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A Bayesian Response-adaptive Covariate-adjusted Randomization Design for Clinical Trials

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Abstract

Accordingly to FDA draft guidance (2010), adaptive randomization (e.g. response-adaptive (RA) randomization) has become popular in clinical research because of its flexibility and efficiency, which also have the advantage of assigning fewer patients to inferior treatment arms. However, these designs lack a mechanism to actively control the imbalance of prognostic factors, i.e. covariates that substantially affect the study outcome. Improving the balance of patient characteristics among the treatment arms could potentially increases the statistical power of the trial. We propose a randomization procedure that is response-adaptive and that also actively balances the covariates across treatment arms. We then incorporate this method into a sequential RA randomization design such that the resulting design skews the allocation probability to the better treatment arm, and also controls the imbalance of the prognostic factors across the arms. The proposed method extends the existing randomization where Ning and Huang (2010) approach requires polytomizing continuous covariates and Yuan (2011) approach uses fixed allocation probability to adjust covariates imbalance.

Keywords: Adaptive design; Clinical trials; Bayesian adaptive design

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. An allocation procedure, randomizing entering patients based on the accrued data so far, is referred to as adaptive. According to FDA draft guidance, 2010, adaptive randomization is a form of treatment allocation in which the probability of patient assignment to any particular treatment is adjusted based on repeated comparative analysis of the allocation and response data accrued so far. Naturally, the randomization schedule across the study can change frequently or continuously over the duration of the study. However, such randomization is adopted when the outcomes are immediate and are observed faster than the study enrolment [1,2].

Response-adaptive randomization

The response-adaptive (RA) randomization scheme has become popular in clinical research because of its flexibility and efficiency. 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.

Covariate-adaptive randomization

Response-adaptive randomization designs have the advantage of assigning fewer patients to inferior treatment arms. However, these designs lack a mechanism to actively control the imbalance of prognostic factors, i.e. covariates that substantially affect the study outcome, across treatment arms. 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. This may not be a serious issue under large samples since asymptotically the randomization automatically balances prognostic factors among treatment groups. However, for trials with small or moderate sample sizes, the imbalance of the prognostic factors can be substantial when using RA randomization designs, and thus causes difficulties to the inference after randomization. For example, in the presence of imbalanced prognostic factors, a direct comparison of marginal efficacy among the treatment arms is biased. Figure 1 illustrates that covariates can exhibit large differences between treatments as the sample size in the trial decreases.

Without considering response, various methods have been proposed to balance covariate distributions across treatment arms during randomization. For a small set of discrete covariates, stratified randomization is an effective method to achieve balance with respect to the covariates across treatment arms. This method, however, breaks down when there is a large number of covariates. Covariate-adaptive randomization (CA) designs have been developed to address this issue. In particular, Pocock and Simon [3] proposed a minimization design to balance prognostic factors in randomization. Wei [4] discussed the use of an urn model for CA randomization. Atkinson [5] proposed optimal biased-coin designs for clinical trials by employing the D-optimality criterion with a linear model. Signorini et al. [6] and Heritier et al. [7] proposed CA randomization procedures that balance interactions between factors when such interactions exist. Scott et al. [8] and McEntegart [9] provided comprehensive reviews on CA randomization.

Proposed covariate-adjusted randomization

We propose a randomization procedure that is response-adaptive and that also actively balances the covariates across treatment arms. Specifically, we develop a new covariate adaptive randomization

