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Letter to the Editor

Selection bias, allocation concealment and randomization design in clinical trials

To the Editor:

The primary goal of randomization in a clinical trial is to prevent selection bias, which could occur if investigators are able to predict the upcoming treatment allocation with a success probability higher than pure random guess. When the patient recruitment decision is influenced by the knowledge of upcoming treatment allocation, selection bias is inevitable, and the validity of the trial result is seriously damaged.

Allocation concealment is defined as the procedure for protecting the randomization process and preventing selection bias so that the treatment to be allocated is not known before the patient is entered into the study [1]. Allocation concealment is affected by two factors: (1) the predictability of treatment allocation and (2) the blinding protection of the treatment allocation before the enrollment of the patient. The allocation predictability depends on the randomization algorithm, and the allocation blinding protection depends on the implementation of the randomization procedure. It is important to realize that failures in treatment allocation blinding protection before patient enrollment is a problem only when the treatment allocation was assigned before the patient is randomized. For example, a treatment allocation sequence is pre-generated based on the selected randomization algorithm, and the so-called patient randomization is to use the next treatment assignment on the allocation list based on the time sequence of patient enrollment. Historically, this type of randomization method had been widely used in clinical trials practice, and treatment allocation concealment schemes, such as sequentially numbered opaque sealed envelopes and pharmacy controlled randomization, were primarily focused on the blinding protection of the allocation sequence [2].

The implementation of a computerized central randomization system such as interactive voice response system (IVRS) or interactive web response system (IWRS) enables the treatment randomization to occur after the patient enrollment. With central randomization, the computer calculates the conditional treatment allocation probability based on the randomization algorithm and the current treatment assignment profile. The patient is assigned to a treatment arm based on the value a real-time generated uniformly distributed random number and the conditional allocation probability. In other words, the pre-generated treatment allocation sequence is not needed, and the risk of allocation blinding failure before patient enrollment is fully eliminated. Without the pre-generated randomization list, allocation concealment is solely determined by the treatment allocation predictability of the randomization algorithm.

Treatment allocation randomness and treatment group balance are two competing demands existing in all randomization algorithms. Simple randomization (SP) has the lowest possible allocation predictability and therefore has been recommended to use, especially when treatment blinding is not available [3]. In practice, the compatibility of treatment groups with regarding to the group size as well as the distribution of baseline confounding factors are desired by investigators based on the considerations of trial power, cost and result interpretation. This motivated the development and implementation of various restricted randomization algorithms in the past few decades, including commonly used permuted block design (PBD) [4], Efron's biased coin design (BCD) [5], Wei's urn design (UD) [6], Soares and Wu's big stick procedure (BSP) [7], Berger's maximal procedure (MP) [8], Zhao and Weng's block urn design (BUD) [9] and the minimization methods proposed independently by Taves [10] and Pocock [11]. Among them, PBD, BSP, MP and BUD use the concept of maximal tolerated imbalance (MTI) and therefore can be easily compared with each other, based on the proportion of deterministic assignment (DA) and the correct guess (CG) probability of treatment allocation [9]. A treatment allocation is deterministic if the probability to allocate the patient to one treatment arm is 1.0. The concept of CG is based on the convergent guessing strategy given by Blackwell and Hodges [12], which is to guess the next treatment allocation as the least represented treatment arm. Table 1 lists the quantitative comparison results for the four randomization designs using MTI.

Among the four designs, BUD and MP have the lowest DA, and BSP has the lowest CG. It is also necessary to recognize that the most important factor affecting treatment predictability is the MTI. PBD with MTI = 4 will has the similar CG as BUD or MP with MTI = 2. For phase 2 or 3 trials with a sample size range from hundreds to thousands, MTI = 2 may not be necessary. Bigger block size (or MTI) for permuted block randomization has been suggested [3,13].

While comparing these four randomization algorithms, it is worth to mention two important properties affecting the selection of randomization designs: (1) the uniformly distributed allocation sequence and (2) the analytical format of conditional allocation probability. The MP assigns an equal

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Table 1
Treatment allocation predictability of randomization designs using maximal tolerated imbalance.

