Reviewer’s report

Title: Defining responders to therapies by a statistical modelling approach applied to randomized clinical trial data

Version: 1 Date: 19 Apr 2019

Reviewer: William Barlow

Reviewer's report:

This manuscript uses statistical methods to get a continuous marker of likelihood to benefit from laquinimod versus placebo for multiple sclerosis. A cutpoint is chosen in order to designate who is likely to benefit and who may not. The study takes advantage of three large randomized trials with the same study design and reasonably comparable populations. While the overall effect of treatment was not significant in all three trials there may be subpopulations that do benefit. The manuscript follows a very planned course in deriving candidate markers from one trial, using the second trial to determine the preferred algorithm, and finally applying the dichotomized marker to the third trial. The marker performed well in identifying a population which benefits (HR=0.44) and one which does not (HR=1.24) with a statistically significant interaction.

Overall the manuscript is very clear and provides an outstanding example of how the statistical methods may be used. There are a few minor issues but there are two more major issues to bring forward:

1. The abstract seemed to suggest that the statistical methods were developed by the authors. Only in the end of the introduction does the method of Zhao et al. get discussed. It was unclear how much of the Zhao paper was used versus what was novel here. It is perfectly acceptable if this is an illustration of a published technique, but it should be clear to the reader.

2. There were some concerns based on Figure 2 about true separation of the distributions. It appears that the sensitivity would be just over 50% and specificity maybe 70%. One might want a stronger marker than this before deciding on a therapy.

More minor issues:

3. The Introduction is one long paragraph. It may need smaller paragraphs but with more discussion of the Zhao method.

4. The three steps of model creation, evaluation, and validation were well explained and clear.
5. The one place that was less clear was how the cutpoint was chosen. It seemed to be based on qualitative judgment rather than a fixed procedure.

6. AUC's in Table 2 are mostly around 0.35 or so. In my experience most AUC's are reported as greater than 0.50 (chance) with higher numbers. These seem to be the complements.

7. The AUC of the interaction model for Table 3 would be useful.

8. The hazard rates on page 8 suggest they are computed separately rather than part of a large single interaction model:

\[
\log \text{hazard} = \log(h_0) + \delta \text{trt} + \theta z + \beta (\text{trt} \times z)
\]

with \( \beta \) being the deviation in treatment effects due to the covariates. This model only estimates one baseline hazard rather than two and then assuming they are the same.

9. Figures 1 and 3 could be moved to a supplement or deleted.

Overall the manuscript is well written with an important technique illustrated well.

**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.

Not applicable

**Are the conclusions drawn adequately supported by the data shown?**
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Yes

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