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Notice: Accepted version subject to English editing.
Sequential Monitoring of Covariate-Adaptive Randomized Clinical Trials

Abstract: The sequential monitoring of covariate-adaptive randomized clinical trials is standard in modern clinical studies. However, the validity of this sequential procedure is not well studied in the literature. Clinical trialists therefore implement the procedure and perform data analysis based on the theory of the sequential monitoring of fixed designs, and many clinical trials are open to question. In this paper, we study the theoretical properties of the sequential procedure and propose some important adjustments to classical statistical inference. Under different scenarios, we derive the asymptotic joint distribution of the sequential test statistics. Further, we estimate the decreased variability of the estimated treatment effect due to covariate-adaptive randomization, so that the sequential test statistics can be adjusted to be an asymptotic Brownian motion and the type I error rate can be controlled in real trials. Numerical results from simulation and the redesign of a clinical trial support our theoretical findings, showing that our procedure can control the type I error rate well, and also demonstrating the advantages of our method in terms of power and early stopping. Both theoretical and numerical results provide important guidance for future practical clinical trials using covariate-adaptive randomization procedures.

Key words and phrases: Brownian motion, linear regression, personalized medicine, stratified permuted block randomization, Pocock–Simon’s randomization, type I error rate.
1. Introduction

Clinical trials are usually complex, involving multiple covariates of interest in addition to the treatment effects. In particular, with the development of bioinformatics, the association between biomarkers and disease has become widely accepted. In the era of personalized medicine, it is desirable to incorporate covariates into clinical trial designs that investigate the heterogeneity of patients' responses to a treatment (Hu, 2012; Hu et al., 2015). The study results may be invalid if there is treatment imbalance over the covariates. Covariate-adaptive randomization (CAR) procedures, which sequentially assign the next patient based on previous assignments and covariates, and the current covariate profile, have been developed to mitigate such imbalances and are extensively used in clinical trials. Stratified permuted block (SPB) randomization and Pocock and Simon's design (1975) are the most popular CAR procedures. Other CAR designs have been developed by Taves (1974), Wei (1978), Nordle and Brantmark (1977), Signorini et al. (1993), Heritier et al. (2005), and Hu and Hu (2012). Clinical trials that use these designs include Iacono et al. (2006), Jakob et al. (2012), Anderson et al. (2000), Gridelli et al. (2003), Krueger et al. (2007), Molander et al. (2007), and Ohtori et al. (2012). A detailed discussion of CAR procedures can be found in Rosenberger and Sverdlov (2008). The theoretical
properties of hypothesis testing based on CAR procedures have recently been developed by Shao et al. (2010) and Ma et al. (2015). However, both papers focused on the final test statistic instead of the sequential statistics (a stochastic process).

While CAR procedures are very popular in clinical trials, interim analysis is also common because of its ethical, administrative, and economic advantages (Jennison and Turnbull, 2000). Sequential monitoring arose from the sequential probability ratio test proposed by Wald (1947) for quality control, and its use in medical research was pioneered by Armitage (1975). Influential papers on sequential monitoring in clinical trial designs include Pocock (1977), O’Brien and Fleming (1979), and Lan and DeMets (1983). Further, Jennison and Turnbull (1997) discussed a series of group sequential analysis methods incorporating covariate information through linear models, general parametric regression models and survival models. However, they did not take into account the problems caused by covariate adaptive designs and the scenario where not all the design covariates were used in the analysis. Tsiatis et al. (1985) and Gu and Ying (1995) derived the joint distribution of sequential parameter estimators from proportional hazards models. More details of sequential monitoring can be found in Jennison and Turnbull (2000). Note that these studies considered the scenarios where
non-adaptive designs are implemented in clinical trials.

Despite the widespread popularity of the combination of CAR procedures with sequential monitoring in real trials and the advantages mentioned above, there have been few theoretical investigations of the sequential procedure. The CAR procedure has two limitations: the complicated correlation structure of the within-stratum imbalances and the discreteness of the allocation function. Furthermore, a special situation often arises in real clinical trials: only some of the covariates used in the randomization procedures are included in the data analysis. For example, Lai et al. (2006) investigated the influences of music on maternal anxiety in kangaroos in a randomized controlled trial. Under similar conditions, female infants are believed to have a significantly greater chance of surviving than male infants, hence permuted block randomization stratified on gender was used to allocate the patients. In the data analysis, a t-test was used to analyze the maternal-anxiety outcomes. The reasons for not using all the covariates include, but are not limited to, (i) it is not easy to explain the practical significance of including certain covariates such as investigation sites in the model; (ii) using too many covariates will lead to theoretical difficulties; (iii) the correct model specification is usually unknown. Consequently, theoretical investigation into the sequential monitoring of CAR procedures has
been hindered for decades. More importantly, the clinical trials that employ this procedure lack complete theoretical support, and many of these trials may be open to question.

