Response to letter: Wenle Zhao and Vance W. Berger, Better alternatives to permuted block randomization for clinical trials with unequal allocation

We thank Drs Zhao and Berger for their interest and suggestions regarding our method for achieving balance in a small clinical trial. The description and observation that we used a 'hierarchical biased coin - adaptive randomization (HBC-AR)' approach is insightful. We are not aware of previous descriptions of this term or methodology in adaptive randomization procedures.

They describe several methods for achieving a non-equal allocation ratio in a randomized controlled trial, including the mass weighted urn (MWU) approach. The weighted urn approach appears to be useful in certain settings, but with the data presented so far, it is unclear to us whether this would have been helpful for our trial. The primary goal of our adaptive randomization was to maintain balance on one binary covariate, and one three-category covariate. As such there were a total of six possible combinations. We additionally were trying to have an approximately 2:1 allocation of treatment to placebo. The MWU approach as described would have accomplished the latter goal, but we are not sure how well it would have balanced the baseline covariates overall for our trial.

In addition, they suggest that the various strategies in the table provide 'more random' allocation decisions. On closer inspection, it appears that the MWU with a tolerated imbalance of 4 has extremely similar randomization vectors to our HBC-AR design in most of the given imbalance situations, except that the MWU design moves to deterministic picks when the imbalance reaches the tolerance. We would be interested in some quantification or standards regarding 'how random' allocation should be as our qualitative evaluation suggests the HBC-AR and MWU(4) designs confer pretty similar randomness, except at the extremes where the MWU is not random at all.

One advantage of our design is that we set the hierarchy based on our clinical needs. In the example trial given in our paper, the placebo proportion was too high after the first two patients, and remained out of the range from 0.23 to 0.43 until after the seventh patient was randomized to treatment. After the eighth patient, the placebo proportion never again moved outside the desired range and the design could focus on balancing the proportion of the baseline covariates across the treatment and control groups.

In order to utilize the MWU approach (we think), we would have needed to set up urns for each of the six different combinations of baseline covariates. Then within each urn, the MWU algorithm would work to keep the ratio near 2:1. The problem with this is that there would not be information flow between these urns. Imbalance in the hydroxyurea positive, moderate ED user urn would not inform decisions regarding randomization for the hydroxyurea positive, heavy ED user urn. In addition, within a 45-subject trial, some of these urns would have limited ability to balance as they would not be drawn from evenly.

We are strong believers in using clinical trial simulation to test any new randomization procedure or design and as discussed in the original paper tested our randomization strategy using simulation. As such it would seem that the ultimate test of whether allocations are random enough, would be to simulate the trial while assuming some sort of treatment effect on the main outcome of the trial, and then using permutation tests to determine how far each of the methods diverged from 'perfect' randomization. Similar to our paper, one would also evaluate how many trials (both from the permutation tests and the various balancing methods) had meaningful imbalance. From our Table 4, we can see that at least 25% of trials using unconstrained randomization had total imbalances of 25% or more when comparing the treatment and control groups.

We appreciate these additional suggestions for balancing strategies and will compare these strategies with the one we proposed using simulation in our future designs.

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Reference
[1] Zhao W, Berger V.W. Better alternatives to permuted block randomization for clinical trials with unequal allocation. Hematology. 2016. doi: 10.1080/10245332.2016.1236996