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Response-adaptive Randomization for Clinical Trials with Adjustment for Covariate Imbalance

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SUMMARY

In clinical trials with a small sample size, the characteristics (covariates) of patients assigned to different treatment arms may not be well balanced. This may lead to an inflated type I error rate. This problem can be more severe in trials that use response-adaptive randomization rather than equal randomization because the former may result in smaller sample sizes for some treatment arms. We have developed a patient allocation scheme for trials with binary outcomes to adjust the covariate imbalance during response-adaptive randomization. We used simulation studies to evaluate the performance of the proposed design. The proposed design keeps the important advantage of a standard response-adaptive design, that is to assign more patients to the better treatment arms, and thus it is ethically appealing. On the other hand, the proposed design improves over the standard response-adaptive design by controlling covariate imbalance between treatment arms, maintaining the nominal the type I error rate, and offering greater power.

Keywords

Adaptive randomization; Clinical trial design; Degree of imbalance

1 Introduction

Randomization, the random assignment of clinical trial participants to different treatment arms, ensures that the observed treatment effect is attributable to the treatment itself rather than to confounding elements. Randomization is the hallmark of clinical trials assessing treatment effects. In recent years, researchers have designed different randomization schemes for clinical trials. The response-adaptive(RA) randomization scheme has become popular in clinical research because of its flexibility and efficiency [1–6]. Based on the accruing history of patients responses to treatment, the RA randomization scheme adjusts the future allocation probabilities, thereby allowing more patients to be assigned to the superior treatment as the trial progresses. As a result, RA randomization can offer significant ethical and cost advantages over equal randomization.

Researchers know that some patient characteristics (covariates) will have a strong effect on the patients clinical response to treatment. To ensure that any observed treatment effect is attributable to the treatment itself rather than to any particular patient characteristic, the research design must balance the potentially confounding patient characteristics among the different treatment arms. Improving the balance of patient characteristics among the treatment arms also potentially increases the statistical power of the trial[7–8]. In this article,

we consider this important problem: achieving a balance in the characteristics of patients assigned to the different treatment arms when using the RA randomization scheme.

To fully understand the importance of controlling covariate imbalance, one must be warned about the great heterogeneity among the patients enrolled in cancer clinical trials. For example, in a clinical trial for acute myeloid leukemia (AML), characteristics that may affect prognosis include patient age, AML subtype, number of previous treatments and relapses, number of healthy blood cells, size and number of leukemia cells, cytogenetic abnormalities, genetic mutations, and the existence of antecedent hematologic disorders. Cytogenetic abnormalities (the deletion or duplication of chromosomes, or other changes in the chromosomes of leukemia cells) are usually classified into three categories according to their prognostic effects: favorable, intermediate, and poor.

Such heterogeneity in patient characteristics has a non-ignorable effect on the outcome of a clinical trial. To fully understand the importance of this issue, we need to consider that significant breakthroughs are rare in the development of new treatments for cancer For example, advances in the treatment of AML have occurred slowly, without any single monumental breakthroughs. The history of treatment development leads us to expect only small differences in treatment effects when comparing a new treatment to a standard treatment. In order to detect and validate such small differences in outcomes between patients receiving a new versus the standard treatment, researchers must carefully balance the patient characteristics (covariates) among the treatment arms in a trial.

Randomization is necessary to avoid the intentional or unintentional assignment of patients with better prognoses to a favored treatment arm. However, for a clinical trial with a small to moderate sample size, the use of a simple equal randomization scheme may still result in a considerable imbalance among the treatment arms, and this may occur solely by chance. Clinical investigators are often concerned that a trial will not be able to show the benefit of a promising new treatment when too many patients with poor prognoses are “randomly” assigned to the experimental treatment arm. A stratified randomization scheme [9] can be used to solve this problem. However, when the number of important covariates is too large, the sample sizes for some strata may be too small to effectively apply a stratified randomization scheme. An example of this involves a trial for adult patients with refractory/relapsed AML. Say that we consider only three covariates for the randomization scheme: patient age (younger than 60 years or 60 years and older), cytogenetics (three prognostic categories as favorable, intermediate or poor), and the number of previous chemotherapy treatments (one or more than one). Using only these three covariates will involve $3 \times 2 \times 2 = 12$ strata. In a typical trial with a sample size between 100 and 200, the number of patients in some strata may be less than 10 because the frequency of assignment to the different strata are not uniform. Randomization in such small strata can result in severely unbalanced patient ratios.

