Reviewer’s report

Title: A DAG-based comparison of interventional effect underestimation between composite endpoint and multi-state analysis in cardiovascular trials

Version: 0 Date: 15 Feb 2017

Reviewer: David Prieto-Merino

Reviewer’s report:

This paper nicely clarifies and illustrates some types of biases than could occur when analysing time to event data, depending on the model that we use. I think the paper reads very well. I could follow the explanations of the models and the procedures of the simulations, but a have some comments about the final "take home message" of this paper:

The authors are simulating two different scenarios to obtain two different kinds of biases: a) When a Z variable associated with the outcome is present and b) when the transition hazards change with number of events. It is shown that for the first scenario the analysis of only first events causes a bias, but in the second scenario the bias occurs with the analysis of recurrent events. I feel the reader can be left with the nagging unanswered question of "what do I do in my next analysis? Should I analyse all recurrent events to avoid selection bias or should I analyse only first events to avoid the other kind of bias?" It would be helpful if the authors could discuss this from a practical point of view… I wonder if doing a third simulation where they introduce both kind "perturbations" (underlying variable Z and the changing hazards) and showing which bias prevails in each situation might help.

Suggestion: Having diagrams similar to that in figure 4 representing the parameters of the simulations might be helpful.

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

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal