SEAMLESS PHASE II/III CLINICAL TRIALS WITH COVARIATE ADAPTIVE RANDOMIZATION

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Supplementary Material

The supplementary materials contain the proof of the main theorem in the paper and additional simulation results from Section 3.

S1 Proof of Theorem 1

In preparation for the proof of Theorem 1, we first prove the following lemmas.

Lemma 1. *Under Condition (A),* N_k/N *converges in probability to* $1/(K+1)$ *as* $N \to \infty$*, for any* $k = 0, 1, \ldots, K$*.*

Proof. It is easy to verify that

$$\frac{N_0}{N} = \frac{1}{K+1} - \frac{\sum_{k=1}^{K}(N_k - N_0)}{N(K+1)}.$$

Applying Condition (A), we find that N_0/N converges in probability to

$1/(K+1)$. It then follows that convergence in probability to $1/(K+1)$ also holds for N_k/N, $k = 1, \ldots, K$. □

Lemma 2. *Under Conditions (A) and (B), define*

$$\boldsymbol{L} = \Big(\frac{N}{K+1}\Big)^{1/2}\Big(\sum_{i=1}^{N} T_{i0}(\varepsilon_{i0} + \beta\Delta_i), \sum_{i=1}^{N} T_{i1}(\varepsilon_{i1} + \beta\Delta_i), \ldots, \sum_{i=1}^{N} T_{iK}(\varepsilon_{iK} + \beta\Delta_i)\Big)^{\mathrm{T}},$$

where $\Delta_i = Z_i - E\{Z_i \mid D(Z_i)\}$. *Then, as* $N \to \infty$, $\boldsymbol{L}$ *converges in distribution to a normal distribution with mean zero and covariance matrix* $\boldsymbol{\Sigma}_{\boldsymbol{L}}$, *where* $\boldsymbol{\Sigma}_{\boldsymbol{L}} = \mathrm{diag}\{\sigma_d^2 \mathbf{1}_{K+1}\}$. *Furthermore,* $\boldsymbol{L}$ *is asymptotically independent of any functions of* $D(Z_i)$.

Proof. Using the argument of Bugni et al. (2019, Lemma C.1), we can show that $\boldsymbol{L}$ and $\boldsymbol{L}^\star + o_p(1)$ are equal in distribution, where $\boldsymbol{L}^\star$ is a random vector that is independent of any functions of $D(Z_i)$, and $\boldsymbol{L}^\star$ converges in distribution to $\mathcal{N}(\mathbf{0}, \boldsymbol{\Sigma}_{\boldsymbol{L}})$ as $N \to \infty$. □

Lemma 3. *Under Conditions (A) and (B), we have, for any* $k = 0, 1, \ldots, K$,

$$\sum_{i=1}^{N} T_{ik}(\varepsilon_{ik} + \beta Z_i) = O_p(N^{1/2}).$$

Proof. By Lemma 2 it suffices to show that

$$\sum_{i=1}^{N} T_{ik} E\{Z_i \mid D(Z_i)\} = O_p(N^{1/2}).$$

For this we note that

$$\begin{aligned}\sum_{i=1}^{N} E\{Z_i \mid D(Z_i)\} &= \sum_{i=1}^{N}\sum_{k=0}^{K} T_{ik} E\{Z_i \mid D(Z_i)\} \\ &= \sum_{i=1}^{N}\left[\sum_{k=1}^{K}(T_{ik}-T_{i0})E\{Z_i \mid D(Z_i)\} + (K+1)T_{i0}E\{Z_i \mid D(Z_i)\}\right].\end{aligned}$$

It follows from the central limit theorem that $\sum_{i=1}^{N} E\{Z_i \mid D(Z_i)\} = O_p(N^{1/2})$, which, together with Condition (B), implies that $\sum_{i=1}^{N} T_{i0}E\{Z_i \mid D(Z_i)\} = O_p(N^{1/2})$. Reapplying Condition (B) gives $\sum_{i=1}^{N} T_{ik}E\{Z_i \mid D(Z_i)\} = O_p(N^{1/2})$ for any $k = 1, \ldots, K$. □

We are now in a position to prove the main results in Theorem 1.

Proof of Theorem 1. Instead of directly deriving the asymptotic distribution of $(\bar{Y}_0, \bar{Y}_1, \ldots, \bar{Y}_K)^{\mathrm{T}}$, we consider a one-to-one linear transform $(\bar{Y}_1 - \bar{Y}_0, \ldots, \bar{Y}_K - \bar{Y}_0, \sum_{k=0}^{K} \bar{Y}_k)^{\mathrm{T}}$. For simplicity we assume $\mu_k = 0$, $k = 0, 1, \ldots, K$. Otherwise we consider $\bar{Y}_k - \mu_k$.

We first derive the asymptotic distribution of $(\bar{Y}_1 - \bar{Y}_0, \ldots, \bar{Y}_K - \bar{Y}_0)^{\mathrm{T}}$. By Lemmas 1 and 3,

$$\bar{Y}_k = \frac{(K+1)\sum_{i=1}^{N} T_{ik}(\beta Z_i + \varepsilon_{ik})}{N} + o_p(N^{-1/2}). \tag{S1.1}$$

It follows from Condition (B) that

$$\bar{Y}_k - \bar{Y}_0 = \frac{K+1}{N}\left\{\sum_{i=1}^{N} T_{ik}(\varepsilon_{ik} + \beta\Delta_i) - \sum_{i=1}^{N} T_{i0}(\varepsilon_{i0} + \beta\Delta_i)\right\} + o_p(N^{-1/2}).$$

Now, we apply Lemma 2 to find that

$$\Big(\frac{N}{K+1}\Big)^{1/2}\Big(\bar{Y}_1-\bar{Y}_0,\ldots,\bar{Y}_K-\bar{Y}_0\Big)^{\mathrm{T}}$$

is asymptotically normal with mean zero and covariance matrix $\mathbf{\Sigma}$, where $\mathbf{\Sigma}=\mathrm{diag}\{\sigma_d^2\mathbf{1}_K\}+\sigma_d^2\mathbf{1}_K\mathbf{1}_K^{\mathrm{T}}$.

