Author's response to reviews

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

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Response report

Response to the comments from reviewer 1

This is the authors' response to the comments in the report made by Robin Henderson.

1. On page 4 in the Background section in the revised manuscript we discuss the immortal cohort analysis and the mortal cohort analysis. We argue that the former is sensible when one wants to compare treatments. For comparison, we have performed a mortal cohort analysis (see Figure 2 in the revised manuscript) in addition to the two main immortal cohort analyses.
2. The numbers of missing values, with respect to monotone missingness, due to death and other causes are presented in Table 2 and Table 4 in the revised manuscript.
3. We have re-analysed the data conditional on not dying in a mortal cohort analysis using the LI method. The results are displayed in Figure 2 in the revised manuscript.
4. A comment on the fact that the DTIC assumption seems unrealistic is given on page 7 in the Missingness and censoring schemes section in the revised manuscript.
5. We have not attempted to include state-by-covariate interaction terms in the linear model of the LI method. The reason for this is that we present a pragmatic procedure of estimating the mean score. Furthermore, results from our previous paper (see item [6] in the reference list in the revised manuscript) showed that this model performed well in similar situations where the state space was finite.
6. Our interest in this paper is to compare the treatment arms with respect to the overall mean.
7. Analytic expressions for the variance appear complicated. Bootstrap estimation is therefore considered to be a sufficient method.
8. A presentation of the respective models used for the LI method and IPW method is given on page 10 in the Results section in the revised manuscript.
9. Figures 1 and 2 in the original manuscript are deleted.
10. The numbers of observed values, with respect to monotone missingness, that are imputed and non-imputed are presented in Table 3 in the revised manuscript.

Response to the comments from reviewer 2

This is the authors' response to the comments in the report made by Juni Palmgren.

1. The readers in mind are both statisticians and clinicians. To make the paper more understandable to non-statisticians, we have added a few sentences regarding the MCAR and MAR assumptions on page 6 in the Methods section in the revised manuscript.
2. We discuss whether one should adjust for all missing values or just those corresponding to ordinary dropouts (non-deaths) on page 4 in the Background section in the revised manuscript. In our two main analyses we consider an immortal cohort, and we argue that this is a sensible approach when one wants to compare treatments. We have also performed a mortal cohort analysis using the LI method. We agree with the reviewer that Figure 2 in the original manuscript is
not compatible with the immortal cohort approach. The figure has therefore been deleted.

3. A comment on why multiple imputation was not considered is given on page 9 in the Single imputation section in the revised manuscript: “Multiple imputation has not been used here since the added complexity was not deemed necessary.” We have avoided the terms ‘valid’ and ‘non-valid’ in the revised manuscript. Instead we use the terms ‘observed’ and ‘missing’, with respect to monotone missingness. This is explained on page 11 in the Results section in the revised manuscript. Keep in mind that a certain score value may be regarded as missing in the analysis without single imputation and observed in the analysis with single imputation.

4. As stated by the reviewer, the analyses and the reporting of results on item-29 and item-30 in the EORTC QLQ-C30 are essentially similar. Therefore, we have decided to focus only on item 30. Consequently, the Results section and the Discussion section are somewhat changed in the revised manuscript compared to the original manuscript. Also, Tables 1-3 and Figures 3-6 in the original manuscript have been deleted since they all correspond to item 29.

5. To indicate that the standard errors increase over time, we have replaced Tables 5 and 6 in the original manuscript with Figures 3 and 6, respectively, in the revised manuscript. A plot of the difference in the observed mean score between arm A and arm B has been included in both Figure 4 and Figure 7 in the revised manuscript. We have decided to keep Figure 9 in the original manuscript, and this corresponds to Figure 5 in the revised manuscript. A comment on why we do not include the MP method in the immortal cohort analysis when single imputation has been applied is given on page 10 in the Single imputation section in the revised manuscript.

6. Some general hints on which of the three procedures we would suggest using in practice is given on page 13 in the Discussion section in the revised manuscript. The software we have used is mentioned on page 5 in the Background section in the revised manuscript. A comment on how to obtain the implementation code is given on page 13 in the Discussion section in the revised manuscript.

Additional changes

1. We have made some grammatical changes and other minor changes throughout the revised manuscript.
2. We have rearranged and altered the text somewhat in the Results section, the Discussion section and the Conclusion section in the revised manuscript.