In this paper, we study clinical trials with the CAR design for randomization and linear regression models for analysis. We obtain the joint distribution of the sequential statistics for the following three scenarios: (1) all the covariates used in the CAR are included in the data analysis; (2) some of the covariates are included; and (3) no covariates are included, which is Student’s t-test. We find that for scenario (1) the joint distribution of the commonly used sequential statistics discussed in Section 2 is asymptotically Brownian motion, which is the asymptotic joint distribution for complete randomization and fixed designs. As mentioned before, clinical trial practitioners often perform data analysis following the sequential monitoring of CAR procedures, assuming that the data are from the sequential monitoring of complete randomization. This finding, for the first time to our knowledge, theoretically justifies and validates all such clinical trials for this scenario.

We also derive the joint distribution of the sequential statistics for scenarios (2) and (3), and we can see its difference from standard Brownian motion. As a result, trials that ignore the difference between CAR proce-
dures and complete randomization could give misleading conclusions. The above theoretical results provide guidance for practical clinical trials, and they are one of the major contributions of this paper. In addition, the asymptotic variances of the sequential statistics for scenarios (2) and (3) indicate that the CAR design shrinks the variability of the estimated treatment effect. We propose an approach to estimate the decreased variance and adjust the sequential statistics, so that the critical values for Brownian motion can still be used, which offers clinical trialists practical steps to deal with these complex situations.

Finally, we perform extensive numerical studies for the above three scenarios in terms of the type I error, power, and early stopping. We also redesign a double-blind randomized two-arm clinical trial conducted by Tilley et al. (1995) to study the properties of the proposed methods. The numerical results support our theoretical findings and demonstrate the advantages of our methods.

In Section 2, we introduce the notation, describe the framework, and formulate the main theorems. In Section 3, we use generated data to numerically study the sequential monitoring of CAR procedures. Numerical results from the redesign of a clinical trial are discussed in Section 4. Conclusion remarks are in Section 5, and the proofs are given in the online
supplementary material.

2. Sequential Monitoring of Covariate Adaptive Randomized Clinical Trials

2.1 Framework

We consider a two-arm randomized sequential experiment, in which \( n \) subjects are randomly assigned to one of the treatments by CAR procedures. Let \( T_i \ (i = 1, \ldots, n) \) index the treatment (1 if treatment 1; 0 if treatment 2). To incorporate the scenario where some randomization covariates are omitted from the data analysis, we introduce two sets of covariates, \((X_1, \ldots, X_p)\) and \((Z_1, \ldots, Z_q)\). For simplicity, we use one-dimensional covariates to describe our framework and theorems. It is easy to generalize the results in this paper to multiple dimensional covariates.

Let \( W_i = (W_i^X, W_i^Z) \) be the covariate vector of the \( i \)th subject, where \( W_i^X = (X_{i1}, \ldots, X_{ip}) \) and \( W_i^Z = (Z_{i1}, \ldots, Z_{iq}) \). In the paper, \((X_1, \ldots, X_p)\) represent the covariates used for both randomization and analysis, and \((Z_1, \ldots, Z_q)\) represent those covariates that are used for randomization, but are not included for analysis. Assume the \( i \)th subject’s response \( Y_i \) follows the following linear model:

\[
Y_i = \mu_1 T_i + \mu_2 (1 - T_i) + X_{i1} \beta_1 + \ldots + X_{ip} \beta_p + Z_{i1} \gamma_1 + \ldots + Z_{iq} \gamma_q + \epsilon_i, \tag{2.1}
\]

where \( \mu_1 \) and \( \mu_2 \) are treatment effects for treatments 1 and 2, \((\beta_1, \ldots, \beta_p)\)
and \((\gamma_1, \ldots, \gamma_q)\) are unknown parameters, and the \(\epsilon_i\) are independent errors with mean 0 and variance \(\sigma^2\). We assume that all the covariates are independent, and without loss of generality, their expectations are all 0, i.e., \(E(X_{ik}) = 0, E(Z_{ij}) = 0, i = 1, \ldots, n, k = 1, \ldots, p, j = 1, \ldots, q\).

We also assume that the errors are independent with the covariates. We write \(\mu = (\mu_1, \mu_2)^T, \eta = (\mu_1, \mu_2, \beta_1, \ldots, \beta_p)^T, \gamma = (\gamma_1, \ldots, \gamma_q)^T, T(n) = (T_1, \ldots, T_n)^T, Y(n) = (Y_1, \ldots, Y_n)^T, \epsilon(n) = (\epsilon_1, \ldots, \epsilon_n)^T\) and

\[
X(n) = \begin{bmatrix}
T_1 & 1 - T_1 & X_{11} & \ldots & X_{1p} \\
T_2 & 1 - T_2 & X_{21} & \ldots & X_{2p} \\
\vdots & \vdots & \vdots & \ddots & \vdots \\
T_n & 1 - T_n & X_{n1} & \ldots & X_{np}
\end{bmatrix}.
\]

In this project, when studying CAR, we discretize all the continuous covariates, and apply CAR designs with respect to these discrete covariate variables. Specifically, let

\[
\tilde{X}_j = \begin{cases} 
X_j & \text{if } j \notin C \\
d_j(X_j) & \text{if } j \in C
\end{cases}
\]

and

\[
\tilde{Z}_j = \begin{cases} 
Z_j & \text{if } j \notin C^* \\
d_j^*(Z_j) & \text{if } j \in C^*
\end{cases},
\]

where \(C = \{l : \text{index of continuous covariates among } X_l, l = 1, \ldots, p\}\), \(C^* = \{l : \text{index of continuous covariates among } Z_l, l = 1, \ldots, q\}\), and \(d_j(\cdot)\)
and $d^*_j(\cdot)$ are discrete functions. Write $\tilde{W}_i^X = (\tilde{X}_{i1}, \ldots, \tilde{X}_{ip})$ and $\tilde{W}_i^Z = (\tilde{Z}_{i1}, \ldots, \tilde{Z}_{iq})$.