Next, we prove the asymptotic normality of $\sum_{k=0}^{K}\bar{Y}_k$ and show that it is asymptotically independent of $(\bar{Y}_1-\bar{Y}_0,\ldots,\bar{Y}_K-\bar{Y}_0)^{\mathrm{T}}$. By (S1.1), we have

$$\begin{aligned}\sum_{k=0}^{K}\bar{Y}_k &= \frac{K+1}{N}\left(\sum_{i=1}^{N}\sum_{k=0}^{K}T_{ik}\varepsilon_{ik}+\beta\sum_{i=1}^{N}Z_i\right)+o_p(N^{-1/2})\\ &= \frac{K+1}{N}\left[\sum_{i=1}^{N}\sum_{k=0}^{K}T_{ik}(\varepsilon_{ik}+\beta\Delta_i)+\beta\sum_{i=1}^{N}E\{Z_i\mid D(Z_i)\}\right]+o_p(N^{-1/2}).\end{aligned}$$

Since $E\{Z_i\mid D(Z_i)\}$ is a function of $D(Z_i)$, it follows from Lemma 2 and the central limit theorem that

$$\Big(N^{-1/2}\sum_{i=1}^{N}\sum_{k=0}^{K}T_{ik}(\varepsilon_{ik}+\beta\Delta_i),\ N^{-1/2}\sum_{i=1}^{N}\beta E\{Z_i\mid D(Z_i)\}\Big)^{\mathrm{T}}$$

converges in distribution to $(\xi_1,\xi_2)^{\mathrm{T}}$ as $N\to\infty$, where ξ_1 and ξ_2 are independent, ξ_1 follows $\mathcal{N}(0,\sigma_d^2)$, and ξ_2 follows $\mathcal{N}(0,\beta^2\mathrm{Var}[E\{Z_i\mid D(Z_i)\}])$. Recall that $\sigma_d^2=\sigma_\varepsilon^2+\beta^2E[\mathrm{Var}\{Z_i\mid D(Z_i)\}]$; then

$$\Big(\frac{N}{K+1}\Big)^{1/2}\sum_{k=0}^{K}\bar{Y}_k$$

converges in distribution to a normal distribution with mean zero and variance $(K+1)(\beta^2\sigma_z^2+\sigma_\varepsilon^2)$.

It also follows from Lemma 2 that $\{\sum_{i=1}^{N} T_{ik}(\varepsilon_{ik}+\beta\Delta_i)-\sum_{i=1}^{N} T_{i0}(\varepsilon_{i0}+\beta\Delta_i)\}$ is asymptotically independent of $\sum_{i=1}^{N}\sum_{k=0}^{K} T_{ik}(\varepsilon_{ik}+\beta\Delta_i)$ and $\sum_{i=1}^{N}\beta E\{Z_i \mid D(Z_i)\}$. Hence, $\sum_{k=0}^{K}\bar{Y}_k$ is asymptotically independent of $(\bar{Y}_1-\bar{Y}_0,\ldots,\bar{Y}_K-\bar{Y}_0)^{\mathrm{T}}$.

Now we can conclude that

$$\Big(\frac{N}{K+1}\Big)^{1/2}\Big(\bar{Y}_1-\bar{Y}_0,\ldots,\bar{Y}_K-\bar{Y}_0,\sum_{k=0}^{K}\bar{Y}_k\Big)^{\mathrm{T}}$$

is asymptotically normal with mean zero and a block-diagonal covariance matrix with matrices $\mathbf{\Sigma}$ and $(K+1)(\beta^2\sigma_z^2+\sigma_\varepsilon^2)$ on the block-diagonal.

Finally, it follows from the continuous mapping theorem that

$$\Big(\frac{N}{K+1}\Big)^{1/2}\Big(\bar{Y}_0,\bar{Y}_1,\ldots,\bar{Y}_K\Big)^{\mathrm{T}}$$

converges in distribution to a normal distribution with mean zero and covariance matrix $\mathbf{V}$ as $N\to\infty$, where $\mathbf{V}=\mathrm{diag}\{\sigma_d^2\mathbf{1}_{K+1}\}+(K+1)^{-1}\beta^2\mathrm{Var}[E\{Z_i \mid D(Z_i)\}]\mathbf{1}_{K+1}\mathbf{1}_{K+1}^{\mathrm{T}}$. □

Bibliography

Bugni, F. A., I. A. Canay, and A. M. Shaikh (2019). Inference under covariate-adaptive randomization with multiple treatments. *Quantitative Economics 10*(4), 1747–1785.

S2 Additional Simulation Results

In this section, we first present simulation results of Scenarios 2 and 3 with discrete stratification covariates, as mentioned in Section 3 in the paper.