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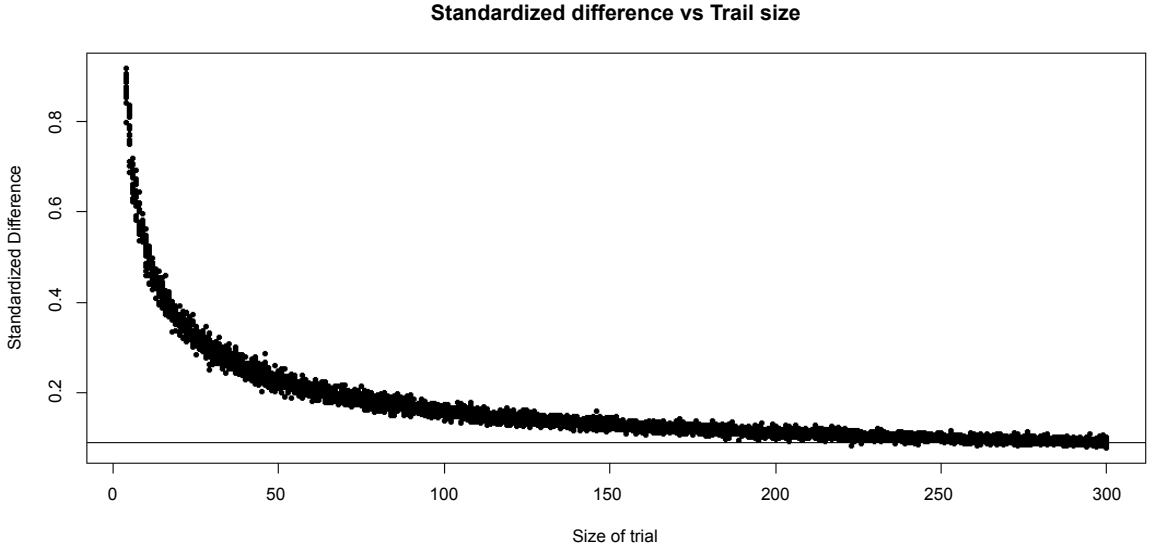

Figure 1: Standardized difference of a N(0,1) covariate between treatments by trial size, where standardized difference = |mean(treatment)-mean(control)|/(pooled standard deviation).

method which assign more patients to treat arm that minimize the probability of covariate imbalance. We then incorporate this method into a sequential RA randomization design such that the resulting design skews the allocation probability to the better treatment arm, and also controls the imbalance of the prognostic factors across the arms. The proposed method extends the existing randomization where Ning and Huang [1] approach requires polytomizing continuous covariates and Yuan et al. [2] approach uses fixed allocation probability to adjust covariates imbalance.

Method

Response-adaptive treatment allocation probability

Patients are enrolled in sequential groups of size $\{N_j\}$, $j = 1, \ldots, J$, where N_j is the sample size of the sequential group j. Typically, before conducting the trial, researchers have little prior information regarding the superiority of the treatment arms. Therefore, initially, for the first j' groups, e.g. $j' = 1$, patients are allocated to K treatment arms with an equal probability $1/K$. The response information observed from these patients then can be used to skew the allocation probability in subsequent groups. Let p_k be the response rate of treatment k, and assign p_k a prior distribution of beta(α_k, β_k), for k = 1, . . ., K. If, among n_k subjects treated in arm k, we observe y_k responses, then

$$Y_k \sim \text{binomial}\ (n_k, p_k) \tag{1}$$

And the posterior distribution of p_k is

$$p_k \mid \text{data} \sim \text{beta}(\alpha_k + x_k, \beta_k + n_k - x_k) \tag{2}$$

During the trial, we continuously update the posterior distribution of p_k, and allocate the next patient to the kth treatment arm according to the posterior probability that treatment k is superior to all others

$$P_{RA}(k) = \Pr(p_k = \max\{p_l, 1 \le l \le K\} \mid \text{data}) \tag{3}$$

A measure of covariate imbalance

The measure of the degree of covariate imbalance should able to: (1) Applicable for both categorical and continuous covariates. The current method [1] can only be used for categorical covariates. Continuous covariates need to be categorized, and it is not always clear how many categories and what cutoff values should be used. (2) Prioritize covariates that need to balance. Some prognostic factors are considered more important than others; it is desirable to assign larger weights to the more important factors when determining the overall imbalance during a randomization procedure. Yuan [2] proposed a prognostic score measure that can accommodate both requirements.

Let x denote a vector of covariate that can be continuous or categorical, y denote the binary outcome variable, and z denote the treatment arm indicator. They assume a standard logistic regression model

$$\text{logit}\left(\Pr\left(y = 1|x, z\right)\right) = \alpha + \mathbf{x}\beta' + \gamma z \tag{4}$$

Where α, β and γ are unknown parameters. And, the prognostic score is defined as

$$\omega(\mathbf{x}) = \mathbf{x}\beta' + \gamma z$$

The prognostic score automatically accommodates continuous and categorical prognostic factors, and assigns weights to prognostic factors according to their importance in predicting the response. Therefore, to balance out the effect of prognostic factors across treatment arms, we actually only need to balance the distribution of the prognostic score during the randomization.