We also need the following notation to formulate the main theorem. Suppose $\tilde{X}_k$ has $s_k$ levels and $\tilde{Z}_j$ has $s^*_j$ levels, and let $W_i = (x^c_{i1}, \ldots, x^c_{ip}, z^c_{i1}, \ldots, z^c_{iq})$ represents the $i$th subject’s covariate profile if $\tilde{X}_{ik}$ is at level $x^c_{ik}$ and $\tilde{Z}_{ij}$ is at level $z^c_{ij}$. Let $\text{DIF}_n$ be the overall difference in patient numbers between two treatments at the end of the trial. Let $\text{DIF}_n^X(k; c_k)$ be the marginal difference with respect to the level $x^c_{ik}$ of covariate $\tilde{X}_k$, and $\text{DIF}_n^Z(j; c^*_j)$ be the marginal difference with respect to the level $z^c_{ij}$ of covariate $\tilde{Z}_j$. Let $\text{DIF}_n(c_1, \ldots, c_p, c^*_1, \ldots, c^*_q)$ be the difference in patient numbers in the stratum containing the subjects with covariates $(x^c_{i1}, \ldots, x^c_{ip}, z^c_{i1}, \ldots, x^c_{iq})$.

Let $\lfloor nt \rfloor$ denote the largest integer not greater than $nt$ for $t \in [0, 1]$. We introduce $t$, the “information time”, to formulate this problem using the Skorokhod topology. Let $\mathcal{T}(\lfloor nt \rfloor) = \sigma(T_1, \ldots, T_{\lfloor nt \rfloor})$ be the sigma-algebra generated by the first $\lfloor nt \rfloor$ treatment assignments, and $\mathcal{X}(\lfloor nt \rfloor) = \sigma(\tilde{W}_1^X, \ldots, \tilde{W}_{\lfloor nt \rfloor}^X)$ and $\mathcal{Z}(\lfloor nt \rfloor) = \sigma(\tilde{W}_1^Z, \ldots, \tilde{W}_{\lfloor nt \rfloor}^Z)$ be the sigma-algebras generated by the first $\lfloor nt \rfloor$ covariate vectors $\tilde{X}$ and $\tilde{Z}$. Then, after $N = \lfloor nt \rfloor$ patients have been assigned, the adaptive randomization selects the next treatment assignment based on $\mathcal{F}(N) = \mathcal{T}(N) \otimes \mathcal{X}(N + 1) \otimes \mathcal{Z}(N + 1)$.

To compare the two treatment effects, we consider the following hy-
A natural statistic including only $X$ to test the above hypothesis at time point $t \in (0, 1]$ is

$$Z_t = \frac{L \hat{\eta}(t)}{\sqrt{\hat{\sigma}(t)^2 L (X([nt])^T X([nt]))^{-1} L^T}},$$

where $L = (1, -1, 0, \ldots, 0)$, $\hat{\eta}(t) = (X([nt])^T X([nt]))^{-1} X([nt])^T Y([nt])$, $\hat{\sigma}(t)^2 = [Y([nt]) - X([nt]) \hat{\eta}(t)]^T [Y([nt]) - X([nt]) \hat{\eta}(t)] / ([nt] - p - 2)$.

The sequential statistics (2.3) are just the commonly used statistics.

### 2.2 Asymptotic Results

Controlling the type I error rate is the primary challenge when sequentially monitoring a clinical trial. The key to this question is the asymptotic joint distribution of the sequential statistics and the subsequent choices of critical values. In the literature, numerous techniques have been proposed for sequentially monitoring a Brownian motion that follows complete randomization. However, CAR procedures lead to considerable difficulties in deriving the joint distributions of the sequential test statistics. Following CAR procedures, the sequential treatment assignments are not independent of the covariate profiles, the observed responses are not independent of previous treatment assignments and covariates, and the observed responses are
not independent of each other. This could be the main reason for the lack of literature on this topic.

Let

\[ Z_{t}^{adj} = \frac{L\hat{\eta}(t)}{\hat{\epsilon}(t) \sqrt{\hat{\sigma}(t)^2 L(\hat{\mathbf{X}}(\lfloor nt \rfloor)^T \hat{\mathbf{X}}(\lfloor nt \rfloor))^{-1} L^T}}, \]

(2.4)

where \( \hat{\epsilon}(t)^2 \) is any consistent estimator of

\[ \frac{\sum_{j \in C^*} \gamma_j^2 \sigma_{\delta_j}^2 + \sigma^2}{\sigma^2 + \sum_{j=1}^{p} \text{Var}(Z_j \gamma_j^T)} \]

(2.5)

in (S1.9) in the online supplementary material, \( \sigma_{\delta_j}^2 = E \left[ \text{Var} \left( \delta_j | d_j^*(Z_j) \right) \right] \), and \( \delta_j = Z_j - E(Z_j | d_j^*(Z_j)) \). We will discuss \( \hat{\epsilon} \) in detail later.