In Scenario 2, four treatments and three discrete stratification covariates (Z_1, Z_2, and Z_3) are considered. The following linear model is used to simulate response $Y_i, i = 1, ..., N + N'$,

$$Y_i = \alpha_0 + \alpha_1 T_{i1} + \alpha_2 T_{i2} + \alpha_3 T_{i3} + \beta_1 Z_{i1} + \beta_2 Z_{i2} + \beta_3 Z_{i3} + \varepsilon_i,$$

where $(\alpha_0, \alpha_1, \alpha_2, \alpha_3, \beta_1, \beta_2, \beta_3)^{\mathrm{T}}$ are unknown parameters; Z_1, Z_2, and Z_3 follow Bernoulli distributions with success rates p_1, p_2, and p_3, respectively; ε_i follows the normal distribution $\mathcal{N}(0, \sigma^2)$; and $T_{ik} = 1$, $k = 1, 2, 3$, if the ith subject is assigned to experimental treatment k, and $T_{ik} = 0$ otherwise. The stratified permuted block design is implemented with respect to all three covariates. In Scenario 3, five treatments and two discrete stratification covariates (Z_1 and Z_2) are considered. The following linear model is used to simulate response $Y_i, i = 1, ..., N + N'$,

$$Y_i = \alpha_0 + \alpha_1 T_{i1} + \alpha_2 T_{i2} + \alpha_3 T_{i3} + \alpha_4 T_{i4} + \beta_1 Z_{i1} + \beta_2 Z_{i2} + \varepsilon_i,$$

where $(\alpha_0, \alpha_1, ..., \alpha_4, \beta_1, \beta_2)^{\mathrm{T}}$ are unknown parameters; Z_1 and Z_2 follow Bernoulli distributions with success rates p_1 and p_2, respectively; ε_i follows the normal distribution $\mathcal{N}(0, \sigma^2)$; and $T_{ik} = 1$, $k = 1, ..., 4$, if the ith sub-

ject is assigned to experimental treatment k, and $T_{ik} = 0$ otherwise. The stratified permuted block design is implemented with respect to both Z_1 and Z_2. In both scenarios, the sample sizes for Stages 1 and 2 are 200 and 400, respectively; the block sizes for the stratified permuted block design are 8 and 10, respectively. The other settings are as in Scenario 1. We obtain similar conclusions to Scenario 1 on the type I error, the power, and the number of replications in which the best treatment is selected for the next stage for Scenario 2 (Tables S1–S2) and Scenario 3 (Tables S3–S4).

Also, we performed other exploratory numerical studies. In Table S5, we consider the case of autocorrelated observations. Specifically, three treatments and two discrete stratification covariates (Z_1 and Z_2) are considered. The following linear model is used to simulate response $Y_i, i = 1, ..., N + N'$,

$$Y_i = \alpha_0 + \alpha_1 T_{i1} + \alpha_2 T_{i2} + \beta_1 Z_{i1} + \beta_2 Z_{i2} + \varepsilon_i,$$

where $(\alpha_0, \alpha_1, \alpha_2, \beta_1, \beta_2)^{\mathrm{T}}$ are unknown parameters; Z_1 and Z_2 follow Bernoulli distributions with success rates p_1 and p_2, respectively; ε_i is autocorrelated as $\varepsilon_i = \rho\varepsilon_{i-1} + \omega_i$, where $-1 < \rho < 1$ and ω_i follows the normal distribution $\mathcal{N}(0, \sigma^2)$; and $T_{ik} = 1, k = 1, 2$, if the ith patient is assigned to experimental treatment k, and $T_{ik} = 0$ otherwise. The stratified permuted block design is implemented with respect to both Z_1 and Z_2. The sample sizes for Stages

1 and 2 are 120 and 500, respectively.

In Table S5, we compare the type I error rate and power of different designs and analysis approaches. We report results for different values of $(p_1, p_2, \rho, \alpha_1, \alpha_2)$ while fixing $\alpha_0 = \beta_1 = \beta_2 = \sigma = 1$. We find that our method can control the type I error rate and greatly increase power compared with the unadjusted t-test. Our approach also returns slightly higher power than the full linear model. We further compare the type I error rate and power when the sample sizes for Stages 1 and 2 are 45 and 60, respectively, in Table S6. Different values of $(p_1, p_2, \rho, \alpha_1, \alpha_2)$ are explored while fixing $(\alpha_0, \beta_1, \beta_2, \sigma) = (1, 0.1, 0.1, 0.27)$. We find that our method can control the type I error rate and is also more powerful than the unadjusted t-test. Even compared to the full linear model, our approach can return about 5% higher power. In Table S7, we explore the Scenario in Table S6, but with one continuous covariate. That is, in this single scenario, the components of the autocorrelation, small sample size, and continuous covariates are all taken into account. Here, let Z_2 follow the standard normal distribution, and the discretization of the continuous covariate and implementation of the CAR design is the same as in Scenario 1. The sample sizes for Stages 1 and 2 are 45 and 60, respectively. We report the type I error rate and power for different parameter values of (α_1, α_2) while fix-

ing $(\alpha_0, \beta_1, \beta_2, \sigma, p_1, q, \rho) = (1, 0.1, 0.1, 0.27, 0.4, 0.6, 0.7)$. We find that our method can control the type I error rate and lead to a higher power than the unadjusted t-test. Compared to the full linear model, our approach can return up to 3% higher power.

