Better alternatives to permuted block randomization for clinical trials with unequal allocation

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To the Editor

Meurer, Connor, and Glassberg recently published ‘Simulation of various randomization strategies for a clinical trial in sickle cell disease’ in this journal, proposed a biased-coin adaptive randomization design for a sickle cell disease trial with a small sample size of 45 and an unequal target allocation of 1:2 between placebo and active treatment, and compared it with the complete randomization and the permuted block randomization via computer simulation [1]. The authors’ effort of seeking a better alternative to the inferior permuted block randomization is laudable, and the implementation of better randomization designs in sickle cell disease trials is important. However, a few issues pertained to this manuscript caught our attention. We would like to share our opinions with the authors as well as readers of the journal.

The desire of balancing important baseline covariates is common in many randomized controlled clinical trials [2]. It is not unique to sickle cell disease trials. Various stratified restricted randomization designs, including the permuted block randomization, have been widely used in clinical trial practice [3]. Some well-known restricted randomization designs, such as Efron’s biased-coin design [4], Wei’s urn design [5], and Soares and Wu’s big stick design [6], are not readily applicable for trials with unequal allocations [2], leaving the field dominated by permuted block randomization. The high proportion of deterministic assignments and the vulnerability to selection bias attributable to permuted block randomization has been well studied and documented in the literature [7–13]. As the proceeds of these research efforts, several restricted randomization designs applicable to unequal allocations have been published in recent years, including the maximal procedure [14], the block urn design [15], the brick tunnel randomization [16], and the mass-weighted urn design [17]. These restricted randomization designs can be stratified by baseline covariate categories in order to achieve balanced covariate baseline [3], and therefore are potential candidates for the subject randomization of the sickle cell disease trial.

The proposed biased-coin adaptive randomization uses a conditional allocation probability adjusted for the observed treatment imbalance [1], and therefore can be classified as a restricted randomization method. While its implementation in a specific disease field could be innovative, both the imbalance-adaptive biased coin probability for treatment assignment and the stratified randomization for baseline covariate balance are well established strategies. To evaluate the performance of this new randomization design, it is essential to compare it to not only the well-known inferior permuted block randomization, but also to those better alternatives currently available.

Most restricted randomization designs use the simple difference between the two treatment group sizes as the imbalance measure for trials with equal allocation [4–6,10]. For two-arm unequal allocation \( r_1/r_2 \), where \( r_1 \) and \( r_2 \) are integers, let \( p_1 = r_1/(r_1 + r_2) \), \( p_2 = r_2/(r_1 + r_2) \), so that \( p_1 + p_2 = 1 \). Treatment imbalance can be defined as \( d = r_2 n_1 - n_1 n_2 \), where \( n_1 \) and \( n_2 \) are the number of subjects previously randomized in the two treatment arms respectively. The performance of a restricted randomization design is fully defined by how the conditional allocation probability adapts to the observed treatment imbalance. For example, in a two-arm trial with 1:2 allocation, the block urn design has the conditional allocation probability for assigning the subject to treatment 1 equals to \( p_1(BUD) = (r_1(k + \alpha) - n_1)/(r_1 + r_2)(k + \alpha) - n_1 - n_2 \), where \( \alpha \) is the parameter for the maximum tolerated imbalance (MTI), and integer \( k = \text{int}((n_1 + n_2)/(r_1 + r_2)) \) is the number of balanced set of treatment assignments among the previously randomized subjects [15]. For the mass-weighted urn design [17], there is \( p_1(MWUD) = \max(p_1 - d/\beta, 0) \), where \( \beta \) is a parameter for the MTI. The maximal procedure ensures that all possible allocation sequences have the same
probability to be selected. The conditional allocation probability converges to its asymptotic value quickly after few assignments. All these three designs enforce the MTI by using deterministic assignments, in order to achieve a consistent imbalance control and to prevent potential chronic bias [12,14], and are easy for implementation [13].

A close examination reveals that the proposed biased-coin adaptive randomization uses a two-step hierarchical imbalance control. It checks the overall treatment imbalance first. Let \(N_1\) and \(N_2\) be the total number of subjects in the entire study previously randomized to arm 1 and 2, respectively. If \(|N_1/(N_1 + N_2) - p_1| > 0.1\), the biased coin probability of \(p_1^* = p_1^{N_1/(N_1+N_2)/p_1}\) is used for assigning the current subject to arm 1. Otherwise, within stratum imbalance is checked, and the biased coin probability of \(p_1 = p_1^{\exp(d/2)}\) is used.

Table 1 compares the proposed biased-coin adaptive randomization to the block urn design, the mass-weighted urn design, and the maximal procedure based on the conditional allocation probability under different values of observed imbalances. All three MTI designs offer a parameter for the investigator to choose the imbalance control limit based on the consideration of the desired balancing and the acceptable allocation randomness. The biased-coin adaptive randomization uses exponential functions in order to avoid the use of deterministic assignments [1]. From the practical point of view, a biased coin probability of greater than 0.95 makes no meaningful difference from a deterministic assignment when selection bias is concerned. For small trials like the reported sickle cell disease study with six baseline covariate strata, the average stratum size is about 8. We recommend that the MTI measured by \(|d| = |2n_1 - n_2|\) be controlled no more than 4. Therefore, the block urn design, the mass-weighted urn design, or the maximal procedure can be good options for this sickle cell disease study.

In short, there exist several restricted randomization designs applicable for unequal allocations. Under the same MTI control, all these designs offer higher allocation randomness than permuted block randomization does. They also provide more effective imbalance control when compared with the BCAR proposed by the authors in that article.

**Disclosure statement**

No potential conflict of interest was reported by the authors.

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