As a valid alternative to a stratified randomization scheme, a covariate-adaptive (CA) randomization scheme incorporates the accumulating information on the distribution of covariates into the next randomization decision [10,11]. In specific terms, a CA randomization scheme allocates a new patient to the treatment arm that would minimize the imbalance of important covariates among the treatment arms. The optimization of such a scheme has been studied [12,13,14,15]. Different from stratified randomization, CA randomization can increase the balance among many covariates simultaneously.

Using the RA randomization scheme, the assignment of a new patient depends on the previous patients’ responses to treatment in the ongoing trial, with an unbalanced allocation probability favoring the treatments observed to have comparatively superior responses.

Consequently, RA randomization will result in small sample sizes for inferior treatment arms. These small sizes can magnify the problems of imbalance among the covariates, inflated type I error rates and low statistical power[16]. There is substantial literature on RA randomization trial designs; however, a method for achieving balance among the patient covariates when using the RA randomization scheme has not been developed. We fill this gap by developing an allocation rule to increase the balance among covariates in a trial design using the RA randomization scheme.

The remainder of the article is organized as follows. In Section 2, we introduce a measure for the degree of imbalance between the treatment arms, and also introduce our new design. We provide the numerical computations and explore the benefit of the proposed design in Section 3, and discuss related issues in Section 4.

2 Response Adaptive Design with Adjustment for Covariate Imbalance

Consider a clinical trial with n patients. Suppose that patients who are sequentially enrolled in a trial are to be assigned to receive one of two competing treatments, A and B. Denote T_i to be an indicator variable that takes the value 0 or 1 according to whether the i^{th} patient receives treatment A or B respectively, and Y_i be the binary response indicator for this patient. We assume that there are J covariates of interest Z_j, $j = 1, \ldots, J$, and they are respectively categorized into different levels denoted by $k = 1, \ldots, L_j$. Define n_{mjk}, $m = 0, 1$; $j = 1, \ldots, J$; $k = 1, \ldots, L_j$ to be the number of patients in the kth level of the jth covariate in treatment arm m.

2.1 A measure of the degree of covariate imbalance

For a trial utilizing equal randomization, a perfectly balanced covariate distribution would satisfy that $n_{0jk} = n_{1jk}$ for all $j = 1, \ldots, J$ and $k = 1, \ldots, L_j$. Prompted by this, a measure of the degree of covariate imbalance can be taken as the sum of the absolute differences $|n_{1jk} - n_{0jk}|$ over all $j = 1, \ldots, J$ and $k = 1, \ldots, L_j$. However, for a RA randomization design, since more patients are assigned to the treatment arm that appears to be better, the targeted covariate balance is no longer assigning equal number of patients of each covariate level to each of the treatment arms. The target shall be modified accordingly to be equalizing the distributions of certain key covariates across treatment arms. Based on this idea, we now try to define a measure of the degree of covariate imbalance for unequal randomization schemes. let n_m be the number of patients that have been assigned to treatment m. Define a metric,

$$D_{jk} = n_{1jk} - (n_{0jk} + n_{1jk}) \frac{n_1}{n_0 + n_1}, \tag{1}$$

which is, under the assumption of equal covariate distributions across treatment arms, the difference between the observed and expected numbers of patients in the level k of the *jth* covariate assigned to treatment B. At the end of the study, the level of overall imbalance between the treatment arms can be measured by combining the imbalances across all levels of all of the covariates,

$$D = \frac{1}{n} \sum_{j=1}^{J} \sum_{k=1}^{L_j} |D_{jk}|. \tag{2}$$

In trials examining multiple treatments ($M > 2$), the above measure of overall imbalance among the treatment arms can be extended by

$$D=\frac{1}{n}\sum_{m=1}^{M-1}\sum_{j=1}^{J}\sum_{k=1}^{L_j}\left|n_{mjk}-\frac{n_m}{\sum_{l=0}^{M-1}n_l}\sum_{l=0}^{M-1}n_{ljk}\right|. \quad (3)$$

