Reviewer’s report

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

Version: 0 Date: 30 Aug 2019

Reviewer: Olga Kuznetsova

Reviewer's report:

The authors describe a very novel application of minimization in the MOST framework. With a large number of intervention arms (16 in the example studied by the authors), only a small number of baseline covariates can be incorporated in the more common stratified permuted block randomization. Minimization, as the authors convincingly demonstrated, allows one to balance on several important baseline characteristics. Examples of minimization application in the context of large number of arms are rare, and present an independent interest. The paper is novel, interesting, and worthy of publication.

Comments.

Major.

1. I would suggest to spend a bit more time on describing the minimization algorithm in the considered example, in particular, making it clear that randomization with minimization is to the 16 different intervention cells.

2. description of the minimization procedure "For each covariate, differences among conditions were assessed using the range between the cell with the maximum value and the cell with the minimum value. Participants were assigned to the cell with the minimum sum of ranges across covariates."

When the range is used to measure the difference within a level of baseline covariate, one needs to calculate the range that would result if the next subject is allocated to each possible intervention, not the current ranges. The goal is to minimize the sum of ranges across the covariates with the next allocation, not to assign the subject to the intervention that provided the smallest range at present. Please describe in more detail how the choice of the assignment was made.

Minor comments:

1. Regarding p. 6 - "Minimization can be specified to include random assignment, but the fundamental procedure is deterministic [7]." Addition of the random element makes the procedure non-deterministic so the sentence needs to be re-phrased. Even without the
random element, presence of ties in group imbalances produces allocations at random and in your example, as you demonstrated, very frequently; more frequently than with a 1:1 permuted block schedule with the block size of 4.

2. in restricted randomization simulations, 3 race/ethnicity levels were used: Hispanic, non-Hispanic Black, or other), while with minimization only Hispanic and non-Hispanic Black categories were included. How were the subjects with the third race/ethnicity category (Other) allocated with minimization? Do you use the same population when examining the three procedures?

3. is average of the difference a good measure of balance? One would rather look at probability of a bad imbalance that happens with say 10% chance

**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.

Yes

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

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?
2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal