, in some networks, there could be a lack of reporting or inconsistency in the measurement of patient characteristics which will further highlight the importance of conducting these types of analyses.

Methods:

- I would explicitly state that the outcome is binary as well as the link function and the likelihood used (e.g. the logit link and binomial likelihood).
- Please state the number of treatment arms in the evidence base.
- RE: MCMC, clarify that there were 40,000 iterations in total including the burn-in (the sentence was a bit confusing).

Results:

- An interpretation of the meta-regression coefficient for the response rate may be helpful (i.e., beta= -0.68; 95% CrI -0.89 to -0.44).
Discussion:

The authors note that the control-group rate adjustment was not done in the original analysis from which the data was abstracted. This should be mentioned in the introduction as it was a question I had early on.

I was wondering if the authors could comment on whether the response rate adjustment has to be specific to the "control/placebo" arm or if analysts could adjust for the response rate in an active treatment group in the network in lieu of the response rate in the control/placebo arm. In the evidence base presented in this manuscript, it makes sense to adjust for the response rate in the placebo arm because it has the greatest number of studies. However, some clinical settings may have a limited number of studies or no studies that include a placebo/control group. In such situations, is there a reason why you would not want to adjust for the response rate in an active treatment arm (perhaps the arm with the greatest number of studies)?

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

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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