In practical applications, the covariates more strongly related to response can be given increased weights by using a weighted sum, $\tilde{D}=\frac{1}{n}\sum_{j=1}^{J}\sum_{k=1}^{L_j}w_j\left|D_{jk}\right|$, to calculate the overall imbalance. The weights used in this sum reflect the relative importance of the covariates. The preceding measure of imbalance cannot be used for continuous covariates. However, we can adopt a suitable categorization of the continuous covariates to continue with the current formulation.

2.2 New design

Our new design uses an RA randomization scheme and adds an adjustment for covariate imbalance between two competing treatment arms. It is a response-adaptive, covariate-adjusted (RACA) randomization design. The RACA randomization design includes an adaptive procedure that is based on the previous patients' responses and information on the covariates of the previous and current patients. Recently, Rosenberger, et al. [17], Zhang, et al. [18] and Hu and Rosenberger [4] proposed a design that considers the interactions between covariates and treatments, and use such information in the randomization to maximize the response rates for patients in the on-going trial. However, the identification of such interaction terms in regression models is not feasible unless the sample size is large. Since we focus on trials with small to moderate sample sizes, we are not considering such interactions. Although both their design and ours use the term "covariate-adjustment" in the name, they have completely different meanings.

For mathematical convenience, we use a Bayesian beta-binomial model to estimate the response rates. The posterior distributions of the responses are used to set up the patient allocation algorithm and selection criterion. Let Y_{im} denote the response of the *ith* subject for the treatment m, where $m = 0, 1$. Ignoring covariates for subjects, we assume that Y_{im} are independently and identically distributed across $i = 1, \ldots, n_m$ and each follows binomial distribution $B_{in}(p_m)$, where p_m has a beta prior distribution with parameters α_m and β_m. Here, we ignore covariates in this assumption, because covariates will not be considered when making a final conclusion about the winner in a trial. We set the parameters $\alpha_0 = \alpha_1 = \beta_0 = \beta_1 = 1$, representing reasonably vague prior information for the response rates. By these assumptions, the posterior distribution of p_m has a closed form: beta distribution with parameters α_m+n_{m1} and $\beta_m + n_{m0}$, where n_{mj} denotes the number of patients with response j in treatment arm m.

During the trial, we continuously update the posterior distributions of p_0 and p_1, and calculate the posterior probability

$$p_A=P(p_0>p_1\left|\text{data}\right). \quad (4)$$

A common way to do the response-adaptive randomization is to assign patients to treatment A with the posterior probability p_A, and to treatment B with probability $1 - p_A$. However, our experience shows that such an algorithm may assign too many patients to the putatively superior group too early. We will assign patients to the treatment A with the following probability,

$$p_{A,RA} = \frac{\sqrt{p_A}}{\sqrt{p_A} + \sqrt{1 - p_A}}, \tag{5}$$

and assign patients to the treatment B with probability $1 - p_{A,RA}$. By Thall et al. [19] and Rosenberger et al.[20], such a formula gives good performance on keeping the balance between treating patients efficiently and collecting information on both arms.

Now we consider to achieve covariate distribution balance between two competing treatment arms for trials utilizing a RA randomization design. When each new patient i with covariate vector $Z_i = (z_{i1}, \ldots, z_{iJ})$ is enrolled, we consider his/her impact on covariate balance by trying to assign him/her to different treatment arms. Using the idea of the biased coin design [21], the assignment that will result in the minimum is given a higher probability $p_{favor} > 0.5$ in the randomization. That is to say,

$$p_{A,CA} = \begin{cases} p_{favor} & \text{if assignment to A minimizes covariate imbalance,} \\ 1 - p_{favor} & \text{if assignment to B minimizes covariate imbalance,} \\ 0.5 & \text{if assignment to A or B gives same covariate imbalance.} \end{cases} \tag{6}$$

Here p_{favor} can be a fixed number or a function that is dependent on the magnitude of the imbalance, which ranges from 0.5 to 1. As p_{favor} increases, the level of the overall imbalance of the trial decreases and the predictability of the treatment assignment increases. For example, Taves [10] used a probability of one in minimizing the imbalance. However, such as a design is deterministic. It is not desirable to completely lose randomness in the randomization. Barbáchano, Coad and Robinson [22] evaluated the predictability of various covariate-adaptive designs. The simulation studies in the next section demonstrate that a fixed value of p_{favor}favor, say of 0.8 or 0.7, can achieve satisfactory performance.

Our main objectives are to assign the new patient to the superior treatment arm with a high probability and to control covariate imbalance. We call our proposed design response-adaptive with covariate-adjustment (RACA). Specifically, we assign a new patient to treatment A with probability $p_{A,RACA}$ and to treatment B with probability $1 - p_{A,RACA}$, where

$$p_{A,RACA} = \frac{p_{A,RA} \cdot p_{A,CA}}{p_{A,RA} \cdot p_{A,CA} + (1 - p_{A,RA})(1 - p_{A,CA})}. \tag{7}$$

If both the covariate imbalance and ethical criteria favor the assignment of a patient to the same treatment, such as in the case of $\min(p_{A,RA}, p_{A,CA}) > 0.5$, then the new patient will be assigned to treatment A with a higher probability compared with the probability when using the simple RA or CA randomization schemes. Otherwise, the new procedure will result in an assignment probability between $p_{A,RA}$ and $p_{A,CA}$. At the end of the trial, if $p_{A,RA} > p_u$(or $p_{A,RA} < p_l$), then treatment A (or B) is selected as the superior treatment. Otherwise, the trial is inconclusive. To achieve desirable operating characteristics, we use simulations to calibrate the pre-specified cut-off points p_u and p_l.

3 Simulation

We conducted simulations to evaluate the performance, under various clinical scenarios, of the proposed RACA design and to compare it with the following designs: simple equal randomization (ER), equal randomization with covariate adjustment (CA) and response-

adaptive (RA) randomization. The patient assignment probabilities under the CA design is determined by (6) without consideration on previous patients responses. That under the RA design is specified by (5) without considering covariate distributions. We used sample sizes of 60 and 100 for each scenario, and set the type I error at 0.10 and 0.05 respectively by choosing different cut-off values p_u and p_l for the four randomization designs. Each simulation comprised 5000 runs.

For covariate adjustment in both the CA and the proposed RACA designs, we set p_{favor} = 0.8. In scenarios with a sample size of 60, we assigned the first 10 patients equally to treatment A or treatment B and started using adaptive randomization at the 11*th* patient. In scenarios with a sample size of 100, we started using adaptive randomization at the 21*st* patient.

3.1 Data generation

In the simulation, patients were sequentially enrolled and assigned to receive one of two competing treatments, A or B. Three binary covariates were generated independently for each patient: Z_1 ~binomial(0.7), Z_2 ~binomial(0.5) and Z_3 ~binomial(0.7). These covariate distributions are based on both of our AML example and other examples. Patient responses (binary) were based on the following logistic regression model:

$$logit\{P(Y=1)\}=\beta_0+\beta_T T+\beta_1 Z_1+\beta_2 Z_2+\beta_3 Z_3,$$

where T is a binary treatment indicator. In scenario 1, we set $\beta_T = 0$, yielding no treatment effect on the response rate. This is a scenario of the null hypothesis. Then we contrasted our proposed design with other randomization designs when treatment B was the superior treatment with a higher response rate. We set $\beta_T = 1$ and $\beta_T = 2$, respectively, in scenario 2 and scenario 3.

