Reviewer's report

Title: Reporting of loss to follow-up information in randomised controlled trials with time-to-event outcomes: a literature survey

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Reviewer: Jan Beyersmann

Reviewer's report:

General:
This is a very useful literature survey on reporting follow-up in leading medical journals. The topic is relevant, and the literature survey and its evaluation have been carefully conducted. While the authors are to be commended for carefully acknowledging the presence of competing risks, I still have some remarks on implications raised by competing events. The key issue is that the Kaplan-Meier curve for a competing risk outcome has no probability interpretation whatsoever. There are some additional remarks on some aspects of the presentation. My major difficulty when reading the paper was the sensitivity analysis, which must be better motivated and explained. I even think that in certain competing risks situations, the present sensitivity analysis does not fully apply. But this does not really compromise the merit of the manuscript as such.

Specific, Competing Risks:
- p4, 1st par: "Censoring [...] by a] competing event". No mistake by the authors, but since this issue is not well understood in practice, it should be clarified: Competing events can be treated as censorings when the aim is an analysis of one (cause-specific) hazard. Competing events must not be treated as censoring when the aim is a probability statement as in a Kaplan-Meier curve. A formalization and proof of these facts is in the book by Andersen et al. 1993, "Statistical Models based on Counting Processes".

- Method section: The Kaplan-Meier curve has no real life probability interpretation whatsoever, if the event under consideration is subject to competing risks. In such a setting, the Kaplan-Meier curve is just
a useless transformation of the empirical cumulative cause-specific hazard into [0,1], but probabilities also depend on the other cause-specific hazard. (One must use the Aalen-Johansen estimator.) As a consequence of this Kaplan-Meier curve without meaning, the LTFU information must be inconsistent. Therefore, I think that in these situations the first problem is inadequate handling of competing risks. This must be made clearer.

Specific, Presentation:
- I miss a brief paragraph why missing LTFU information is a concern. Statistical difficulties are: Results only hold on the "observed/observable time interval", censoring increases variance. On the other hand, unequal LTFU between groups is not a statistical problem - it can be handled in, e.g., a Cox model. The problem is of a different nature, because unequal LTFU is not expected in a well conducted clinical trial.

Specific, Sensitivity Analysis, p6:
- I had trouble to understand quickly why and how you did it. Please add a rationale. My understanding is that the procedure applies if your calculation gave a higher risk set than reported. Then you consider different scenarios of what has happened to these "censorings". (Censoring may not be a good name here. They are rather "inconsistent ghosts" or something.) Your presentation suggests that you did this for a certain time point, namely the last time point, say s, before minimum follow-up. Does this mean that you only looked at events at time s, and assumed "censorings" to have happened at this time, too? Or did you look at events up to time s, i.e., in [0,s], for constructing your 2x2 contingency table? I would think that the latter would be more adequate. Please clarify.

- I do not think that the sensitivity analysis as it is applies in the competing risks setting. Say, you look at progression, the competing event being death without prior progression. There is no point in imputing progression events as a consequence of "censoring due to death". The analysis reported in such a paper might very well be meaningful for the cause-specific hazard (of progression), whatever
your sensitivity analysis says. However, you might compute the equal-case scenario _only_ which would try to evaluate the result for the composite endpoint (death or progression, whatever comes first).

Minor:
- p5, calculation of number at risk: Please add that for complete data, the Kaplan-Meier curve is 1 minus the usual empirical cdf.
- p5, calculation of number at risk: Please clarify: Were there also studies with no. of patients at risk higher than calculated? Your presentation suggests that this was not the case.
- p5, calculation of number at risk and competing risks: How did you resolve inconsistencies that could be traced back to competing risks? I don't really see at first glance how you can do that, because the Kaplan-Meier curve has nor real life probability interpretation anymore.
- Results: Please report how many of the inconsistent results was due to misuse of Kaplan-Meier for competing risks.
- Your ref 8 Mathoulin-Pelissier et al. shows the relevance of the competing risks problem: Their Table 1 shows that Time to Progression was analyzed in 27 out of 125 studies. But in the text, Mathoulin-Pelissier et al. say that (only) five papers accounted for competing risks. So, at least 22 out of 27 who studied progression (probably) did it wrong!

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
I declare that I have no competing interests.