Reviewer’s report

Title: Simulation and minimization: Technical advances for factorial experiments designed to optimize clinical interventions

Version: 0 Date: 30 Aug 2019

Reviewer: William Grant

Reviewer's report:

For three different randomization methods, this paper provides an interesting description of balance and equivalence of covariates. However, the issue of predictability is not addressed appropriately and the paper therefore fails to show the relative strengths and weaknesses of different randomization methods. Also, by only considering simple randomization, stratified-block randomization, and minimization, the paper leaves a gaping hole in the spectrum of possible randomization methods un-analyzed. There are a number of important randomization methods (big-stick rule, the maximal procedure, biased-coin procedures) that are more predictable than simple randomization but less predictable than stratified-block randomization. These are procedures that are worth comparing to those included in the paper.

Several statements in the paper reveal an incomplete and sometimes incorrect understanding of the issues of predictability and selection bias. In Table 1, the authors describe stratified-block randomization as a method that "prevents selection bias but introduces some predictability." Potential selection bias cannot be prevented when there is predictability. Also, the authors seem to dismiss the potential for bias because it is complex for exact probabilities of treatments to be predicted. Page 6 states "predictions are often very complex and hard to keep track of in one's mind." While this is true of the exact probabilities of treatments, simple guessing rules can be highly successful. One does not need to know exact probabilities to create bias, one simply has to be able to guess which treatment is more likely than another. On page 10, the authors state that unpredictability was "yes/no." So if the next treatment is 99% predictable, does this mean they counted unpredictability as "no?" They might as well just omit the issue of predictability from their analysis and stick to analyzing balance.

A strength of the paper is that the writing is articulate and the methods are clearly described.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes
Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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I am able to assess the statistics

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