Author's response to reviews

Title: Alternative statistical methods for estimating efficacy of interferon beta-1b for multiple sclerosis clinical trials

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Author's response to reviews: see over
Dear Editors,

Thank you for your letter concerning our manuscript entitled “Alternative statistical methods for estimating efficacy of interferon beta-1b for multiple sclerosis clinical trials.” The authors very much appreciate the detailed and constructive comments from the reviewers.

In the letter enclosed, we provided our specific responses to the comments from two reviewers. We used a professional native English copyediting service to help us copyediting the paper. We hope that you find the manuscript is now suitable for publishing in BMC Medical Research Methodology.

Yours sincerely,

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Reviewer 1

1) Page 2 - Abstract – Background
The objective must be stated more clearly and appropriately. I don’t like the sentence “to utilize additional information…”. It is important to stress from the very beginning that we are analyzing the outcomes of MS according to a “broader” point of view. Furthermore, lingering on the aspect of including “additional covariates” is in my view a minor issue of this paper and might be misleading from the central aspect of assessing the outcomes differently to improve treatment effect estimation. Please rephrase this sentence in a more focused way (the last sentence in the Background Section on page 4 could be of great help).

Response:
Thank you for your comments.
We rephrased the sentence and tried to focus the objective directly.

2) Page 2 - Abstract – Results
“each models” should be “each model”.

Response:
Thank you. We corrected it.

3) Page 2 - Abstract – Conclusions
“The precision of estimation”. Please stress that it is “treatment estimation”.
Again, a better focus to the entire sentence should be given.

Response:
Thank you. We changed to stress that it is “treatment estimation”.

4) Page 3 – Background
“When using these models, it is important to pay attention to the nature of the models because the results of the estimation are highly dependent on the clinical
situation [15]”. Even though a more than appropriate reference is provided, if possible, I would like to see here a clarifying example.

Response:
We would like to say that it is important to select appropriate models that fit to the clinical situation. We added some comments and an example after the sentence.

5) Page 4 – Background
“These regression models enable us to estimate the treatment effect with considering the important covariates that might affect the outcomes, whereas just the relapse rates not [16]”. This sentence is really awkward. Please rephrase it.

Response:
We rephrased the sentence.

6) Page 9 – Results
“larger bias” should be used instead of “bigger bias”. Please correct it.

Response:
Thank you. We corrected it.

7) Page 10 – Results
I cannot understand why ‘out of the blue’ an adjustment for a set of covariates is taken into account. Please clarify the need for this and what it possibly adds to the main objective of this paper.

Response:
When we analyze the treatment effect of the real clinical trial data, we should take into account the important covariates that affect the outcome. In this paper, we investigate not only the performance of several models, but also estimate the treatment effect of the real clinical trial data. If we estimate the adjusted treatment effect with these prognostic factors, we can expect that the efficacy of the treatment estimation would be increased. We can also obtain the effects of these covariates. We have included only the treatment
effect in the simulation study, but we think that it is important to show the results of the real clinical trial data in real way, with covariates.
Reviewer 2

1) Questions:
In the simulation, the authors generated values for time by using random numbers between 0 and 1 and reading which value of time corresponded with a Weibull cumulative probability of exactly the magnitude of each random number. In the text, they should state on what ground they did choose the specific Weibull distribution parameters gamma and delta for observation/censoring time and for time to event in the two scenarios? It appears from table 1 that the bias and the mean square error (MSE) for all the models are very sensitive to the scenario chosen.
Were the Weibull parameters in the two scenarios chosen a priori by looking at the natural distributions from the real life data, or were they chosen a posteriori to fit better with the expectations?

Response:
Thank you for your comments.
We chose the Weibull parameters a priori. In the simulation study, we think that it is important to simulate as realistic as possible. We used another MS clinical trial data with placebo cohort for determining the parameters for the simulation study. (The data set is different from the data that we showed as the real IFN-beta clinical trial data application.) We found that the distribution of the time to recurrent events of the cohort fitted Weibull distribution with the parameters which we used.

2) Presentation.
Although written in good English with a generally good clarity, the article is difficult to read. The readability would improve greatly, if the authors refrained from denoting their models as "Model 1, Model 2", etc. but in stead throughout the article (and in the tables and figures) used the full name of the model, e.g. "Cox", "Andersen-Gill", "Prentice-Williams-Peterson", "Wei-Lin-Weissfeld", "Lee-Wei-Amato", "Poisson regression", "GEE-Poisson model", especially in the results-section. It will certainly help the reader, who will not need to look back as many times.

Response:
Thank you. We changed the model numbers to the full name of the models.

3) In the conclusion, the authors could stress (as they did in the discussion) that they prefer the Poisson regression model with Generalized Estimating Equations (GEE).

Response:
We changed the sentence in the conclusion to stress our preference.

4) Discretionary revisions:
It would be helpful to some, if the appendix also provided the readers with SPSS-codes, as many scientists only use SPSS. However, if the authors are not familiar with SPSS, it will probably be too much to ask for.

Response:
We agree that SPSS-codes would be much helpful. We have found that we can handle SPSS only for time-to-first-event Cox regression, Poisson regression, and GEE-Poisson regression, but unfortunately we cannot find out the way for extended Cox regression analyses. We are afraid we cannot provide SPSS-codes in this study.