During randomization, we assign an incoming patient to the treatment arm such that the imbalance of the prognostic score across the treatment arms is minimized. To achieve this objective, we use the Kolmogorov-Simirnov (KS) statistic as a measure of imbalance between two treatment arms. Let $\boldsymbol{w}_k$ denote the vector of prognostic scores for patients assigned to the kth treatment arm, and $S_{kk'}$ denote the KS statistic based on $\boldsymbol{w}_k$ and $\boldsymbol{w}_{k'}$ for $k \neq k'$. Then the overall imbalance among K treatment arms is measured by

$$S = \sum_{k=1}^{K-1} \sum_{k'=k+1}^{K} S_{kk'} \tag{5}$$

Covariate-adjusted treatment allocation probability

Let $S^{(k)}$ denote the value of S if the incoming new patient is assigned

to the *k*th treatment arm where smaller value of $S^{(k)}$ indicate less imbalance. Thus, the value of $S^{(k)}$ can be used to calculate the posterior probability that assigning this patient to treatment k minimized the overall covariate imbalance

$$P_{CA}(k) = \Pr(S^{(k)} = \min\{S^{(l)}, 1 \le l \le K\} \mid \text{data})$$

Without the prior information, the non-informative prior can be used to obtain the posterior distribution. In clinical practice, the covariates that needs to balance, are often known and pre-specified before the trial. And, the history data on the covariate effect are often available. Therefore, such prior information can be used to determine which prognostic factors need to be balanced and what's the effect size in the model (4) before conducting the randomization. Under the Bayesian framework, we elicit an informative prior of β based on historical data, and continuously update the posterior mean of β using the observed data during the ongoing trial.

Response-adaptive covariate-adjusted (RACA) treatment allocation probability

The idea of RACA randomization is to allow new incoming patients a better chance of being allocated to a superior treatment regimen based on cumulative information from previous patients, and adjust the allocation according to individual covariate information. Specifically, we assign a new patient to treatment k with probability $P_{RACA}(k)$,

$$P_{RACA}(k) = \frac{P_{RA}^{\tau 1}(k) P_{CA}^{\tau 2}(k)}{\sum_{l=1}^{K} P_{RA}^{\tau 1}(l) P_{CA}^{\tau 2}(l)} \quad (6)$$

where τ1 and τ2 are the tuning parameters. There are two purposes for using tuning parameters. Firstly, we use the tuning parameter τ1 and τ2 to control the AR rate; if τ1 = τ2 = 0, then $P_{RACA}(k) = 1/K$, leading to ER. A larger value of tuning parameters would lead to a higher imbalance in allocation of patients between the arms and vice versa. Secondly, we can set different values of τ1 and τ2 to control the preference of RA and CA. If τ1 < τ2, we assign more weight to CA than RA, and vice versa. Furthermore, RACA randomization equivalent to RA if τ2 = 0, and CA if τ1 = 0.

If both the covariate imbalance and ethical criteria favor the assignment of a patient to the same treatment, then the new patient will be assigned to that treatment with a higher probability compared with the probability when using the simple RA or CA randomization schemes. Otherwise, the randomization procedure will result in an assignment probability between P_{RA} and P_{CA}.

Early stopping and decision rules

- Futility: if Pr ($p_k < p.min \mid$ data) > θ_u, where *p*.min denotes the clinical minimum response rate, that is, there is strong evidence that treatment *k* is inferior to the clinical minimum response rate, we drop treatment arm *k*.
- Superiority: if Pr ($p_k > p.target \mid$ data) > θ_l, where *p*.target denotes the target response rate, that is, there is strong evidence that treatment *k* is superior to prespecified response rate, we terminate the trial early and claim the treatment *k is promise*.
- At the end of the trial, if Pr ($p_k > p.min \mid$ data) > θ_t, then treatment k 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 θ_u, θ_l, and θ_t.