3.2 Simulation results

We evaluated the performance of the proposed RACA randomization design, which adjusts for covariate imbalance, and compared it to the performance of ER, CA and RA randomization designs. In Table 1, we list the average number of patients (with standard deviation) assigned to each treatment arm, the chance of a treatment being selected as superior, the average number of patients who achieved treatment success, and the average degree of imbalance measured at the end of the trial.

In scenario 1, by choosing $p_u = 0.95$ and $p_l = 1 - p_u$, the empirical probability of choosing arm A (or arm B) in 5,000 simulations under simple equal randomization is 0.049 (0.048), which is around 0.05(0.05), and corresponds to a two-sided type I error rate of 0.10 in a frequentist design. Among the adaptive randomization designs we studied, we found the following ranges of two-sided type I error rates: the CA randomization design had the smallest (0.047+0.040=0.087); the RA randomization design had the largest (0.065+0.063=0.128); and the proposed RACA randomization design had a two-sided type I error rate close to 0.10 (0.045+0.047=0.092). Similar phenomena of the conservative type I error rates by the CA randomization design were reported in Table 10.2 and Table 10.3 of Crowley and Ankerst [23], when the Log-rank test was used under various scenarios of covariate distributions.

Because there was no effective treatment in scenario 1, on average, all designs assigned an equal number of patients to each treatment arm. However, the variations in the number of patients assigned to the two arms were quite different. For example, the standard deviation of the number of patients assigned to treatment A when using the RA randomization design

was almost two and a half times higher than that under equal randomization. In general, the RACA randomization design has a higher variability than the CA randomization design, but a lower variability than the RA randomization design. As expected, the proposed RACA and the CA randomization designs both exhibited a clearly superior ability to achieve covariate balance between treatment arms, with a degree of imbalance that was around 70 % smaller than that achieved by equal or RA randomization.

In scenario 2 and scenario 3, we evaluated the power under the four randomization designs when treatment B was the superior treatment. As noted above, when the same cut-off values p_u and p_l were used, the type I error rates of the CA (0.087) and RA (0.128) designs were substantially lower and higher respectively than that of ER (0.097). The proposed RACA design compromised between the CA and RA designs, and had a type I error rate (0.092) between theirs, which was much closer to the nominal level than either of them. For a fair comparison of power, we chose a different cut-off value for each of CA, RA and RACA designs to ensure that each design had a two-sided type I error rate sufficiently close to 0.10. Then, the probabilities of selecting treatment B can be interpreted as the levels of power at a significance level of 0.10.

In contrast to the ER and CA designs, the RA and RACA designs assigned more patients to the better treatment arm B. For example, in scenario 2, the RA and the RACA designs assigned, on average, 40 and 38 out of 60 patients to arm B respectively. Due to the unbalanced allocation probability in favor of the superior treatment arm, more patients achieved treatment success when the RA or RACA design was used, comparing with the ER and CA designs. In scenario 3, the total number of patients who achieved treatment success was 50 under the RA design, 49 under the RACA design, and 44 under either the ER or CA design.

The power was comparable between the ER and CA designs (respectively 0.49 vs 0.50 in scenario 2 and 0.90 vs 0.92 in scenario 3). The RA design suffered a power loss (0.42 and 0.83 respectively in scenarios 2 and 3). The RACA design gained some power back (0.50 and 0.89 respectively in scenarios 2 and 3). In addition, the proposed RACA design had a much smaller degree of imbalance than the RA randomization design in scenarios 2 and 3 (respectively 0.07 vs 0.26 and 0.13 vs 0.28).

