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Evaluation of bias for outcome adaptive randomization designs with binary endpoints

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Clinical trial designs applying outcome adaptive randomization (OAR) sequentially change randomization probabilities basing on observed outcomes. Compared to the conventional equal randomization procedure, OAR has the feature to assign more patients to the better treatment arm and yield higher overall response rates for patients in the trial. However, the true response rates tend to be underestimated in OAR trials. Although the bias converges to zero asymptotically as the sample size increases, it is non-negligible in small trials. In this paper, we evaluated the bias of OAR designs with binary endpoints, with the allocation probabilities implemented under two respective randomization procedures, namely, the sequential maximum likelihood procedure (SMLE) and the doubly adaptive biased coin design (DBCD). We found that the patterns of bias are similar between the two adaptive randomization procedures. When the true response rate is less than 10%, we discover that the bias can be as large as 20% of the true response rates if the sample size is less than 30; the absolute value of the bias, however, remains small. To better gauge the magnitude of the bias, we derived some large-sample strategies to approximate the bias for two target allocation proportions and two randomization procedures. In addition, we conducted simulation studies to quantify the magnitude of the bias in finite samples to assess the accuracy of the asymptotic approximations. We also provided an intuitive explanation for the cause of the underestimation under OAR, and discussed remedies to alleviate bias in the OAR design. A deeper understanding of this bias can help us design better OAR trials and provide more accurate estimates.

Keywords and phrases: Adaptive design, Clinical trial, Estimation.

1. INTRODUCTION

Outcome adaptive randomization (OAR) design has attracted considerable attention in both statistical and clinical communities. With this design, patients are dynamically assigned to the treatment groups using a modified allocation probability based on the current observed data. The general goal of the OAR design is to offer patients in the trial a higher chance to be assigned to the better treatment group, with the accumulated information. This concept can be traced back to the work of [21] and [17], in which they developed some nonrandomized outcome adaptive treatment allocation procedures. In the 1960s, [23] introduced a well-known nonrandomized outcome adaptive allocation procedure: play-the-winner rule. Subsequently, [22] introduced a randomized play-the-winner rule, which formally incorporated the outcome when calculating the randomization probability. Since then, many other OAR designs have been proposed [5, 9]. [7] provided a thorough theoretical evaluation of the characteristics of different outcome adaptive randomization procedures.

When a clinical trial is launched, the difference between the effects of the treatments being evaluated is not known. Hence, equal randomization is reasonable because it is consistent with the equipoise principle, when randomization is considered in clinical trials. As the trial moves along and the information about the treatment difference accumulates, it makes sense to allow patients to have a higher chance of being assigned to the better performing arm(s) by aligning the randomization probability with treatment efficacy. The process can continue until sufficient information accumulates to make a decision on which treatment is better (or no difference), then, the trial can be stopped. Compared to the conventional trial design of equal randomization (ER), OAR designs allow more patients to be assigned to the better treatment, hence have potential to benefit more patients. However, it still remains controversial to use AR methods in clinical trials. There has been an active debate in the literature recently [19, 6, 11, 2] regarding the pros and cons of AR in terms of whether AR is ethical or not and its operating characteristics. General speaking AR focuses more on the "individual ethics" with the goal to treat the next patient better based on the available, cumulative information. On the other hand, ER puts emphasis on "collective ethics" with the goal to benefit the entire population. In many instances, OAR designs have been shown to be superior to the traditional fixed randomization designs in terms of treating patients best in the trial [12]. However, the procedure can have considerable variability [20]. From theoretical

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point of view, statistical inference is usually based on the asymptotic properties of the estimators using samples from identical independent distributions. However, OAR procedures induce complicated dependence structures; hence, the observed data are no longer independent. How does this affect the finite and large-sample properties of the estimators? Only limited answers can be found in the literature. For example, [4] reported bias of the estimators for adaptive urn designs. [19] also discussed the existence of bias, if there is parameter drift. In a recent publication, [3] discussed the estimator bias induced by the process of adaptive randomization in response adaptive clinical trials. They discovered the bias induced in the maximum likelihood estimate for binary outcome in OAR designs. Two approaches were introduced to improve the estimator precision.