The following theorem offers vital theoretical support for the sequential monitoring of CAR procedures, and its implications for the practical procedure will be discussed in Section 2.4.

**Theorem 1.** Let \( B_{t}^{adj} = \sqrt{t} Z_{t}^{adj} \) in the space \( D[0,1] \) with the Skorohod topology. Suppose a covariate adaptive design satisfies \( DIF_n = O_p(1) \), \( DIF_n^X(k; c_k) = O_p(1), k = 1, \ldots, p \), and \( DIF_n^Z(j; c_j^*) = O_p(1), j = 1, \ldots, q \).

Then under \( H_0 \), \( B_{t}^{adj} \) is asymptotically a standard Brownian motion in distribution. Therefore, the sequence of test statistics \( \{Z_{t_1}^{adj}, \ldots, Z_{t_K}^{adj}, 0 \leq t_1 \leq t_2 \leq ... \leq t_K \leq 1 \} \) has the asymptotic canonical joint distribution defined by Jennison and Turnbull (2000), i.e.,

(i) \( \{Z_{t_1}^{adj}, \ldots, Z_{t_K}^{adj}\} \) is multivariate normal;
(ii) \( EZ_{t_i}^{adj} = 0 \);

(iii) \( Cov(Z_{t_i}^{adj}, Z_{t_j}^{adj}) = \sqrt{t_i/t_j}, \ 0 \leq t_i \leq t_j \leq 1. \)

Under \( H_1 \),

\[
\mathcal{B}_t^{adj} = \frac{\sqrt{n}(\mu_1 - \mu_2)t}{2 \sqrt{\sum_{j \in C^*} \gamma_j^2 \sigma_j^2 + \sigma^2}}
\]

converges to a standard Brownian motion.

This theorem reveals the effect of CAR procedures on the joint distribution of the sequential statistics, which is asymptotically the same as that of complete randomization after adjustment. In practice, clinical trialists implement this procedure assuming that it is exactly the same as complete randomization. From this theorem, we can easily see the gap and even calculate the difference given the parameter values. To the best of our knowledge, this paper provides the theoretical foundation for this procedure for the first time. Some other remarks are as follows.

**Remark 1.** (1) The conditions on the overall and marginal differences in patient numbers between two treatments in the theorem hold for a variety of CAR procedures such as the stratified permuted block randomization.

(2) Note that the asymptotic variance \((2.5)\) of \( Z_t \) is always less than 1; it represents that the variability of the estimated treatment effect has been reduced by the CAR designs.
(3) Because of the reduced variability of the estimated treatment effect, using the traditional estimator of this variance in the statistics will lead to a conservative type I error rate. In addition, without adjustment, the power will also be adversely affected, which effectively increases the sample size needed and is not consistent with the original aim of sequential monitoring.

2.3 Data analysis with full dataset and Student’s t-test statistic.

Here, we discuss two special cases of the above scenario, i.e., data analysis with all the covariates used in the randomization, and Student’s t-test without any covariates. First, assume that the \( i \)th subject’s response \( Y_i \) follows the following linear model:

\[
Y_i = \mu_1 T_i + \mu_2 (1 - T_i) + X_i \beta_1 + \ldots + X_i \beta_p + \epsilon_i, \quad (2.6)
\]

where the notation is the same as in model (2.1). We implement the CAR and perform data analysis with all the covariates in model (2.6). To compare the two treatment effects and to perform hypothesis test (2.2), we use the test statistic (2.3) at time point \( t \). Then we have the following theorem.

**Theorem 2.** Let \( B_t = \sqrt{t}Z_t \) in the space \( D[0,1] \) with the Skorohod topology. Suppose a covariate adaptive design satisfies \( DIF_n = O_p(1) \) and 
\[
DIF_n^X(k; c_k) = O_p(1), k = 1, \ldots, p.
\]

Then under \( H_0 \), \( B_t \) is asymptotically a standard Brownian motion in distribution. Therefore, the sequence of
test statistics \( \{Z_{t_1}, ..., Z_{t_K}, 0 \leq t_1 \leq t_2 \leq ... \leq t_K \leq 1\} \) has the asymptotic canonical joint distribution defined by Jennison and Turnbull (2000). Under \( H_1 \), \( B_i^{adj} - (\sqrt{n}(\mu_1 - \mu_2)t) / (2\sigma) \) converges to a standard Brownian motion.

A major difference between the first two theorems is that we do not have to adjust the sequential statistic (2.3) in this case, because its asymptotic properties are exactly the same as those of complete randomization.

Another special case occurs when the CAR is used to sequentially allocate patients, and the data is analyzed with Student’s t-test, or equivalently using the following model:

\[
Y_i = \mu_1 T_i + \mu_2 (1 - T_i) + \epsilon_i, \ i = 1, \ldots, n.
\] (2.7)

To make the notation consistent with that of the previous sections, we assume that the responses follow the following model:

\[
Y_i = \mu_1 T_i + \mu_2 (1 - T_i) + Z_{i1}\gamma_1 + \ldots + Z_{iq}\gamma_q + \epsilon_i, \ i = 1, \ldots, n.
\] (2.8)

Let \( E = (1, -1) \) and

\[
Tr(n) = \begin{bmatrix}
T_1 & 1 - T_1 \\
T_2 & 1 - T_2 \\
\vdots & \vdots \\
T_n & 1 - T_n \\
\end{bmatrix}.
\]
Via a similar argument to that in Section 2.2, the statistic for testing the hypothesis (2.2) at time point $t \in (0, 1]$ is

\[ Z_{t}^{\text{adj}2} = \frac{E \hat{\mu}(t)}{\hat{\epsilon}(t) \sqrt{\hat{\sigma}(t)^2 E(T_r([nt])^T T_r([nt]))^{-1} E^T}}, \]  

where $\hat{\mu}(t) = (T_r([nt])^T T_r([nt]))^{-1} T_r([nt])^T Y([nt]), \hat{\sigma}(t)^2 = [Y([nt]) - T_r([nt]) \hat{\mu}(t)]^T [Y([nt]) - T_r([nt]) \hat{\mu}(t)] / ([nt] - 2)$, and $\hat{\epsilon}(t)^2$ is a consistent estimator of

\[ \sum_{j \in C^*} \gamma_j^2 \sigma_{\delta j}^2 + \sigma^2 \]

\[ \sigma^2 + \sum_{j=1}^{p} \text{Var}(Z_j \gamma_j^T). \]

We then have the following theorem.

**Theorem 3.** Let $B_t^{\text{adj}2} = \sqrt{t} Z_t^{\text{adj}2}$ in the space $D[0, 1]$ with the Skorohod topology. If a covariate adaptive design satisfies $DIF_n = O_p(1)$ and $DIF_{n}^{Z}(j; c_j) = O_p(1), j = 1, \ldots, q$, $B_t^{\text{adj}2}$ and $Z_t^{\text{adj}2}$ have the same properties as $B_t^{\text{adj}}$ and $Z_t^{\text{adj}}$ in Theorem 1, respectively.

As explained in the Introduction, stratified permuted block randomization and Student’s t-test are the most popular combination in real clinical trials. The above theorem offers a way to control the type I error rate when sequentially monitoring this procedure.

**2.4 Choice of $\hat{\epsilon}$ and critical values to control the type I error rate.**

First, we discuss how to obtain the consistent estimator ($\hat{\epsilon}(t)$) based on the data collected by information time $t$. In some cases it may be
preferable to perform data analysis with sequential statistics using partial covariates, but it is reasonable to make adjustments to the critical values, or equivalently to the test statistics, with all the data available. Different approaches such as bootstraps to obtain \( \hat{\epsilon} \) might be available depending on the specific models, and these estimators may have diverse desirable features. To make our methods acceptable to a wide audience, we propose a simple approach based on linear models. For each interim look, we fit model (2.1) with full data to obtain consistent estimators of \( \gamma \) and \( \sigma \). By the law of large numbers, we can also easily obtain consistent estimators of \( \sigma_{\delta_j} \) and \( Var(Z_j) \) based on the observed covariates, and the consistency of \( \hat{\epsilon} \) follows fundamental large-sample theory (Lehmann, 2004).

Although CAR procedures sequentially update information and the allocation probability, the joint distribution of the adjusted sequential test statistics is still a Brownian motion or the canonical joint distribution defined by Jennison and Turnbull (2000). As a result, numerous existing techniques could be used when sequentially monitoring a CAR. These techniques include, but are not limited to, Pocock’s test, O’Brien and Fleming’s test, the tests of Wang and Tsiatis (1987), the tests of Haybittle (1971) and Peto et al. (1976), the equivalence test, spending functions, stochastic curtailment, and repeated confidence intervals.
In this paper, we focus on choosing appropriate critical values to control the type I error rate, and we exemplify this procedure by using spending functions. In particular, for the numerical studies in the next section, we assume that sequential hypothesis tests will be performed at three time points: $t_1 = 0.2$, $t_2 = 0.5$, and $t_3 = 1$. We also assume that the following three sets of boundaries from Proschan et al. (2006) can be used to control the nominal type I error rate of 0.05: O’Brien–Fleming-like boundaries $(4.877, 2.963, 1.969)$, linear boundaries $(2.576, 2.377, 2.141)$, and Pocock-like boundaries $(2.438, 2.333, 2.225)$. More details can be found in Proschan et al. (2006). In the numerical studies, to save space we give results only for the O’Brien–Fleming boundary; it is the most popular one in clinical trials and the other boundaries give similar conclusions.

