Reviewer's report

Title: A Method to Reduce Imbalance for Site-Level Randomized Stepped Wedge Implementation Trial Designs

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Reviewer: Alan Girling

Reviewer's report:

The paper draws attention to the difficulties associated with achieving "mean-balanced" allocation of clusters to the waves/sequences of a stepped-wedge design, and proposes a method based on eliminating, as far as possible, any linear trends in site characteristics across the time-waves. This is a well-motivated enterprise, but I have some major concerns over its execution.

1. Where it can be achieved, mean-balance - such as would be achieved by strict stratification - is surely a more desirable outcome than mere sequential balance since the latter is consistent with identifiable quadratic trends in the site variables. Yet the IMB criterion gives no premium at all to a design that is exactly (or approximately) mean-balanced as opposed to one that is merely sequentially balanced. For example, for a binary characteristic (= 1 or 2), the allocations (1 1 1) (2 2 2) (1 1 1) and (1 2 1) (1 2 1) (1 2 1) both have IMB = 0, yet the latter is perfectly balanced while the former is clearly not. In an extreme case this could mean that the opportunity for a perfect stratification on the characteristic might be missed in favour of a design where all 2-clusters are pre-destined to occupy the middle wave. (This could be avoided by choosing a criterion that is sensitive to both forms of imbalance.)

2. In discussions of balance criteria for parallel studies it is more-or-less automatic that the clusters will have equal probabilities of assignment to any arm. Departures from randomness usually arise only because of imbalance between pairs/triples etc of clusters in the allocation. This cannot be relied on in the present context. The final design will be chosen at random from a limited selection (34, in the example) in which the clusters may not appear equally often in each wave. For example, any 'unusual' cluster is more likely to occupy a middle-wave position. (In a parallel study it would be equally likely to be allocated to any arm.) It would be a good idea to display the prior assignment probabilities for each cluster so that the departure from randomness can be assessed. In general departures from randomness may affect the performance of statistical tests and compromise the face-validity normally associated with randomised studies.

3. It is proposed (P9) to standardise all continuous variables to unit standard deviation to make them more homogeneous. Then they are automatically replaced by tertiles (incidentally rendering the standardisation redundant). In expressing a continuous variable in categorical form, all information about the ordering of the variable is lost. The proposed approach makes no distinction at all between ordered and unordered categories. For example, for 4 ordered
categories (A<B<C<D), the fact that A D B C is a more balanced sequence than A B C D would be missed. The only balance-improvements considered are those that split apart clusters in the same category.

4. Minor points

a. P5 line99. It is confusing to say that time and region are completely confounded. In the ordinary sense of the word 'time' refers to the timing of an observation, and is in fact cross-classified with Region in such a stepped-wedge design. Similarly P8, line 151 and line 164.

b. P6 Lines 104-8. The analogy with a BIB design is not immediately compelling, particularly as there are only two treatments in a SWD. What is proposed is a restricted randomisation scheme which, unlike BIB, does not ensure exact compliance with a balancing condition.

c. P11 line 220. The sentence seems to imply that the reverse sequence is a "redundancy". But N=1680 can be obtained only if the reverse sequence is counted separately. Suggest remove sentence beginning "The reverse sequence …"

d. P11 line 231. Whether the SRS method is reliable will surely depend on the size of the problem?

e. P13 The objection to stratification is that it won't often be feasible. The proposed method is more vulnerable to bias.

f. P14 line 293. I don't understand the meaning of "bounds on the differences among the standard deviations across the time-waves". Please clarify.

g. P14 line 295. Reference to cases and controls, (intervened/non-intervened) needs clarification. Presumably this is not the "intervention" in the study, but some other characteristic?

h. P16 line 348. This reads like a throwaway remark that doesn't refer to anything concrete in the paper. What are these long-established principles, and how are they to be applied in parallel designs beyond what is already standard methodology for achieving balance?
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