The operating characteristics for the four randomization designs with a sample size of 100 are shown in Table 2. For the scenario of the null hypothesis (scenario 1), we studied the type I error rates by choosing $p_u = 0.975$ and $p_l = 0.025$, which correspond to a two-sided type I error rate of 0.05 in a frequentist design. Again, neither the CA nor the RA design had a correct test size: 0.041 (too low) for CA randomization and 0.065 (too high) for RA randomization. The proposed RACA design compromised well between these two designs and achieved a good balance with a two-sided type I error rate of 0.050. The degree of covariate imbalance when using the proposed RACA randomization design was similar to that when using the CA design (0.05 and 0.04, respectively). Both values were greatly reduced compared to those achieved when using the ER and RA randomization designs (0.23 and 0.22, respectively).

Before proceeding to do power analysis for these designs, we chose a different cut-off value for each of the CA and AR designs so that they all have a fixed significance level of 0.05. The simulation results were consistent with those obtained with a sample size of 60. The power of the proposed RACA design was higher than the RA randomization design (0.53 vs 0.47 in scenario 2 and 0.96 vs 0.92 in scenario 3), and was comparable to that by the ER and CA designs. Both the RA and the RACA designs assigned more patients to the superior treatment arm and achieved more treatment successes than the ER and CA designs. On

average, when respectively using the RACA and RA randomization designs, 79.2 and 81.9 patients were assigned to arm B out of a total of 100 patients, and a total of 82.9 and 83.8 successes were achieved. When using ER or the CA randomization design, on average, 50.1 patients were assigned to arm B, with a respective total of 73.8 and 72.8 successes achieved. About 10 more successes out of 100 patients were achieved by the RA or RACA designs than that by the ER or CA design.

In summary, considering the number of treatment successes achieved, the advantage of the response-adaptive randomization designs (RA and RACA) over the other two equal randomization designs (ER and CA) was clear. This demonstrates an important ethical advantage of the response-adaptive designs. The proposed RACA randomization design improved over the original RA randomization design by controlling covariate imbalance, maintaining the type I error to its nominal level, and achieving higher power.

4 Discussion

We have developed a response-adaptive randomization design with the added consideration of balancing the important covariates among the treatment arms. As with a standard AR randomization design, our proposed design incorporates information on patient response that accumulates during the trial, and can assign more patients to the superior treatment, thereby allowing more patients to achieve treatment success. Unlike a standard RA randomization design, our proposed design can control the covariate imbalance between the treatment arms. Consequently, the new design can help balance patient characteristics between different treatment arms, and thereby control the inflated type I error rates that occur in RA randomization as a result of unbalanced patient populations. For simplicity, we have described the proposed design in the context of two competing treatments with binary responses. However, the design can be easily generalized to cases with multiple treatments and/or other types of responses, such as survival time data.

For easy comparison of the operating characteristics of the proposed design with other designs, we conducted the simulations without any early stopping rules. This does not mean the proposed or any other designs should be used without early stopping rules in practice. Appropriate early stopping rules can be applied to our proposed design and other designs. See, for example, Pocock [24], O'Brien and Fleming and Jennison [25] and Turnbull [26] for a review. When there is sufficient evidence to show that one treatment is more effective than others, the trial can be stopped early to increase the study efficiency and support good trial ethics. Applying early stopping rules to an RA randomization design could result in smaller sample sizes as thus more severely imbalanced covariates, and in turn, more severely inflated type I error rates. Hence, in such a situation, the adjustment for covariate imbalance is even more important for the sake of maintaining nominal type I error rates, and our proposal is intended to be used in such a situation.

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Table 1

Operating characteristics with equal randomization and adaptive randomization; adaptive randomization starts at the 11th patient