Simulation Study

We conducted simulations to evaluate the performance, under various clinical scenarios, of the proposed RACA design (two setting: RACA2 with τ1 = τ2 = 1, RACA3 with τ1 = 1 and τ2 = 2) to compare it with the following designs: simple equal randomization (ER), CA randomization, RA randomization, and RACA design with Yuan's method (RACA1). The patient assignment probabilities under the CA design is determined by (7) without consideration on previous patient's responses. That under the RA design is specified by (3) without considering covariate distributions. We used sample sizes of 90 for each scenario. We assigned the first 15 patients equally to three treatments (A, B, or C) and started using the adaptive randomization at the 16th patient.

We generated data from the following model,

$$\text{logit}(\Pr(y = 1 \mid x, z)) = \alpha + \boldsymbol{\beta}\_1\ \text{gender} + \boldsymbol{\beta}\_2\ \text{age} + \boldsymbol{\beta}\_3\ \text{bmi} + \boldsymbol{\beta}\_4\ \text{race} + \boldsymbol{\beta}\_5\ \text{trt1} + \boldsymbol{\beta}\_6\ \text{trt2}$$

where trt1 and trt2 is treatment indicator variable with trt1 = 1 for treatment B, trt2 = 1 for treatment C, and trt1 = trt2 = 0 for treatment A. We generated the continuous variable of age from uniform distribution with min = 25, max = 80, and BMI from N (35, sd = 10). Two binary indicator variable, gender and race, are generated from Bernoulli distributions with success probabilities of 0.6 and 0.3. The values of α, β_1, β_2, β_3, β_4 are set to be -0.28, 2.1, -0.144, 0.08, and -1.5, respectively. In scenario 1, by setting $\beta_5 = \beta_6 = 0$, we obtain no differential treatment with clinical minimal response rate ($P_1 = P_2 = P_3 = 0.1$). Then we contrasted our proposed design with other randomization designs when treatment B and C was the superior treatment with a higher response rate. We set β5 = 1.378 and β_6 = 2.428 in scenario 2, corresponding to $P_1 = 0.1$, $P_2 = 0.2$ and $P_3 = 0.3$. The minimum clinical response rate (*p.min*) is 0.1 and the target response rate (*p.target*) is 0.25. At the end of the study, the null hypothesis of equal treatment efficacy is rejected if Pr ($p_k > p.min \mid$ data) > *0.9* A total of 1,000 independent simulations were performed for each setting and randomization method. Note that when stopping rules are applied, the actually used sample size varies under different designs, which makes the comparison between designs difficult. To facilitate the comparison, we carried out simulations both with and without early stopping.

Table 1 shows the simulation results without early stopping based on the fixed sample size of 90. For each design, we list the average number of patients (with standard deviation) assigned to each treatment arm, the chance of a treatment being selected as promising, the average number of patients who achieved treatment success, the average degree of imbalance in terms of prognostic score, and the percentage of significant imbalance (the p-value of KS statistics less than 0.05) (Table 1).

In scenario 1 (response rate equal to p.min), all designs assigned an equal number of patients to each treatment arm. However, the variations in the number of patients assigned were quite different where EQ design has the smallest variation among all designs, variation of CA design is very close to EQ design, RA design has the largest variation, and the magnitude of three RACA design's variation is between CA and RA design. Without control the covariate among treatment, there are 12.8% chance that the covariate between treatments will be significantly different at the end of trial for EQ design, and 12.7% for RA design. All three RACA design can achieve low percentage of significant covariate imbalance where the proposed method perform better than Yuan's method and we can obtain even smaller percentage of significant covariate imbalance via adjusting the values of τ1, τ2.