In Table S8, we consider the case of heteroskedasticity when the error term is correlated with the covariate. Three treatments and two discrete stratification covariates (Z_1 and Z_2) are considered. The following linear model is used to simulate response $Y_i, i = 1, ..., N + N'$,

$$Y_i = \alpha_0 + \alpha_1 T_{i1} + \alpha_2 T_{i2} + \beta_1 Z_{i1} + \beta_2 Z_{i2} + \varepsilon_i,$$

where $(\alpha_0, \alpha_1, \alpha_2, \beta_1, \beta_2)^{\mathrm{T}}$ are unknown parameters; Z_1 and Z_2 follow Bernoulli distributions with success rates p_1 and p_2, respectively; ε_i follows the normal distribution $\mathcal{N}(0, \sigma_1^2)$ if $Z_{i1} = 0$, and ε_i follows the normal distribution $\mathcal{N}(0, \sigma_2^2)$ if $Z_{i1} = 1$; and $T_{ik} = 1, k = 1, 2$, if the ith patient is assigned to experimental treatment k, and $T_{ik} = 0$ otherwise. The stratified permuted block design is implemented with respect to both Z_1 and Z_2. The sample sizes for Stages 1 and 2 are 120 and 500, respectively. In Table S8, we report results for different values of (α_1, α_2) while fixing $(\alpha_0, \beta_1, \beta_2, \sigma_1, \sigma_2, p_1, p_2) = (1, 1, 1, 1, 1.5, 0.5, 0.5)$. We find that our method can control the type I error rate and lead to a greatly increased power compared with the unadjusted t-test. Our approach also returns slightly higher

power than the full linear model.

In Table S9, we consider the treatment-covariate interaction. Three treatments and two discrete stratification covariates (Z_1 and Z_2) are considered. The following linear model is used to simulate response $Y_i, i = 1, ..., N + N'$,

$$Y_i = \alpha_0 + \alpha_1 T_{i1} + \alpha_2 T_{i2} + \beta_1 Z_{i1} + \beta_2 Z_{i2} + \beta_3 Z_{i1} T_{i1} + \beta_4 Z_{i2} T_{i2} + \varepsilon_i,$$

where $(\alpha_0, \alpha_1, \alpha_2, \beta_1, \beta_2, \beta_3, \beta_4)^{\mathrm{T}}$ are unknown parameters; Z_1 and Z_2 follow Bernoulli distributions with success rates p_1 and p_2, respectively; ε_i follows the normal distribution $\mathcal{N}(0, \sigma^2)$; and $T_{ik} = 1, k = 1, 2$, if the ith patient is assigned to experimental treatment k, and $T_{ik} = 0$ otherwise. The stratified permuted block design is implemented with respect to both Z_1 and Z_2. The sample sizes for Stages 1 and 2 are 120 and 500, respectively. In Table S9, we report results for different values of (α_1, α_2) while fixing $(\alpha_0, \beta_1, \beta_2, p_1, p_2) = (1, 1, 1, 0.5, 0.5)$. We find that our method can control the type I error rate and lead to a much higher power than the unadjusted t-test. Our approach also returns slightly higher power than the full linear model.

In Table S10, we consider the nonlinear covariate effects in the regression model with three treatments, one discrete stratification covariate and one continous covariate (Z_1 and Z_2). The following linear model is used to

simulate response $Y_i, i = 1, ..., N + N'$,

$$Y_i = \alpha_0 + \alpha_1 T_{i1} + \alpha_2 T_{i2} + \beta_1 Z_{i1} + \beta_2 Z_{i2}^2 + \varepsilon_i,$$

where $(\alpha_0, \alpha_1, \alpha_2, \beta_1, \beta_2)^{\mathrm{T}}$ are unknown parameters; Z_1 follow Bernoulli distributions with success rates p_1, and Z_2 follows the standard normal distribution; ε_i follows the normal distribution $\mathcal{N}(0, \sigma^2)$; and $T_{ik} = 1, k = 1, 2$, if the ith patient is assigned to experimental treatment k, and $T_{ik} = 0$ otherwise. The stratified permuted block design is implemented with respect to both Z_1 and dicretized Z_2 as in Scenario 1. The sample sizes for Stages 1 and 2 are 120 and 500, respectively. In Table S10, we report results for different values of (α_1, α_2) while fixing $(\alpha_0, \beta_1, \beta_2, \sigma, p_1, q) = (1, 1, 0.5, 1, 0.5, 0.5)$. The results show that our proposed method can control the type I error rate and lead to a clear improvement in the power compared with the unadjusted t-test. Also, the proposed method tend to be more powerful than the full linear model.

In Tables S11 and S12, we consider the situations where errors are not normally distributed in the regression model with three treatments and two discrete stratification covariates (Z_1 and Z_2). In these two tables, the following linear model is used to simulate response $Y_i, i = 1, ..., N + N'$,

$$Y_i = \alpha_0 + \alpha_1 T_{i1} + \alpha_2 T_{i2} + \beta_1 Z_{i1} + \beta_2 Z_{i2} + \varepsilon_i,$$

where $(\alpha_0, \alpha_1, \alpha_2, \beta_1, \beta_2)^{\mathrm{T}}$ are unknown parameters; Z_1 and Z_2 follow Bernoulli distributions with success rates p_1 and p_2, respectively; and $T_{ik} = 1, k = 1, 2$, if the ith patient is assigned to experimental treatment k, and $T_{ik} = 0$ otherwise. The stratified permuted block design is implemented with respect to both Z_1 and Z_2 as in Scenario 1. The sample sizes for Stages 1 and 2 are 120 and 500, respectively. In Table S11, ε_i follows the Student's t-distribution with 3 degrees of freedom, and we report results for different values of (α_1, α_2) while fixing $(\alpha_0, \beta_1, \beta_2, p_1, p_2) = (1, 1, 1, 0.5, 0.5)$. The results show that our proposed method can control the type I error rate and lead to a clear improvement in the power compared with the unadjusted t-test. In Table S12, ε_i follows the Log-normal distribution $\mathcal{LN}(0, 2)$, and we report results for different values of (α_1, α_2) while fixing $(\alpha_0, \beta_1, \beta_2, p_1, p_2) = (1, 1, 1, 0.5, 0.5)$. The results show that our proposed method can well control the type I error rate.