Randomization algorithm	MTI = 2		MTI = 4		MTI = 6	
	DA	CG	DA	CG	DA	CG
Permuted block design	0.333	0.708	0.200	0.665	0.143	0.643
Big stick procedure	0.250	0.625	0.125	0.563	0.083	0.542
Maximal procedure	0.166	0.666	0.038	0.598	0.014	0.569
Block urn design	0.167	0.667	0.021	0.613	0.003	0.590

Note: Computer simulation data based on two arm equal allocation ratio and sample size $n = 300$.

probability to all possible allocation sequences under the pre-specified sequence length and the MTI [8]. This feature provides the theoretical foundation for randomization tests for trial results. It also applies to SP and PBD, but not to BSP and BUD. On the other side, almost all aforementioned randomization algorithms have a closed analytical format for the conditional allocation probability except MP. With MP, the treatment allocation sequence must be pre-generated, even with a central randomization system, and therefore the risk of concealment failure due to imperfect blinding of allocation assignment before patient randomization remains. In addition to this, the only algorithm provided by Salama et al. [14] for the generation of MP allocation sequence is much complex compared to other randomization designs. The lack of the analytical format for the conditional allocation probability and the requirement for the pre-generated allocation sequence create limitation on the use of MP in clinical trial practice.

The above comparisons have been limited to the four randomization algorithms using MTI. If the purpose of using MTI is to prevent serious imbalances in treatment group sizes and therefore to protect the power of the trial, the commonly practice of using small MTI, such as 2, 3 or 4, can be challenged. Consider a trial comparing two independent binomial proportions testing the hypothesis $H_0 : p_A = p_B$ versus $H_1 : p_A \neq p_B$ for the specific alternative $|p_A - p_B| = |0.55 - 0.25| = 0.30$, with significance level $\alpha = 0.05$ and sample size $n = 100$, the power under perfect balance would be 87.6% and will lose about 0.5% if the imbalance between the two arms reaches 12. For a trial with a large sample size of $n = 1400$ and specific alternative $|p_A - p_B| = |0.32 - 0.25| = 0.07$, the power under perfect balance will be 82.74% and will lose no more than 0.1% if the imbalance between the two arms goes to 50. These quantitative results indicate that the use of small MTI, such as 2, 3 or 4, in trials with a moderate or large sample size to protect the power is not necessary. When a bigger MTI is used in a central randomization system without a pre-generated allocation sequence list, the risk of treatment allocation concealment failure will be significantly reduced. Based on the formula provided by Matts and Lachin [15], when PBD with a block size of $b = 30$ is used, i.e., MTI = 15, the proportion of DA will be $1 / (b / 2 + 1 = 0.0625)$. When BSP, MP or BUD is used, the expected number of deterministic assignment will be practically negligible. In practice, a moderate MTI, such as 6 or 8, is suggested when the sample size is small or balanced treatment group sizes at interim analyses is desired, or some temporal confounding factors are of concern. Otherwise, using MTI 10 or 12 will be sufficient to protect the power and meanwhile to provide sound allocation concealment for selection bias prevention.

When a restricted randomization algorithm is designed to prevent serious imbalances in baseline confounding factors between treatment groups, stratification or minimization has been widely used, but both faces challenges. With the increase of the number of stratification variables, the number of strata increases and the average stratum size decreases in exponential rates. This pushes the use of small MTI in order to control the overall imbalance in treatment group sizes and consequently increases the treatment allocation predictability. The minimization method has been heavily criticized for its lack of randomness [16]. Zhao et al. proposed a minimal sufficient balancing (MSB) strategy aimed to minimize the treatment allocation predictability while preventing serious imbalances in baseline covariates and treatment group sizes [17]. With the MSB strategy, simple randomization will be used for patient treatment allocation, unless some imbalances exceed their pre-specified limits, and the treatment assignment for the current patient can effectively reduce the imbalance. In such cases, a biased coin allocation will be used. With MSB, imbalances are evaluated based on the p-value of some selected tests, such as a t-test for the equality of the means of a continuous covariate and a chi-squared test for a categorical covariate. Computer simulation results have shown that when a biased coin probability of 0.65 is used to simultaneously prevent serious imbalances, defined as $p < 0.3$, in 5 baseline covariates for a two-arm trial with a sample size of 624, on average, 58.8% treatment allocations will be pure random, the correct guess probability will be 56.2% and there will be no deterministic assignments [17].

To summarize, in order to prevent selection bias and protect treatment allocation concealment, one should increase the imbalance tolerance level, avoid using pre-generated allocation sequence and use real-time central randomization.

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