3. Numerical Studies

In this section, we study the finite-sample properties of the procedure and demonstrate our theoretical findings via numerical results. In Tables 1–3, we present our theoretical findings. In Tables 4 and 5, we numerically study the robustness of our method under two scenarios of model mis-specification. In Table 6, we specially study the performance of our method when sparse samples occur at some levels of covariates that are used for the CAR design.
For Tables 1–3, suppose 500 patients sequentially enter a clinical trial, and the responses follow

\[ Y_i = \mu_1 T_i + \mu_2 (1 - T_i) + Z_{i1} \gamma_1 + Z_{i2} \gamma_2 + \epsilon_i, \ i = 1, \ldots, 500, \]  

(3.1)

where \((\mu_1, \mu_2, \gamma_1, \gamma_2)\) are unknown parameters, and \(\epsilon_i\) are independent errors from the normal distribution \(N(0,1)\). In this paper, we study three randomization procedures, i.e., complete randomization, the Pocock–Simon procedure (PS), and the stratified permuted block randomization (SPB). The covariate adaptive designs are based on \(Z_1\) and \(Z_2\). We give numerical results for a data analysis with the full dataset and model (3.1) (“Full” in the tables) and a partial dataset and the following model including only \(Z_1\) (“Partial” in the tables):

\[ Y_i = \mu_1 T_i + \mu_2 (1 - T_i) + Z_{i1} \gamma_1 + \epsilon_i, \ i = 1, \ldots, 500. \]  

(3.2)

We also give results for Student’s t-test without any covariates (“t-test” in the tables). Note that we do not distinguish \(X\) and \(Z\) here for space efficiency. For each CAR, we give results for both the adjusted and unadjusted sequential statistics; PS, PS-adj, SPB, and SPB-adj represent the four cases. In Tables 1–3, we report results where \(Z_1\) and \(Z_2\) are binary covariates with a success rate of 0.5 (“discrete” in the tables) and where \(Z_1\) and \(Z_2\) follow the normal distribution \(N(0,1)\) (“continuous” in the tables).
We tried other settings for the covariates and similar results were obtained. When the CAR procedures are implemented with continuous covariates, we discretize them in the following way:

\[ \tilde{z} = \begin{cases} 1 & \text{if } z < z_{0.4} \\ 0 & \text{if } z \geq z_{0.4} \end{cases}, \]

where \( z_{0.4} \) is the 0.4-quantile of the standard normal distribution. All the results are based on 10000 replications.

In Table 1, we give the type I error rate assuming that the responses follow model (3.1) with \((\mu_1, \mu_2, \gamma_1, \gamma_2) = (0.5, 0.5, 1, 1)\). We found that when all the covariates are used in the data analysis, the sequential monitoring of all three randomization procedures without adjustment can control the type I error rate well, which is consistent with Theorem 2. As a result, we do not have to adjust the sequential statistics in this case. Actually, the sequential monitoring of complete randomization in all the cases in this section has no problem in controlling the type I error rate. We also find that the sequential monitoring of CAR procedures with the proposed adjusted sequential statistics can protect the type I error rate when not all the covariates are included in the data analysis, whereas the rate is conservative without adjustments. Further, data analysis with Student’s t-test is more conservative than that based on partial covariates. As mentioned
before, the theorems allow an explicit calculation of the gap between the unadjusted rate and the adjusted rate for different scenarios. The above numerical results are consistent with the theoretically derived discrepancy.

Table 1: Type I error rate for different scenarios

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</tr>
</tbody>
</table>

In Table 2, we give the power assuming that the responses follow model (3.1) with \((\mu_1, \mu_2, \gamma_1, \gamma_2) = (0.5, 0.75, 1, 1)\), and the other settings are the same as before. The value of \(\mu_2\) is chosen so that the power is around 0.8 for the sequential monitoring of complete randomization when the “full” model is used. We find that the sequential monitoring of CAR procedures produces similar results to those for the sequential monitoring of complete randomization in terms of power and early stopping when both covariates...
are included in the data analysis. When only one covariate is included in the data analysis, the sequential monitoring of CAR with adjusted sequential statistics can increase the power. In Table 3, we study early stopping under the scenarios in Table 2. We report the total number of stops at the first two looks, which means early stopping, among 10000 replications. The sequential monitoring of CAR designs with adjusted sequential statistics stops the trials much earlier than the other approaches do.

<table>
<thead>
<tr>
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<th></th>
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<th></th>
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<tr>
<td></td>
<td>discrete</td>
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<td>discrete</td>
<td>continuous</td>
<td>discrete</td>
<td>continuous</td>
</tr>
<tr>
<td>CR</td>
<td>0.795</td>
<td>0.796</td>
<td>0.715</td>
<td>0.507</td>
<td>0.634</td>
<td>0.366</td>
</tr>
<tr>
<td>PS</td>
<td>0.802</td>
<td>0.795</td>
<td>0.727</td>
<td>0.500</td>
<td>0.651</td>
<td>0.320</td>
</tr>
<tr>
<td>SPB</td>
<td>0.800</td>
<td>0.799</td>
<td>0.725</td>
<td>0.501</td>
<td>0.652</td>
<td>0.318</td>
</tr>
<tr>
<td>PS-adj</td>
<td>NA</td>
<td>NA</td>
<td>0.800</td>
<td>0.665</td>
<td>0.801</td>
<td>0.566</td>
</tr>
<tr>
<td>SPB-adj</td>
<td>NA</td>
<td>NA</td>
<td>0.800</td>
<td>0.663</td>
<td>0.801</td>
<td>0.565</td>
</tr>
</tbody>
</table>

