Reviewer's report

Title: Assessing quality of life in a randomized clinical trial: Correcting for missing data

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Reviewer: Robin Henderson

Reviewer's report:

This is a well written and well constructed paper which nicely illustrates the use of up-to-date methods for dealing with dropout in longitudinal data. The paper is based on the analysis of quality of life measurements for people being treated for non-small cell lung cancer. The study started with 197 people with measurements available for analysis, but by week 96 only 33 people provided data. Failure to account for possible selection effects could lead to misleading conclusions. The authors compare three methods for such selection effect adjustment: a recently proposed linear increments model, a more well known inverse probability weighting approach, and a Markov process method, which is possible for responses on a finite state space, as in the application. The authors make the sensible point that use of several methods brings some robustness to conclusions, should those methods give similar results. (If they don't, and we have no way of verifying assumptions, then at least we would know that results are suspect. This wouldn't happen if only one approach was adopted.)

Points

These are mainly on presentation and are intended to be helpful.

1. After a nice clear start and introduction to the data, the authors discuss objectives, which is refreshing and often omitted. They target the mean response in a hypothetical dropout-free population. Since one form of dropout is due to death, the authors say they imagine an \"immortal cohort\". This is silly and certain to raise suspicions of readers, even if the authors state that the paper is illustrative. But there is no need for it. Since the maximum follow-up time seems to be 96 weeks, the authors have a perfectly proper objective of estimating quality of life in the hypothetical but believable situation of treatment advances guaranteeing 2-year survival. This is a perfectly proper objective, which would inform the search for treatment improvement - if QoL would be poor anyway then there is less incentive.

2. The number of people dropping out because of death or other causes should be stated. Perhaps some simple survival analysis should be included for exploratory purposes.

3. If there is a decent mixture of death and dropout (with a non-negligible number of each) it might be worth re-analysing the data conditional on not dying but in
the hypothetical absence of dropout. This would be another genuinely realistic objective, as argued in the cited Dufoil et al paper. I think all three methods can accommodate this.

4. The DTIC condition seems unrealistic. But it is no worse than the standard MAR assumption. This might be mentioned.

5. Since we have a finite state space, the expected increment depends crucially on the current state - at the extremes there can be no increment in one direction for instance. This means current state has to be included in the linear term (5), and moreover a simple linear effect in current state would be unrealistic. The fix is to include state by covariate interaction terms. Has this been attempted?

6. The IPW and MP sections suggest that interest is in the overall mean, with no covariate adjustment. Is this reasonable?

7. Should methods of error estimation for the estimated means be discussed in the methods section? Bootstrap is used in the application. Is this the only method?

8. The analysis is thorough but I would have preferred to have more on the dropout model used for IPW.

Minor

9. Figures 1 and 2 could be deleted without much loss - Figure 1 for sure.

10. I like the careful precision of the history notation of page 5.

11. I suggest the number of imputed values be given for each wave.

**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.