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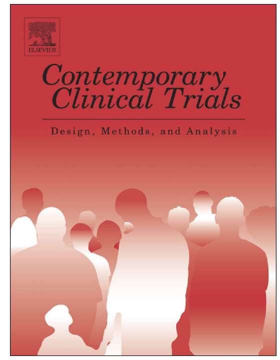

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Guessing strategies for treatment prediction under restricted randomization with unequal allocation

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To the Editor:

One of the primary goals of subject randomization in clinical trials is to prevent selection bias [1], which could occur if investigators are able to predict the upcoming treatment allocation with a success probability higher than pure random guess [2]. With real-time central randomization, the risk of selection bias in the subject randomization process can be eliminated when an unrestricted randomization, also known as complete randomization, is used 1. Motivated by considerations of trial efficiency, operation cost, and interpretation of trial results, restricted randomization methods are commonly used in practice in order to control treatment imbalances across the entire study and/or within baseline covariate strata [1]. Any benefit in treatment balance comes with a cost in allocation randomness. When comparing different randomization designs and choosing one for a specific trial, investigators tend to pay more attention to imbalance control than to allocation randomness protection, partly because of the lack of well-defined quantitative measures for the allocation randomness [4].

Currently, the proportion of deterministic assignments and the correct guess probability are two measures used by researchers [4]. A treatment assignment is considered as deterministic when the conditional allocation probability for any arm equals 1.0. In 1957, Blackwell and Hodges proposed the convergence guessing strategy for the allocation randomness assessment in two-arm equal allocation trials. It predicts the treatment which has hitherto occurred less often be the next assignment [5]. In recent years, unequal allocation gains more applications in clinical trials [6], partially due to the emerging of Bayesian adaptive designs [7] and response adaptive randomization [8]. To evaluate the performance of different randomization designs under unequal allocations, the convergence guessing strategy has been extended from equal allocation to unequal allocation scenarios in recent publications [2-4,6-12]. In the book titled Selection bias and covariate imbalances in randomized clinical trials, Berger described two guessing strategies for unequal allocations under the names of convergent prediction and directional prediction with illustration examples [2]. Zhao et al used the so-called convergence guessing strategy for the treatment predictability assessment for unequal allocations when comparing different randomization schemes [4,10-12]. However, explicit definitions for both the convergence guessing strategy and the directional guessing strategy for unequal allocation have not been given yet. Researchers could be confused or misled when choosing a guessing strategy for the calculation of correct guess predictability. In this article, we set up a general framework for treatment guessing strategies based on the conditional allocation probability and the treatment imbalance for two or multi-arm trials with equal or unequal allocations.

Consider an m-arm trial with a target allocation of $\mathbf{R} = (r_1, r_2, \cdots, r_m)$, where r_j $(j = 1, 2, \cdots m)$ are positive integers without common divisors greater than 1. Let $\mathbf{N} = (n_1, n_2, \cdots, n_m)$ be the treatment assignment distribution prior to the randomization of the current subject, $\mathbf{P} = (p_1, p_2, \cdots, p_m)$ be the conditional allocation probability, and $\mathbf{D} = (d_1, d_2, \cdots, d_m)$ be the treatment imbalance between the current allocation ratio and the target allocation ratio:

$$d_j = \frac{n_j}{n} - \frac{r_j}{r} \qquad (j = 1, 2, \cdots, m) \tag{1}$$

where $n = \sum_{j=1}^{m} n_j$, $r = \sum_{j=1}^{m} r_j$. Let Ψ represent the randomization algorithm used in the study. To evaluate the treatment predictability of Ψ, the following conditions are assumed:

1. The investigator has the information of the target allocation **R**, the current treatment distribution **N**; and therefore, the treatment imbalance **D** as a function of **R** and **N**.
2. The investigator has the information of the randomization algorithm Ψ; and is able to calculate the conditional allocation probability **P** based on **R**, **N**, and Ψ.

As described by Blackwell and Hodges, the convergence guessing strategy predicts the treatment which has hitherto occurred less often be the next assignment [5]. When extended to unequal allocation scenarios, the treatment which has hitherto occurred less often can be interpreted as the treatment which has been least represented in the current treatment distribution as regards to the target allocation. In other words, the treatment with the minimum value of imbalance d is predicted. We name this prediction as the minimum imbalance guess:

$$d_g = \min_{1 \le j \le m}(d_j) \tag{2}$$

It is important to notice that under the definition (1), there is $\sum_{j=1}^{m} d_j = 0$. Therefore, the minimum imbalance d_g defined by (2) must be non-positive.

For example, with $r_1 : r_2 = 2:1$, $n_1 = 5$, $n_2 = 2$, there are $d_1 = 5/7 - 2/3 = 1/21$ and $d_2 = 2/7 - 1/3 = -1/21$. The minimum imbalance guess will predict treatment 2 as the next assignment. When two or more treatments meet condition (2), the minimum imbalance guess predicts one from them completely at random. In other words, each of these treatments will have an equal chance being predicted as the next assignment, without regard to the target allocation ratio.

