Reviewer’s report

Title: Individual Patient Data Network Meta-Analysis using either Restricted Mean Survival Time Difference or Hazard Ratios: is there a difference? A case study on locoregionally advanced nasopharyngeal carcinomas

Version: 0 Date: 04 Jun 2018

Reviewer: Kristina Dietz

Reviewer's report:

I apologise for the delay in the submission of my review (due to illness).

Overall recommendation: Reject.

Two main reasons:

1) Limited original contribution: The article does present a better version of an existing method. This method was, however, not developed by the authors, but applied to a novel context (network-meta-analysis). Area metrics have been used as superior alternative to point-estimates for continuous time-series data such as event-related potentials for decades.

2) Largely descriptive focus: To qualify as a methodology article, I think the article would need to move beyond its current descriptive focus. This would require a much more concise reporting of the current content to make space for an extensive exploration of why and when metrics differ. Otherwise I would suggest to submit the article to a different category, and as the Research category of Systematic Reviews does not quite seem appropriate, that may mean submission to a different journal.

Comments

This is a well written, clear (albeit dense) article that addresses an alternative method of treatment benefit for time-to-event data (replacing a point estimate with an area estimate) important to the majority of clinical trials (e.g. licencing applications) and related health technology assessments (e.g. NICE approval in the UK). The methods employed are strong (e.g. prospectively registered protocol, clearly specified, logical choice of primary and secondary outcomes, but see comment re: choice of 10 and 5-year follow-up points). The original contribution is application context (network meta-analysis) rather than method per se (area measures are not new).
Figures and Tables (esp. Table 2 and Figure 1) provide nice, compact representation of results. I would move Supplementary Figure 2 to the main body of the publication.

The article is good, but not excellent, because the focus is on *if* metrics differ (i.e. largely descriptive) with some consideration of *how* they differ, but only tangential consideration of *why* and *when* (inferential). As this is a methodology article, I would expect a detailed exploration of why and when the metrics differ (inferential), because it can reasonably be expected that any area metric will differ from point estimate. Methodologically, the key is to understand why metrics will differ and in what way under varying conditions, but the article barely touches upon these questions. The authors do make some important observations in passing (e.g. difference not solely attributable to non-proportional hazards or extrapolation), but largely relegate a detailed exploration of why and when to further research, namely simulation studies. Overall, the article seems to lean more towards estimation of clinically relevant outcomes than methodology development and it might be better to submit the article in a category reflecting this.

Suggestions

One type of figure that would be essential to this article if submitted in the methodology section, but is entirely missing, are raw curves from which HR and rmstD(t*) are calculated, grouped by effect (i.e. no difference between metrics, difference in one direction (HR < rmstD(t*)), difference in other direction (HR < rmstD(t*)). I would de-emphasise significance (p values), especially given number of comparisons (suggest to consider FDR procedure to correct). I would consider relegating all but Table 2, Figure 1, and Supplementary Figure 2 to the appendix to make space for these figures if necessary.

P. 7, line 20: Specify why and how a 10 and 5 year follow-up period was chosen in reference 15 (and therefore current article).

As a very minor comment, it would be good to be consistent in decimal use. Currently, some p values are reported to 3 decimal places, most to 2, I would suggest to report all to 3 places.

Level of interest

Please indicate how interesting you found the manuscript:

An article of importance in its field that should be highlighted to relevant networks

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Acceptable
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