Reviewer’s report

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

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Reviewer: Sayan Dasgupta

Reviewer’s report:

In this article, the authors study a survival framework with composite endpoints, motivated by a randomized controlled clinical trial in heart failure patients. They use the concept of directed acyclic graphs (DAG) to investigate potential sources of bias in treatment effect estimates, and based on their findings, they propose proportional hazards-based multi-state models for this setting, that move beyond the paradigm of considering first events only. The article is clearly written and easy to follow. Following are some of my comments:

1. Page 7, line 33: Is \( \delta_{ij} \) missing from the definition of \( N_i(t) \)?

2. One major concern for this article is its novelty - I don't doubt the insight that is achieved here through interpreting the problem through DAGS, but apart from that, this paper appears to be a simulation exercise. Hence I believe one way to strengthen this article would be by expanding the simulation section. For example, one thing that can be done is considering the situation when an unobserved frailty is present while varying transition hazards between different episodes.

3. The Results section can be strengthened by adding a table that summarizes the simulations (much like the plots) but with estimates and their standard errors to make it clearer.

4. A heuristic explanation for the bias in the treatment effect estimates for the composite outcome when \( \beta_1 \) is not equal to \( \beta_2 \) would make for better understanding(Figures 6 and 8).

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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