Blackwell and Hodges also indicated that the convergent guessing strategy maximizes the probability of correct guess [5]. To achieve this goal in unequal allocation scenario, the guessing strategy must predict the treatment with the maximum conditional allocation probability:

$$p_g = \max_{1 \le j \le m}(p_j) \tag{3}$$

The conditional allocation probability depends not only on the target and current allocations **R** and **D**, but also the randomization algorithm Ψ. For the same example with $r_1 : r_2 = 2:1$, $n_1 = 5$, $n_2 = 2$, if the permuted block randomization (PBR) with a block size of $b = 6$ is used, the conditional allocation probability can be obtained based on an urn model [4]:

$$p_1 = \frac{(br_1 / r)[1 + \mathrm{int}(n / b)] - n_1}{b + \mathrm{int}(n / b) \times b - n_1 - n_2} = \frac{3}{5}, \qquad p_2 = 1 - p_1 = \frac{2}{5} \tag{4}$$

Here function $\mathrm{int}(x)$ returns the largest integer less than or equal to x. Therefore, treatment 1 is predicted as the next assignment. We name this as the maximum probability guess. When two or more treatments meet condition (3), the maximum probability guess predicts one of them completely at random.

For randomization algorithms with a conditional allocation probability as a monotonic function of the current treatment imbalance, the minimum imbalance guess and the maximum probability guess predict the same treatment under equal allocation. Therefore, the distinction between the two guessing strategies is not critical. For unequal allocations, the maximum probability guess has been used under the name of convergence guess [2-4,9-12], and the minimum imbalance guess is similar to the directional guess [2]. Without explicit definitions like (2) and (3), the name of convergence guess might be mistakenly considered as the minimal imbalance guess. We believe that replacing the names of convergence guess and directional guess with maximum probability guess and minimal imbalance guess will help researches to better understand the logic and the calculation of the two guessing strategies.

Shown in Table 1 are treatment prediction examples under the maximum probability guessing strategy and the minimum imbalance guessing strategy for a two-arm 2:1 allocation trial using the permuted block randomization with block size of 6. Included in Table 1 are 18 assignments from three different permutation blocks. A complete list containing all 15 unique permutation blocks reveals that the correct guess probabilities for the maximum probability guessing strategy and the minimum imbalance guessing strategy are 74.44% and 72.22%, respectively. Based on the definition, the maximum probability guessing strategy maximizes the correct guess probability, and therefore, is recommended to be used for the quantitative evaluation of allocation randomness for randomization designs.

Table 1. Treatment Guessing Strategy Comparison

Two-arm 2:1 allocation, permuted block randomization with block size =6

Sequence	Block	Assignment	Current Treatment Distribution		Conditional Allocation Probability		Current Treatment Imbalance		Maximum Probability Guess	Minimum Imbalance Guess
			n_A	n_B	p_A	p_B	d_A	d_B		
1	AAAABB	A	0	0	2/3	1/3	0	0	A	A/B
2		A	1	0	3/5	2/5	1/3	-1/3	A	B
3		A	2	0	1/2	1/2	1/3	-1/3	A/B	B
4		A	3	0	1/3	2/3	1/3	-1/3	B	B
5		B	4	0	0	1	1/3	-1/3	B	B
6		B	4	1	0	1	2/15	-2/15	B	B
7	ABABAA	A	4	2	2/3	1/3	0	0	A	A/B
8		B	5	2	3/5	2/5	1/3	-1/3	A	B
9		A	5	3	3/4	1/4	-1/6	1/6	B	A
10		B	6	3	2/3	1/3	0	0	A	A/B
11		A	6	4	1	0	-1/6	1/6	A	A
12		A	7	4	1	0	-1/15	1/15	A	A
13	BAAABA	B	8	4	2/3	1/3	0	0	A	A/B
14		A	8	5	4/5	1/5	-2/3	2/3	A	A
15		A	9	5	3/4	1/4	-1/6	1/6	A	A
16		A	10	5	2/3	1/3	0	0	A	A/B
17		B	11	5	1/2	1/2	1/12	-1/12	A/B	B
18		A	11	6	1	0	-1/15	1/15	A	A

Treatment allocation randomness is a critical property of the subject randomization procedure. Many will claim that investigators are too busy to mess around with complicated prediction strategy, and so therefore are not actively trying to predict future allocations. Are they really going to compute conditional allocation probabilities? And the answer, of course, is that they don't have to. The simplicity of the maximum probability guessing strategy allows investigators to predict with no more detailed information than bacteria who never read Darwin would need to evolve nevertheless. The intention of this letter is to provide a generally applicable formula for a standardized measure of the treatment predictability for two or multi-arm trials with equal or unequal allocations.

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