Finally, we report some additional results for Tables 2 and 4 in the main paper.

Table S1: Type I error rate (percentage) in seamless trial with four treatments and three discrete covariates.

	(p_1, p_2, p_3, σ)	Allocation	*t-test*	*lm*	*BS-t*	*Adjusted-t*
Simes	$(0.5, 0.5, 0.5, 1.0)$	SPB	0.81	4.44	5.00	5.19
		CR	4.56	4.70	-	-
	$(0.4, 0.5, 0.6, 1.0)$	SPB	0.76	4.50	5.16	4.93
		CR	4.57	4.67	-	-
	$(0.4, 0.5, 0.6, 1.5)$	SPB	2.05	4.49	5.22	4.76
		CR	4.57	4.30	-	-
Dunnett	$(0.5, 0.5, 0.5, 1.0)$	SPB	1.03	5.16	5.58	5.75
		CR	5.18	4.97	-	-
	$(0.4, 0.5, 0.6, 1.0)$	SPB	0.90	5.00	5.66	5.42
		CR	5.37	5.03	-	-
	$(0.4, 0.5, 0.6, 1.5)$	SPB	2.37	5.15	5.78	5.24
		CR	5.32	5.05	-	-

Table S2: Power (percentage) and number (M) of replications in which the best treatment is selected for Stage 2 in seamless trial with four treatments and three discrete covariates.

	$(\alpha_1, \alpha_2, \alpha_3)$	Allocation	*t-test*	*lm*	*BS-t*	*Adjusted-t*	M
Simes	$(0.28, 0.16, 0.14)$	SPB	50.97	75.02	74.93	75.59	6006
		CR	53.15	73.85	-	-	5407
	$(0.26, 0.16, 0.14)$	SPB	44.72	70.44	70.97	71.46	5565
		CR	48.69	69.59	-	-	5091
	$(0.24, 0.16, 0.14)$	SPB	38.74	65.77	66.18	67.08	5138
		CR	44.86	65.20	-	-	4758
	$(0.22, 0.16, 0.14)$	SPB	33.71	61.08	61.61	62.66	4741
		CR	41.17	60.49	-	-	4446
	$(0.20, 0.16, 0.14)$	SPB	28.98	56.68	57.03	58.17	4276
		CR	38.04	55.98	-	-	4129
Dunnett	$(0.28, 0.16, 0.14)$	SPB	53.41	76.13	76.28	76.63	6006
		CR	54.99	75.07	-	-	5407
	$(0.26, 0.16, 0.14)$	SPB	46.83	71.84	72.56	72.88	5565
		CR	50.89	71.09	-	-	5091
	$(0.24, 0.16, 0.14)$	SPB	40.98	67.46	68.22	68.45	5138
		CR	46.84	66.92	-	-	4758
	$(0.22, 0.16, 0.14)$	SPB	35.80	62.83	63.30	64.28	4741
		CR	43.40	62.32	-	-	4446
	$(0.20, 0.16, 0.14)$	SPB	30.94	58.61	58.89	60.01	4276
		CR	40.02	57.57	-	-	4129

Table S3: Type I error rate (percentage) in seamless trial with five treatments and two discrete covariates.

	(p_1, p_2, σ)	Allocation	*t-test*	*lm*	*BS-t*	*Adjusted-t*
Simes	$(0.5, 0.5, 1.0)$	SPB	1.24	5.01	4.72	4.88
		CR	4.82	4.34	-	-
	$(0.4, 0.6, 1.0)$	SPB	1.19	4.31	4.65	4.68
		CR	4.59	4.32	-	-
	$(0.4, 0.6, 1.5)$	SPB	2.37	4.48	4.71	4.57
		CR	4.61	4.62	-	-
Dunnett	$(0.5, 0.5, 1.0)$	SPB	1.63	5.10	5.34	5.32
		CR	5.06	5.14	-	-
	$(0.4, 0.6, 1.0)$	SPB	1.53	5.22	5.42	5.38
		CR	5.15	5.09	-	-
	$(0.4, 0.6, 1.5)$	SPB	2.98	5.05	5.45	5.08
		CR	5.26	5.12	-	-

Table S4: Power (percentage) and number (M) of replications in which the best treatment is selected for Stage 2 in seamless trial with five treatments and two discrete covariates.

	$(\alpha_1, \alpha_2, \alpha_3, \alpha_4)$	Allocation	*t-test*	*lm*	*BS-t*	*Adjusted-t*	M
Simes	$(0.30, 0.16, 0.14, 0.12)$	SPB	55.00	70.45	70.84	71.32	5512
		CR	55.25	70.71	-	-	4975
	$(0.28, 0.16, 0.14, 0.12)$	SPB	49.65	66.60	66.47	67.32	5142
		CR	51.29	66.58	-	-	4666
	$(0.26, 0.16, 0.14, 0.12)$	SPB	44.02	62.41	62.43	63.04	4692
		CR	47.01	62.48	-	-	4326
	$(0.24, 0.16, 0.14, 0.12)$	SPB	39.16	58.27	58.06	59.35	4304
		CR	43.35	58.13	-	-	4033
	$(0.22, 0.16, 0.14, 0.12)$	SPB	34.76	54.39	54.15	55.24	3896
		CR	39.42	53.94	-	-	3679
Dunnett	$(0.30, 0.16, 0.14, 0.12)$	SPB	57.44	72.13	72.34	72.74	5512
		CR	57.70	72.36	-	-	4975
	$(0.28, 0.16, 0.14, 0.12)$	SPB	52.32	68.52	68.42	69.06	5142
		CR	53.48	68.89	-	-	4666
	$(0.26, 0.16, 0.14, 0.12)$	SPB	46.75	64.54	64.40	65.07	4692
		CR	49.94	64.93	-	-	4326
	$(0.24, 0.16, 0.14, 0.12)$	SPB	41.76	60.44	60.29	61.26	4304
		CR	46.23	60.59	-	-	4033
	$(0.22, 0.16, 0.14, 0.12)$	SPB	37.38	56.55	56.54	57.54	3896
		CR	42.72	56.87	-	-	3679

Table S5: Type I error rate (percentage), power (percentage) and number (M) of replications in which the best treatment is selected for Stage 2 in seamless trial with autocorrelated observations.

