Reviewer’s report

Title: How to design a dose-finding study using the Continual Reassessment Method

Version: 0 Date: 22 Jan 2018

Reviewer: Shing Lee

Reviewer's report:

The manuscript by Wheeler et al. serves as a structure framework for designing a dose-finding clinical trial using the Continual Reassessment Method (CRM). It compiles information from multiple sources and publications regarding the selection of parameters for the CRM, as well as software packages. In addition, it provides guidance on how to conduct and report trials designed using the CRM and illustrates all of the above in the context of two examples. A tutorial for the CRM was published in 2006 by Garrett-Mayer E in Clinical Trials. Since then many papers have been published regarding the calibration of model parameters for the CRM, and many software packages have been developed, so it is helpful to have a new tutorial. However, other dose-finding design parameters have been discussed in the paper by Garrett-Mayer and should be referred to. This paper should also be referenced, as there is substantial overlap between the two especially in sections 2 and 3. I think having a tutorial that is focused on examples and the selection of parameters in the context of the example would be very helpful for statisticians not working in this area. Also, the illustration of the software packages in the context of an example would also be helpful. The paper would also benefit from better organization to make it more accessible to a reader who is not familiar with this area. A few suggestions are provided below along with other comments.

Comments:

1) In several places in the introduction, references should be added. For example, in the Introduction page 1 line 59, page 2 lines 2-3.

2) It is confusing having the selection of the skeleton and the dose-toxicity model before the selection of the number of doses and other parameters. It may be better to define the model parameters and the CRM problem formulation and even dose assignment algorithm very briefly in section 2 and talk about the selection of all parameters in section 3 as part of designing a trial.

3) In section 3, it may be helpful to state all the design parameters and specifications that are needed to design a CRM trial before going into each one and then have a separate section on dose assignments or move this to section 2 with the background on CRM.
4) For the selection of design parameters, it would be helpful to have bulleted list of choices.

5) In section 3.5, you can reference the coherence paper by Cheung 2005 Biometrika.

6) In section 3.7, more details on the selection of the scenarios regarding the spacing of the true probabilities would be helpful. These could be discussed in the context of an example.

7) More details should be provided in the Examples on how the design parameters that were mentioned were chosen, instead of just mentioning them. It may be fine to just illustrate on example, but in detail.

8) It may be useful to illustrate an application of one of the software packages in the context of an example as well or in the appendix.

Minor:

1) Reference 21 should be reference 28 in the last paragraph before section 3.

2) In section 3.2 last paragraph, the fourth line of text, where it says "Data from patients in the trial are used to update the prior distribution on the model parameters." Do you mean posterior?

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