To gain a deeper understanding of the performance of OAR, we study the properties of the response rate estimators through both theoretical derivation and extensive simulation studies. We focus on the binary endpoint of a patient having either a desired response to the treatment (i.e., response) or not having a desired response to the treatment (i.e., no response). In this study, we consider two target proportions for allocating patients to treatment 1, $q_2/(q_1+q_2)$ [22] and $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$ [18], where $q_1 = 1-p_1$, $q_2 = 1-p_2$, and (p_1, p_2) are the response rates in treatment arms 1 and 2. Furthermore, the allocation probabilities can be implemented under two respective randomization procedures, namely, the sequential maximum likelihood procedure (SMLE) [16] and the doubly adaptive biased coin design (DBCD) [8]. We will use these settings to study the bias of the response rate estimators.

This paper is organized as follows: Section 2 displays the detailed theoretical derivation to approximate the bias of the response rate estimators in OAR under two different target allocation proportions and two different randomization procedures. Section 3 presents the performance of the approximated and simulated bias in several scenarios by varying the true response rates. The results are shown in tables and figures with detailed theoretical derivations in Appendix A. Discussions follow in Section 4, for which we provide both the theoretical and intuitive explanations of the cause of bias, and offer practical advice regarding how to reduce the bias and how the underestimated response rates can be adjusted when conducting OAR trials.

2. METHODS

In a two-arm clinical trial with size n in which the binary treatment responses are immediately available, we denote the response rate as p_1 for treatment 1, and p_2 for treatment 2. Suppose $Y_1(n) \sim Bin(N_1[n], p_1)$ and $Y_2(n) \sim Bin(N_2[n], p_2)$, where $Y_i(n)$ and $N_i(n)$ denote the respective number of responses and patients assigned to treatment i based on the first n patients for $i \in \{1, 2\}$. These random variables follow binomial distributions.

The maximum likelihood estimator of p_i at stage n can be shown as $\hat{p}_i = Y_i(n)/N_i(n)$, where $i \in \{1, 2\}$. We notice that the form of the estimator is similar to that in the non-adaptive design, except that the denominator of the OAR estimator is random.

Suppose we use the SMLE and set the allocation probability for treatment i as $\hat{\rho}_i(p_1, p_2) = \sqrt{\hat{p}_i}/(\sqrt{\hat{p}_1} + \sqrt{\hat{p}_2})$, where $i \in \{1, 2\}$. The bias of $\hat{p}_1$ and $\hat{p}_2$, which are expressed as $\hat{p}_1 - p_1$ and $\hat{p}_2 - p_2$ respectively, can be approximated by

$$-p_1 q_1 \left[\frac{\sqrt{p_2}}{2np_1^{\frac{3}{2}}} + \frac{p_1^{\frac{3}{2}}(p_2+1) + 2p_1 p_2^{\frac{3}{2}} + 4p_2^{\frac{3}{2}}}{4n^2 p_1^3 \sqrt{p_2}} \right]$$

$$-p_2 q_2 \left[\frac{\sqrt{p_1}}{2np_2^{\frac{3}{2}}} + \frac{p_2^{\frac{3}{2}}(p_1+1) + 2p_1^{\frac{3}{2}} p_2 + 4p_1^{\frac{3}{2}}}{4n^2 p_2^3 \sqrt{p_1}} \right]$$

The derivation steps are provided in Appendix A.

If instead we set the probability of allocating patients to treatment 1 as $\hat{\rho}_1 = \hat{q}_2/(\hat{q}_1 + \hat{q}_2)$, we can use the same steps to derive the asymptotic bias. The result is shown in Table 1, and the steps are described in Appendix A.

Another randomization procedure we consider is the DBCD, which can be thought of as a generalization of the SMLE. Hu and Zhang (2004) proposed a satisfied edition of the allocation function for a different desired proportion function, ρ_i

$$g^{(\alpha)}(0, \hat{\rho}_i) = 1, \quad g^{(\alpha)}(1, \hat{\rho}_i) = 0$$

$$g^{(\alpha)}(\frac{N_i}{n}, \hat{\rho}_i) = \frac{\hat{\rho}_i(\hat{\rho}_i/\frac{N_i}{n})^\alpha}{\hat{\rho}_i(\hat{\rho}_i/\frac{N_i}{n})^\alpha + (1-\hat{\rho}_i)((1-\hat{\rho}_i)/(1-\frac{N_i}{n}))^\alpha},$$

where $i \in \{1, 2\}$ and α is the tuning parameter controlling the degree of randomization imbalance. In this study, we set $\alpha = 2$ [8]. The bias approximation of $\hat{p}_1$ and $\hat{p}_2$ for the DBCD are shown in Table 1, and the derivation steps are listed in Appendix A.