	$(p_1, p_2, \rho, \alpha_1, \alpha_2)$	Allocation	*t-test*	*lm*	*BS-t*	*Adjusted-t*	M
Simes	$(0.4, 0.6, 0.4, 0, 0)$	SPB	1.64	4.12	4.92	4.54	-
		CR	4.90	4.78	-	-	-
	$(0.4, 0.6, 0.4, 0.26, 0.20)$	SPB	64.67	78.25	79.15	78.78	5912
		CR	65.42	78.11	-	-	5834
	$(0.4, 0.6, 0.4, 0.24, 0.20)$	SPB	59.95	74.26	75.34	75.02	5603
		CR	61.39	74.45	-	-	5562
	$(0.4, 0.6, 0.4, 0.22, 0.20)$	SPB	55.30	70.10	71.33	71.04	5288
		CR	57.30	70.15	-	-	5279
	$(0.5, 0.5, 0.3, 0, 0)$	SPB	1.56	4.15	4.91	4.63	-
		CR	4.74	4.77	-	-	-
	$(0.5, 0.5, 0.3, 0.26, 0.20)$	SPB	66.90	81.43	81.98	81.86	6054
		CR	67.18	81.13	-	-	5780
	$(0.5, 0.5, 0.3, 0.24, 0.20)$	SPB	61.91	77.31	78.36	78.25	5735
		CR	63.07	77.34	-	-	5511
	$(0.5, 0.5, 0.3, 0.22, 0.20)$	SPB	56.67	73.23	74.60	74.07	5420
		CR	58.97	73.24	-	-	5214
Dunnett	$(0.4, 0.6, 0.4, 0, 0)$	SPB	1.83	4.37	5.04	4.86	-
		CR	5.49	5.20	-	-	-
	$(0.4, 0.6, 0.4, 0.26, 0.20)$	SPB	65.66	78.93	79.73	79.57	5912
		CR	66.49	78.88	-	-	5834
	$(0.4, 0.6, 0.4, 0.24, 0.20)$	SPB	60.76	75.23	75.99	75.97	5603
		CR	62.60	72.25	-	-	5562
	$(0.4, 0.6, 0.4, 0.22, 0.20)$	SPB	56.15	71.14	71.96	72.02	5288
		CR	58.62	71.29	-	-	5279
	$(0.5, 0.5, 0.3, 0, 0)$	SPB	1.64	4.60	5.11	5.01	-
		CR	5.15	5.13	-	-	-
	$(0.5, 0.5, 0.3, 0.26, 0.20)$	SPB	68.08	82.15	82.46	82.50	6054
		CR	68.05	81.62	-	-	5780
	$(0.5, 0.5, 0.3, 0.24, 0.20)$	SPB	62.95	77.99	78.86	78.93	5735
		CR	64.14	77.90	-	-	5511
	$(0.5, 0.5, 0.3, 0.22, 0.20)$	SPB	57.98	74.13	75.19	74.85	5420
		CR	59.91	73.97	-	-	5214

Table S6: Type I error rate (percentage), power (percentage) and number (M) of replications in which the best treatment is selected for Stage 2 in seamless trial with autocorrelated observations and small sample size.

	$(p_1, p_2, \rho, \alpha_1, \alpha_2)$	Allocation	*t-test*	*lm*	*BS-t*	*Adjusted-t*	M
Simes	$(0.4, 0.6, 0.7, 0, 0)$	SPB	3.17	3.54	4.83	5.18	-
		CR	4.97	5.00	-	-	-
	$(0.4, 0.6, 0.7, 0.22, 0.16)$	SPB	79.92	81.11	84.03	84.38	6844
		CR	77.91	78.20	-	-	6712
	$(0.4, 0.6, 0.7, 0.20, 0.16)$	SPB	74.86	76.24	79.24	80.07	6261
		CR	72.72	73.32	-	-	6147
	$(0.4, 0.6, 0.7, 0.18, 0.16)$	SPB	69.28	71.27	74.46	75.33	5620
		CR	67.48	68.02	-	-	5597
	$(0.5, 0.5, 0.8, 0, 0)$	SPB	3.00	3.34	4.33	4.49	-
		CR	4.83	4.92	-	-	-
	$(0.5, 0.5, 0.8, 0.22, 0.16)$	SPB	70.93	72.54	75.34	76.51	6676
		CR	69.14	69.35	-	-	6572
	$(0.5, 0.5, 0.8, 0.20, 0.16)$	SPB	65.43	66.75	70.48	71.61	6131
		CR	63.66	64.25	-	-	6069
	$(0.5, 0.5, 0.8, 0.18, 0.16)$	SPB	59.79	61.42	65.64	66.47	5582
		CR	58.91	59.11	-	-	5558
Dunnett	$(0.4, 0.6, 0.7, 0, 0)$	SPB	4.00	4.20	5.09	5.28	-
		CR	6.00	5.76	-	-	-
	$(0.4, 0.6, 0.7, 0.22, 0.16)$	SPB	81.29	82.13	84.28	84.48	6844
		CR	79.68	79.28	-	-	6712
	$(0.4, 0.6, 0.7, 0.20, 0.16)$	SPB	76.45	77.24	79.41	80.26	6261
		CR	74.73	74.47	-	-	6147
	$(0.4, 0.6, 0.7, 0.18, 0.16)$	SPB	71.10	72.23	74.69	75.67	5620
		CR	69.67	69.20	-	-	5597
	$(0.5, 0.5, 0.8, 0, 0)$	SPB	3.77	3.84	4.69	4.66	-
		CR	5.96	5.75	-	-	-
	$(0.5, 0.5, 0.8, 0.22, 0.16)$	SPB	72.79	73.57	75.97	76.82	6676
		CR	71.48	70.95	-	-	6572
	$(0.5, 0.5, 0.8, 0.20, 0.16)$	SPB	67.44	68.19	70.83	71.94	6131
		CR	66.12	65.84	-	-	6069
	$(0.5, 0.5, 0.8, 0.18, 0.16)$	SPB	61.87	62.71	66.18	66.73	5582
		CR	61.30	60.77	-	-	5558