Method	Arm	Response rate	# of patient assigned (SD)	Pr(selected)	#of positive response	degree of imbalance	Percentage of significantly imbalanced covariate
Scenario1: p1=p2=p3=0.1							
EQ (τ1=τ2=0)	A	0.1	30.21 (4.17)	0.077	8.91	0.26	0.128
	B	0.1	29.97 (4.04)	0.077			
	C	0.1	29.83 (4.21)	0.075			
RA (τ1=1,τ2=0)	A	0.1	29.17 (17.51)	0.053	8.92	0.25	0.127
	B	0.1	30.70 (18.01)	0.054			
	C	0.1	30.13 (17.97)	0.061			
CA (τ1=0,τ2=1)	A	0.1	30.11 (4.63)	0.061	8.93	0.15	0.002
	B	0.1	30.12 (4.44)	0.061			
	C	0.1	29.77 (4.45)	0.062			
RACA1	A	0.1	30.70 (14.61)	0.068	8.95	0.19	0.023
	B	0.1	29.36 (14.08)	0.062			
	C	0.1	29.94 (14.24)	0.067			
RACA2 (τ1=τ2=1)	A	0.1	29.70 (11.71)	0.056	9.15	0.17	0.002
	B	0.1	30.35 (11.45)	0.061			
	C	0.1	29.95 (11.88)	0.06			
RACA3 (τ1=1,τ2=2)	A	0.1	30.54 (9.05)	0.053	9.1	0.16	0.002
	B	0.1	29.38 (8.82)	0.053			
	C	0.1	30.08 (9.08)	0.058			
Scenario 2: p1=0.1,p2=0.2,p3=0.3							
EQ (τ1=τ2=0)	A	0.1	30.11 (4.15)	0.058	17.54	0.25	0.124
	B	0.2	30.00 (4.04)	0.587			
	C	0.3	29.89 (4.23)	0.969			
RA (τ1=1,τ2=0)	A	0.1	15.75 (7.84)	0.048	21.28	0.23	0.114
	B	0.2	26.55 (15.98)	0.422			
	C	0.3	47.69 (17.18)	0.856			
CA (τ1=0,τ2=1)	A	0.1	29.84 (4.37)	0.061	17.96	0.14	0
	B	0.2	30.35 (4.47)	0.59			
	C	0.3	29.81 (4.57)	0.949			
RACA1	A	0.1	16.90 (6.88)	0.04	21.08	0.18	0.02
	B	0.2	26.26 (11.86)	0.486			
	C	0.3	46.84 (13.17)	0.942			
RACA2 (τ1=τ2=1)	A	0.1	18.11 (5.68)	0.047	20.87	0.16	0
	B	0.2	27.45 (9.01)	0.499			
	C	0.3	44.44 (10.28)	0.958			
RACA3 (τ1=1,τ2=2)	A	0.1	20.61 (5.82)	0.049	20.66	0.15	0
	B	0.2	27.54 (8.19)	0.53			
	C	0.3	41.85 (9.48)	0.964			

Table 1: Simulation results without early stopping.

In scenario II, the response rates are different across treatment $P_1 = 0.1$, $P_2 = 0.2$ and $P_3 = 0.3$. In contrast to the ER and CA designs, the RA and all three RACA design assigned less patients to the inferior treatment A. Comparing the patients' positive response, EQ and CA designs achieved smallest number of positive response, and RA designs got highest number. The number of positive response was slightly reduced by adding CA to RA design. However, all three RACA designs got the degree of covariates imbalance reduced and achieved higher statistical power than RA design. For example, for treatment C, the power of RA design was 0.856, while that of the RACA2 design was 0.958. And, the proposed method obtained smaller degree of covariate imbalance than Yuan's method while preserved larger statistical power. It is worth to note that changing τ2 from 1 to 2 achieved less degree of covariate imbalance while assigning more patients to inferior treatment. The choice of τ1 and τ2 depends on the trial setting and the consideration of ethical and statistical issues.

Table 2 shows simulation results with early stopping ($\theta_u = \theta_l = 0.9$). In the presence of early stopping, the actual sample sizes used in trials vary under different designs. Therefore, in addition to the summary statistics that are similar to those listed in Table 2, we also reported the average sample size across 1000 simulated trials. The simulation results are similar to those achieved without stopping rules. Compared with the RA design, the proposed RACA design has a substantially lower percentage of significantly imbalanced covariates and higher statistical power. For example, in scenario II, the power under the RA design were 0.439 for treatment B and 0.818 for treatment C, while that under the RACA (τ1 = τ2 = 1) design was 0.525 and 0.878 respectively. Moreover, compared with the CA designs, the RACA design allocated fewer patients to the inferior treatment. For example, in scenario II, the number of patients assigned to the inferior treatment was 20.28 under the CA designs, while that under the proposed RACA (τ1 = τ2 = 1) design was only 17.94 (Table 2).