Next, we discuss the performance of the proposed method when the model is mis-specified. In Table 4, we consider the case where $Z_1$ follows a Bernoulli distribution with a success rate of 0.5 and $Z_2$ is correlated with
Table 3: Early stopping for different scenarios

<table>
<thead>
<tr>
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<th>Partial</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
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<td>continuous</td>
<td>discrete</td>
</tr>
<tr>
<td>CR</td>
<td>1595</td>
<td>1680</td>
<td>1262</td>
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<tr>
<td>PS</td>
<td>1621</td>
<td>1643</td>
<td>938</td>
</tr>
<tr>
<td>SPB</td>
<td>1599</td>
<td>1682</td>
<td>892</td>
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<tr>
<td>PS-adj</td>
<td>NA</td>
<td>NA</td>
<td>1694</td>
</tr>
<tr>
<td>SPB-adj</td>
<td>NA</td>
<td>NA</td>
<td>1680</td>
</tr>
</tbody>
</table>

$Z_1$ in the following way:

$$P(Z_2 = 1 | Z_1 = 1) = 0.8 \text{ and } P(Z_2 = 1 | Z_1 = 0) = 0.4.$$  

The other settings are the same as before. We report the type I error rate when $(\mu_1, \mu_2) = (0.5, 0.5)$, and (in the same table for space efficiency) the power and early stopping results when $(\mu_1, \mu_2) = (0.5, 0.75)$. We can see that our adjusted sequential statistics work well when the two covariates are correlated, and adjustment is not needed when both covariates are included in the data analysis. Our method can greatly increase the power and stop the trial significantly earlier. Without adjustment, using fewer covariates will lead to a lower power, and adjustment can help us to obtain similar
powers for different scenarios.

Table 4: Type I error rate ($\alpha$), power, and early stopping when two covariates are correlated

<table>
<thead>
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<th>Partial</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\alpha$</td>
<td>Power</td>
<td>Early stopping</td>
</tr>
<tr>
<td>CR</td>
<td>0.046</td>
<td>0.799</td>
<td>1648</td>
</tr>
<tr>
<td>PS</td>
<td>0.052</td>
<td>0.802</td>
<td>1696</td>
</tr>
<tr>
<td>SPB</td>
<td>0.048</td>
<td>0.791</td>
<td>1619</td>
</tr>
<tr>
<td>PS-adj</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>SPB-adj</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

In Table 5, we consider another scenario of model mis-specification where there are unobserved covariates that influence the responses. We assume that the responses follow

$$Y_i = \mu_1 T_i + \mu_2 (1 - T_i) + Z_{i1}\gamma_1 + Z_{i2}\gamma_2 + Z_{i3}\gamma_3 + \epsilon_i, i = 1, \ldots, 500, \quad (3.3)$$

where $\gamma_3 = 1$ and $Z_3$ follows Bernoulli distribution with a success rate of 0.6. Other settings are the same as Tables 1-4. Since $Z_3$ is assumed to be unobservable, the SPB randomization design and the Pocock and Simon’s design are implemented with respect to only $Z_1$ and $Z_2$. “Full” in Table 5 means that both $Z_1$ and $Z_2$ are included in the data analysis, and “Partial” means that only $Z_1$ is included in the data analysis. Our proposed method (i) is robust under this scenario in terms of the type I error rate,
(ii) increases the power, and (iii) stops the trial much earlier compared to using the unadjusted statistics.

Table 5: Type I error rate ($\alpha$), power, and early stopping when there is one unknown covariate

<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\alpha$</td>
<td>Power</td>
<td>Early stopping</td>
<td>$\alpha$</td>
<td>Power</td>
</tr>
<tr>
<td>CR</td>
<td>0.050</td>
<td>0.702</td>
<td>1194</td>
<td>0.052</td>
<td>0.625</td>
</tr>
<tr>
<td>PS</td>
<td>0.048</td>
<td>0.706</td>
<td>1182</td>
<td>0.031</td>
<td>0.638</td>
</tr>
<tr>
<td>SPB</td>
<td>0.053</td>
<td>0.712</td>
<td>1230</td>
<td>0.033</td>
<td>0.642</td>
</tr>
<tr>
<td>PS-adj</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.050</td>
<td>0.709</td>
</tr>
<tr>
<td>SPB-adj</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.053</td>
<td>0.714</td>
</tr>
</tbody>
</table>

In Table 6, we investigate the performance of our method when sparse samples occur at some levels of covariates that are used for the CAR design. Specifically, we consider the case where $Z_1$ follows a Bernoulli distribution with a success rate of 0.5, but $Z_2$ follows a Bernoulli distribution with a success rate of 0.9. Other settings are the same as Table 4. The advantages of our methods displayed in previous tables remain under this scenario. Therefore, the proposed method is robust when there are sparse samples at certain covariate levels.

