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Two-Stage Randomized Trials: Outstanding Issues

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Editor

Tamura et al. [1] wrote a nice article describing a two-stage randomized design. Some collaborators and I described a rather similar design in the literature [2], but there were some issues with the conducting an exact analysis of the data arising from such a design. Since the various stages are conducted to address similar, if not identical, questions, it makes sense to conduct a single comprehensive analysis, rather than separate analyses by stage. As is well known, exact analyses for randomized trials are conditional permutation tests [3]. Conducting permutation tests in the simplest case of a single 2x2 contingency table involves fixed margins, and the cell counts are permuted in all possible ways to keep the margins fixed. With a 2x2 table, there is but one degree of freedom which, for convenience, we may define as the number of placebo non-responders. Call this quantity X . In the first stage, X is a random quantity that will vary across the permutations. But in the second stage, X is fixed. This may not be a problem if we treat the tables from the two stages separately, but, as noted, this is inefficient, and it is unclear, at least to me, how one would permute both sets of data simultaneously to conduct a single comprehensive permutation test. Certainly when we compare the data in the second stage to its peers, these peers are defined in part by having the same table total. And yet when the data from the first table are permuted, this would entail changing also the table total for the second table. I will note in passing that I do hold these authors in a rather high regard, so it is entirely possible that they can come up with a satisfactory solution to this problem, and I would encourage them to address this issue.

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