Table S7: Type I error rate (percentage), power (percentage) and number (M) of replications in which the best treatment is selected for Stage 2 in seamless trial with autocorrelated observations, small sample size, and one continuous covariate.

	(α_1, α_2)	Allocation	*t-test*	*lm*	*BS-t*	*Adjusted-t*	M
Simes	$(0, 0)$	SPB	3.20	3.49	3.49	5.03	-
		CR	4.99	5.08	-	-	-
	$(0.22, 0.16)$	SPB	78.58	81.51	83.17	83.78	6752
		CR	76.49	78.79	-	-	6628
	$(0.20, 0.16)$	SPB	73.25	76.66	78.24	79.39	6187
		CR	71.30	74.10	-	-	6116
	$(0.18, 0.16)$	SPB	67.80	71.61	73.08	74.65	5629
		CR	66.58	69.11	-	-	5558
Dunnett	$(0, 0)$	SPB	3.83	4.07	4.72	5.26	-
		CR	6.01	5.94	-	-	-
	$(0.22, 0.16)$	SPB	80.22	82.56	83.50	84.00	6752
		CR	78.23	79.96	-	-	6628
	$(0.20, 0.16)$	SPB	75.14	78.08	78.29	79.70	6187
		CR	73.57	75.48	-	-	6116
	$(0.18, 0.16)$	SPB	69.72	72.94	73.38	75.12	5629
		CR	68.86	70.78	-	-	5558

Table S8: Type I error rate (percentage), power (percentage) and number (M) of replications in which the best treatment is selected for Stage 2 in seamless trial with heteroskedasticity.

	(α_1, α_2)	Allocation	*t-test*	*lm*	*BS-t*	*Adjusted-t*	M
Simes	$(0, 0)$	SPB	2.13	4.50	5.25	5.03	-
		CR	4.67	4.74	-	-	-
	$(0.28, 0.22)$	SPB	61.73	72.82	73.41	73.71	5878
		CR	62.58	73.14	-	-	5739
	$(0.26, 0.22)$	SPB	57.51	69.07	69.98	69.86	5569
		CR	59.21	69.65	-	-	5499
	$(0.24, 0.22)$	SPB	53.22	65.64	65.91	66.53	5308
		CR	55.42	65.73	-	-	5266
Dunnett	$(0, 0)$	SPB	2.38	4.84	5.46	5.34	-
		CR	5.20	5.06	-	-	-
	$(0.28, 0.22)$	SPB	62.95	73.78	73.98	74.38	5878
		CR	63.90	74.08	-	-	5739
	$(0.26, 0.22)$	SPB	58.98	70.10	70.49	70.62	5569
		CR	60.31	70.56	-	-	5499
	$(0.24, 0.22)$	SPB	54.85	66.57	66.87	67.37	5308
		CR	56.92	66.75	-	-	5266

Table S9: Type I error rate (percentage), power (percentage) and number (M) of replications in which the best treatment is selected for Stage 2 in seamless trial with treatment-covariate interaction.

	(α_1, α_2)	Allocation	*t-test*	*lm*	*BS-t*	*Adjusted-t*	M
Simes	$(0, 0)$	SPB	1.03	4.39	4.98	4.90	-
		CR	4.64	4.77	-	-	-
	$(0.22, 0.17)$	SPB	49.26	71.49	71.90	72.10	5866
		CR	52.66	70.76	-	-	5596
	$(0.20, 0.17)$	SPB	43.44	66.40	67.26	67.22	5535
		CR	48.39	66.02	-	-	5340
	$(0.18, 0.17)$	SPB	38.09	61.60	62.51	62.82	5209
		CR	44.42	61.85	-	-	5072
Dunnett	$(0, 0)$	SPB	1.23	4.86	5.30	5.22	-
		CR	5.14	5.10	-	-	-
	(0.220.17)	SPB	50.39	72.28	72.77	72.71	5866
		CR	53.87	71.62	-	-	5596
	$(0.20, 0.17)$	SPB	44.70	67.14	67.95	68.04	5535
		CR	49.50	67.25	-	-	5340
	$(0.18, 0.17)$	SPB	39.37	62.67	63.33	63.68	5209
		CR	45.86	62.94	-	-	5072

Table S10: Type I error rate (percentage), power (percentage) and number (M) of replications in which the best treatment is selected for Stage 2 in seamless trial with nonlinear covariate effects.