4. Redesign of clinical trial evaluating treatment for rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory disorder typically af-
Table 6: Type I error rate ($\alpha$), power, and early stopping when sparse samples occur at certain covariate levels

<table>
<thead>
<tr>
<th></th>
<th>Full</th>
<th>Partial</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\alpha$</td>
<td>Power</td>
<td>Early stopping</td>
</tr>
<tr>
<td>CR</td>
<td>0.053</td>
<td>0.796</td>
<td>1588</td>
</tr>
<tr>
<td>PS</td>
<td>0.049</td>
<td>0.795</td>
<td>1650</td>
</tr>
<tr>
<td>SPB</td>
<td>0.051</td>
<td>0.792</td>
<td>1591</td>
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<tr>
<td>PS-adj</td>
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<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>SPB-adj</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

fecting the small joints and causing painful swelling. It will eventually result in bone erosion and joint deformity. Tilley et al. (1995) conducted a clinical trial to assess the safety and efficacy of minocycline in the treatment of rheumatoid arthritis. This is a double-blind randomized trial of oral minocycline or a placebo. A total of 219 patients entered the trial; 109 were assigned to the treatment group and 110 to the placebo group.

Here, we redesign the clinical trial and focus on the measurement of the change in hematocrit. Low hematocrit is common in patients with rheumatoid arthritis. After removing some missing data, we obtained summary statistics and parameter estimators in a linear model using information for 205 patients (108 treatment, 107 control). Two binary covariates are used in the model: $Z_1$ is the indicator of “oral corticosteroids used at entry” with a success rate of 0.32, and $Z_2$ is education status with a success rate
of 0.46 ($Z_2 = 0$ for high school graduation or below, $Z_2 = 1$ for at least some college). The fitted model is

$$\hat{y}_i = -1.66 + 1.67T_i + 1.69Z_1 + 1.21Z_2, \quad (4.1)$$

with the residual following the normal distribution $N(0, 3.39^2)$.

In this section, we generate covariate data based on the above summary statistics, sequentially allocate the patients using CAR, and generate responses based on the fitted model (4.1). To provide more information, we use different time points from the previous sections to perform the sequential monitoring; these are $t_1 = 0.5$, $t_2 = 0.8$, and $t_3 = 1$. The corresponding boundaries to keep the overall type I error at 0.05 are O'Brien–Fleming-like boundaries (2.963, 2.266, 2.028), linear boundaries (2.241, 2.252, 2.247), and Pocock-like boundaries (2.157, 2.288, 2.347). We report results (see Table 7) only for stratified permuted block randomization and O'Brien–Fleming-like boundaries, since this is the most popular combination and other settings give similar results. The results are consistent with the previous numerical studies. CAR procedures work well if all the covariates used for the randomization are included in the model. Otherwise, our adjustments are needed to improve the power. In addition, our method with adjusted sequential statistics can stop the trial earlier, based on the number of stops at the first two looks. Note that this real data has a relatively large variance of error.
It becomes dominant in the asymptotic variance of the sequential statistics, and the effect of covariate adaptive design is not quite significant. Even in this special situation, we can see that our method shows improvement. We also provide results for a sample size of 100 to show the small-sample performance of our method. Our method greatly improves the performance in this case.

Table 7: Evaluation of power and early stopping for stratified permuted block randomization in real-data analysis

<table>
<thead>
<tr>
<th></th>
<th>Sample size</th>
<th>SPB</th>
<th>Early stopping</th>
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<th>Early stopping</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Power</td>
<td>Early stopping</td>
<td>Power</td>
<td>Early stopping</td>
</tr>
<tr>
<td>Full</td>
<td></td>
<td>0.94</td>
<td>8178</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Partial</td>
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<td>8081</td>
<td>0.942</td>
<td>8196</td>
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<tr>
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<td>4770</td>
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<td>4399</td>
<td>0.689</td>
<td>4880</td>
</tr>
</tbody>
</table>

5. Conclusion

The properties of the sequential monitoring of covariate-adaptive ran-
domized clinical trials is not well studied in the literature. In this paper, we have derived the joint distribution of the sequential statistics for three common scenarios in clinical trials that use CAR procedures for randomization and linear regression models for analysis. Based on these theoretical properties, we have proposed practical approaches to make use of existing critical values to control the type I error rate. We have also numerically studied different procedures and redesigned a clinical trial. The results demonstrated that the type I error rate can be protected as indicated by our theoretical conclusions, and they also showed the advantages of the combination of sequential monitoring and covariate adaptive designs.

There are several important directions for future research. First, we have studied data analysis for continuous responses with linear regression. Binary responses with logistic regression are a natural generalization. Many other types of responses and models deserve study; difficulties could be introduced by the nonexistence of a closed form of the parameter estimators. Second, we have made use of the $\alpha$-spending function to control the type I error rate. Other methods may provide diverse advantages; these include optimal spending functions (Anderson, 2007) and beta spending functions. Third, a generalized structure of covariates could be investigated for other scenarios in real clinical trials. Fourth, other approaches to adjust the se-

**Supplementary Materials**

The proofs are in the online supplementary materials.

**Acknowledgements**

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