Method	Arm	#{Arm} Ave(SD)	Pr(*selected*)	#{Success} Ave(SD)	Degree of imbalance
Scenario 1:(β_0, β_T, β_1, β_2, β_3) = (0, 0, 1.3, 0.6, 0.4); p_u = 0.95; p_l = 0.05					
ER					
	A	29.98(3.85)	0.049	34.78(3.81)	0.29
	B	30.02(3.85)	0.048		
CA					
	A	29.97(4.44)	0.047	34.77(3.81)	0.07
	B	30.03(4.44)	0.040		
RA					
	A	29.95(9.46)	0.065	34.84(3.85)	0.28
	B	30.05(9.46)	0.063		
RACA					
	A	30.12(7.41)	0.045	34.79(3.76)	0.08
	B	29.88(7.41)	0.047		
Scenario 2:(β_0, β_T, β_1, β_2, β_3) = (0, 1, 1.3, 0.6, 0.4);Type I error=0.10					
ER					
	A	29.87(3.80)	0.00	40.54(3.62)	0.29
	B	30.13 (3.80)	0.49		
CA					
	A	29.83(4.48)	0.00	40.52(3.68)	0.09
	B	30.17(4.48)	0.50		
RA					
	A	19.62(8.29)	0.00	42.56(3.78)	0.26
	B	40.37(8.29)	0.42		
RACA					
	A	21.70(7.20)	0.00	42.12(3.66)	0.07
	B	38.29(7.20)	0.50		
Scenario 3:(β_0, β_T, β_1, β_2, β_3) = (0, 2, 1.3, 0.6, 0.4); Type I error=0.10					

Method	Arm	#{Arm} Ave(SD)	Pr(*selected*)	#{Success} Ave(SD)	Degree of imbalance
ER					
	A	29.93(3.90)	0.00	44.16(3.50)	0.29
	B	30.07 (3.90)	0.90		
CA					
	A	29.97(4.40)	0.00	44.26(3.43)	0.08
	B	30.03(4.40)	0.92		
RA					
	A	13.22(6.00)	0.00	49.51(3.07)	0.28
	B	46.77(6.00)	0.83		
RACA					
	A	15.56(6.25)	0.00	48.80(3.10)	0.13
	B	44.44(6.25)	0.89		

Table 2

Operating characteristics with equal randomization and adaptive randomization; adaptive randomization starts at the 21st patient

Method	Arm	#{Arm} Ave(SD)	Pr(*selected*)	#{Success} Ave(SD)	Degree of imbalance
Scenario 1:(β_0, β_T, β_1, β_2, β_3) = (0, 0, 1.3, 0.6, 0.4); p_u = 0.975; p_l = 0.025					
ER					
	A	49.86(5.04)	0.025	57.88(4.83)	0.23
	B	50.14(5.04)	0.025		
CA					
	A	49.99(5.80)	0.020	57.90(4.87)	0.04
	B	50.01(5.80)	0.021		
RA					
	A	50.19(14.78)	0.030	58.00(4.99)	0.22
	B	49.81(14.78)	0.035		
RACA					
	A	50.07(11.25)	0.024	57.87(4.95)	0.05
	B	49.93(11.25)	0.026		
Scenario 2:(β_0, β_T, β_1, β_2, β_3) = (0, 1, 1.3, 0.6, 0.4);Type I error=0.05					
ER					
	A	49.90(5.03)	0.00	67.48(4.70)	0.22
	B	50.10 (5.03)	0.54		
CA					
	A	49.99(5.80)	0.00	67.41(4.68)	0.04
	B	50.01(5.80)	0.58		
RA					
	A	28.46(11.44)	0.00	71.66(4.89)	0.20
	B	71.54(11.44)	0.47		
RACA					
	A	32.38(10.41)	0.00	70.85(4.78)	0.06
	B	67.62(10.41)	0.53		
Scenario 3:(β_0, β_T, β_1, β_2, β_3) = (0, 2, 1.3, 0.6, 0.4); Type I error=0.05					

Method	Arm	#{Arm} Ave(SD)	Pr(*selected*)	#{Success} Ave(SD)	Degree of imbalance
ER					
	A	49.93(4.96)	0.00	73.78(4.30)	0.22
	B	50.07 (4.96)	0.97		
CA					
	A	49.94(5.84)	0.00	72.75(4.46)	0.04
	B	50.06(5.84)	0.97		
RA					
	A	18.06(6.87)	0.00	83.79(3.77)	0.17
	B	81.94(6.87)	0.92		
RACA					
	A	20.85(7.67)	0.00	82.91(3.92)	0.08
	B	79.15(7.67)	0.96		