Reviewer’s report

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

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Reviewer: Fabio Pellegrini

Reviewer’s report:

I am happy with this paper. Some minor essential revisions are needed. In its specific field this manuscript is welcome. Indeed, overall in MS, much more methodological attention should be provided to information available on outcomes at issue.

Of course the authors’ approach is not new: a thorough review of these methods applied to natalizumab has already been given by YC Wang et al (J Neurological Sci 2009; 285:206–211; reference 12 of this manuscript) and a cornerstone paper regarding counting processes by MP Sormani et al. goes back to 1999 (J Neurol Sci 1999;163:74–80).

This manuscript appropriately details for the different readership all the aspects concerning the underlying mathematical models. The simulation data section is a plus (the above mentioned paper by YC Wang contained only a worked example based on real data), as well as the Appendix providing worked examples in SAS code.

A revision of this manuscript by a native English speaker is needed.

Minor Essential Revisions

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).

Page 2 - Abstract – Results

“each models” should be “each model”.

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.

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.

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.

Page 9 – Results

“larger bias” should be used instead of “bigger bias”. Please correct it.

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.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

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

Declaration of competing interests:

In the past five years received honoraria for speaking by Biogen Idec.