	(α_1, α_2)	Allocation	*t-test*	*lm*	*BS-t*	*Adjusted-t*	M
Simes	$(0, 0)$	SPB	3.07	4.72	5.34	5.11	-
		CR	4.48	4.43	-	-	-
	$(0.28, 0.22)$	SPB	70.41	76.35	77.10	77.12	5886
		CR	69.80	75.06	-	-	5801
	$(0.26, 0.22)$	SPB	66.12	72.88	73.69	73.61	5599
		CR	66.16	71.56	-	-	5544
	$(0.24, 0.22)$	SPB	61.93	68.96	70.06	69.71	5321
		CR	62.37	68.10	-	-	5272
Dunnett	$(0, 0)$	SPB	3.51	5.02	5.56	5.29	-
		CR	5.10	4.85	-	-	-
	$(0.28, 0.22)$	SPB	71.03	76.83	77.82	77.45	5886
		CR	70.87	75.90	-	-	5801
	$(0.26, 0.22)$	SPB	67.23	73.54	74.52	73.90	5599
		CR	67.32	72.50	-	-	5544
	$(0.24, 0.22)$	SPB	63.16	69.81	71.05	70.33	5321
		CR	63.57	69.21	-	-	5272

Table S11: Type I error rate (percentage), power (percentage) and number (M) of replications in which the best treatment is selected for Stage 2 in seamless trial with residual errors follow the Student's t-distribution.

	(α_1, α_2)	Allocation	*t-test*	*lm*	*BS-t*	*Adjusted-t*	M
Simes	$(0, 0)$	SPB	2.94	4.81	5.25	5.23	-
		CR	4.25	4.57	-	-	-
	$(0.50, 0.30)$	SPB	84.59	87.83	88.33	88.00	7072
		CR	83.19	87.48	-	-	6879
	$(0.45, 0.30)$	SPB	79.34	84.02	84.40	84.09	6579
		CR	78.41	83.37	-	-	6468
	$(0.40, 0.30)$	SPB	73.19	78.42	78.85	79.11	6075
		CR	72.52	78.16	-	-	5995
Dunnett	$(0, 0)$	SPB	3.22	5.10	5.52	5.40	-
		CR	4.76	4.95	-	-	-
	$(0.50, 0.30)$	SPB	84.97	88.14	88.57	88.34	7072
		CR	83.65	87.99	-	-	6879
	$(0.45, 0.30)$	SPB	80.16	84.28	84.48	84.48	6579
		CR	79.26	83.95	-	-	6468
	$(0.40, 0.30)$	SPB	73.99	79.13	79.33	79.68	6075
		CR	73.45	78.97	-	-	5995

Table S12: Type I error rate (percentage), power (percentage) and number (M) of replications in which the best treatment is selected for Stage 2 in seamless trial with residual errors follow the Log-normal distribution.

	(α_1, α_2)	Allocation	*t-test*	*lm*	*BS-t*	*Adjusted-t*	M
Simes	$(0, 0)$	SPB	3.58	4.38	5.10	4.73	-
		CR	3.79	4.12	-	-	-
	$(1.7, 1.2)$	SPB	88.75	88.93	88.71	89.36	7562
		CR	88.23	88.12	-	-	7461
	$(1.5, 1.2)$	SPB	84.37	85.17	84.54	85.27	6635
		CR	83.99	84.40	-	-	6576
	$(1.3, 1.2)$	SPB	79.43	80.64	79.78	80.64	5586
		CR	79.26	80.26	-	-	5545
Dunnett	$(0, 0)$	SPB	4.05	4.94	5.29	5.20	-
		CR	4.17	4.70	-	-	-
	$(1.7, 1.2)$	SPB	88.89	89.19	88.88	89.46	7562
		CR	88.53	88.47	-	-	7461
	$(1.5, 1.2)$	SPB	84.55	85.49	84.85	85.50	6635
		CR	84.36	84.85	-	-	6576
	$(1.3, 1.2)$	SPB	79.97	81.34	79.97	81.08	5586
		CR	79.69	80.70	-	-	5545

Table 2 Continued: Power (percentage) and number (M) of replications in which the better treatment is selected for Stage 2 in seamless trial with three treatments and two discrete covariates.

	(α_1, α_2)	Allocation	*t-test*	*lm*	*BS-t*	*Adjusted-t*	M
Simes	$(0.20, 0.16)$	SPB	46.39	65.29	66.78	66.45	5697
		CR	50.13	64.74	-	-	5517
	$(0.18, 0.16)$	SPB	40.67	60.18	61.47	61.44	5370
		CR	45.82	60.10	-	-	5255
Dunnett	$(0.20, 0.16)$	SPB	47.52	66.35	67.52	67.25	5697
		CR	51.47	65.94	-	-	5517
	$(0.18, 0.16)$	SPB	42.15	61.26	62.61	62.21	5370
		CR	47.15	61.47	-	-	5255

Table 4 Continued: Power (percentage) and number (M) of replications in which the better treatment is selected for Stage 2 in seamless trial with three treatments, one discrete covariate, and one continuous covariate.

	(α_1, α_2)	Allocation	*t-test*	*lm*	*BS-t*	*Adjusted-t*	M
Simes	$(0.20, 0.16)$	SPB	30.52	66.15	55.38	55.12	5632
		CR	38.10	65.57	-	-	5495
	$(0.18, 0.16)$	SPB	26.10	60.88	50.53	50.18	5316
		CR	34.63	60.64	-	-	5278
Dunnett	$(0.20, 0.16)$	SPB	31.81	66.99	56.34	56.26	5632
		CR	39.27	66.71	-	-	5495
	$(0.18, 0.16)$	SPB	27.40	62.28	51.33	51.20	5316
		CR	36.10	61.89	-	-	5278