Discussion

We have developed a Bayesian RACA randomization design for

Method	Arm	Response rate	Sample size	# of patient assigned (SD)	Pr(selected)	degree of imbalance	Percentage of significantly imbalanced covariate
Scenario 1: p1=p2=p3=0.1							
EQ (τ1=τ2=0)	A	0.1	60.12	19.85 (13.69)	0.056	0.35	0.11
	B	0.1		20.11 (13.71)	0.061		
	C	0.1		20.15 (13.69)	0.057		
RA (τ1=1,τ2=0)	A	0.1	58.06	19.30 (14.18)	0.061	0.33	0.097
	B	0.1		19.67 (14.19)	0.063		
	C	0.1		19.09 (13.98)	0.06		
CA (τ1=0,τ2=1)	A	0.1	61.01	20.89 (13.69)	0.06	0.29	0.018
	B	0.1		20.11 (13.58)	0.061		
	C	0.1		20.59 (13.65)	0.063		
RACA1	A	0.1	57.01	18.45 (14.13)	0.064	0.34	0.079
	B	0.1		19.38 (14.03)	0.068		
	C	0.1		19.16 (14.17)	0.062		
RACA2 (τ1=τ2=1)	A	0.1	57.39	19.00 (13.95)	0.051	0.32	0.038
	B	0.1		19.18 (14.01)	0.052		
	C	0.1		19.21 (14.07)	0.056		
RACA3 (τ1=1,τ2=2)	A	0.1	60.13	20.62 (14.06)	0.052	0.3	0.032
	B	0.1		19.90 (14.03)	0.057		
	C	0.1		19.60 (14.06)	0.048		
Scenario 2: p1=0.1,p2=0.2,p3=0.3							
EQ (τ1=τ2=0)	A	0.1	68.48	19.89 (13.33)	0.056	0.32	0.154
	B	0.2		25.44 (12.69)	0.538		
	C	0.3		23.16 (12.10)	0.881		
RA (τ1=1,τ2=0)	A	0.1	63.71	17.16 (14.03)	0.056	0.32	0.153
	B	0.2		23.33 (13.93)	0.439		
	C	0.3		23.22 (11.97)	0.818		
CA (τ1=0,τ2=1)	A	0.1	70.51	20.28 (13.33)	0.057	0.25	0.018
	B	0.2		26.41 (12.13)	0.521		
	C	0.3		23.81 (11.93)	0.913		
RACA1	A	0.1	65.97	17.98 (14.12)	0.044	0.3	0.071
	B	0.2		24.56 (13.30)	0.511		
	C	0.3		23.43 (12.02)	0.855		
RACA2 (τ1=τ2=1)	A	0.1	67.67	17.94 (14.11)	0.048	0.27	0.041
	B	0.2		24.92 (13.24)	0.525		
	C	0.3		24.81 (11.66)	0.878		
RACA3 (τ1=1,τ2=2)	A	0.1	68.49	18.89 (14.13)	0.052	0.26	0.038
	B	0.2		25.10 (13.03)	0.533		
	C	0.3		24.50 (11.78)	0.886		

Table 2: Simulation results with early stopping.

multiple-arm clinical trials. We first use a prognostic score method [2] to measure the covariate imbalance among treatment arms, then next patients' allocation probability is based on the posterior probability that assigning this patient to which treatment that minimize the covariate imbalance. We then incorporated this CA design into a RA design. The resulting design combines the advantages of CA and RA randomizations. It allocates more patients to efficacious arms, while also balancing the covariates across the treatment arms during the randomization process, as demonstrated in the simulation studies. 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.

Conclusion

In summary, the simulation results show that the proposed RACA design successfully combined the advantages of the RA and the CA designs. Like the RA design, RACA design effectively skewed the allocation probability toward the superior arm. It allocated substantially fewer patients to the inferior treatment arm compared with the EQ and CA designs. On the other hand, in terms of balancing the covariates, the performance of RACA design was comparable to the CA designs. A better balance of covariates under the RACA design often translated into lower type I error rate (when the efficacy of treatments are the same) or a higher statistical power (when the efficacy of treatments are different). Moreover, the proposed RACA design performs better than Yuan's method in term of covariate balancing without loss of statistical power. And, both designs assigned fewer patients to inferior treatment at the same level. Furthermore, the proposed RACA design is more flexible than Yuan's method. In clinical practice, with the proposed RACA design, the user can fully skew the patient allocation probability between "pure" response-adaptive and "pure" covariate-adaptive based on the trial prospective.

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