Lemma 1. *When $p_1 < p_2$, the absolute value of bias of $\hat{p}_1$ is greater than that of $\hat{p}_2$. This holds for all the 4 settings in Table 1. The proof can be found in Appendix A.*

3. SIMULATIONS

To check the performance of the derived bias, we conducted simulation studies to quantify the magnitude of the bias in several settings under both the SMLE and DBCD. In the simulations, we consider only binary endpoints in a two-arm study. First, we assign one start-up patient to each arm and arbitrarily assign the fractional responses of each of those two patients proportional to the assumed true response rates for the convenience of starting the randomization procedure in the simulations. These two start-up patients and their responses are removed when calculating the final estimated response rates. In the following adaptive randomization procedure, each incoming patient is assigned to arm 1 with probability $\hat{\rho}_1$ or $g^{(2)}(N_1/n, \hat{\rho}_1)$, in the SMLE or DBCD, respectively, and $\hat{\rho}_1$ is the estimated target alloca-

Table 1. Approximated bias of $\hat{p}_1$ and $\hat{p}_2$

for different procedures and target allocation proportions

ρ_1	SMLE	
	Bias of $\hat{p}_1$	Bias of $\hat{p}_2$
$\frac{\sqrt{p_1}}{\sqrt{p_1}+\sqrt{p_2}}$	$-p_1q_1\left[\frac{\sqrt{p_2}}{2np_1^{\frac{3}{2}}}+\frac{p_1^{\frac{3}{2}}(p_2+1)+2p_1p_2^{\frac{3}{2}}+4p_2^{\frac{3}{2}}}{4n^2p_1^3\sqrt{p_2}}\right]$	$-p_2q_2\left[\frac{\sqrt{p_1}}{2np_2^{\frac{3}{2}}}+\frac{p_2^{\frac{3}{2}}(p_1+1)+2p_1^{\frac{3}{2}}p_2+4p_1^{\frac{3}{2}}}{4n^2p_2^3\sqrt{p_1}}\right]$
$\frac{q_2}{q_1+q_2}$	$-p_1q_1\left[\frac{1}{nq_2}-\frac{2q_1+q_2-3}{n^2q_2^2}\right]$	$-p_2q_2\left[\frac{1}{nq_1}-\frac{q_1+2q_2-3}{n^2q_1^2}\right]$
ρ_1	DBCD	
	Bias of $\hat{p}_1$	Bias of $\hat{p}_2$
$\frac{\sqrt{p_1}}{\sqrt{p_1}+\sqrt{p_2}}$	$-p_1q_1\left[\frac{\sqrt{p_2}}{2np_1^{\frac{3}{2}}}-\frac{p_1^{\frac{3}{2}}(p_2-3)+2p_1p_2^{\frac{3}{2}}-12p_2^{\frac{3}{2}}}{12n^2p_1^3\sqrt{p_2}}\right]$	$-p_2q_2\left[\frac{\sqrt{p_1}}{2np_2^{\frac{3}{2}}}-\frac{p_2^{\frac{3}{2}}(p_1-3)+2p_1^{\frac{3}{2}}p_2-12p_1^{\frac{3}{2}}}{12n^2p_2^3\sqrt{p_1}}\right]$
$\frac{q_2}{q_1+q_2}$	$-p_1q_1\left[\frac{1}{nq_2}-\frac{2q_1+q_2-3}{n^2q_2^2}\right]$	$-p_2q_2\left[\frac{1}{nq_1}-\frac{q_1+2q_2-3}{n^2q_1^2}\right]$

p_1 and p_2 are the true response rates; $q_1 = 1 - p_1$ and $q_2 = 1 - p_2$; ρ_1 is the target allocation proportion for treatment 1; the derivation of the approximated bias is listed in Appendix A.

tion proportion. It can be $\sqrt{\hat{p}_1}/(\sqrt{\hat{p}_1}+\sqrt{\hat{p}_2})$ or $\hat{q}_2/(\hat{q}_1+\hat{q}_2)$. We fix the true response rates p_1 and p_2 under 9 settings,

$$\begin{aligned}&\big[(p_1=0.1,p_2=0.2),(p_1=0.1,p_2=0.3),\\&(p_1=0.1,p_2=0.4),(p_1=0.2,p_2=0.3),\\&(p_1=0.2,p_2=0.4),(p_1=0.3,p_2=0.3),\\&(p_1=0.3,p_2=0.5),(p_1=0.5,p_2=0.7),\\&(p_1=0.5,p_2=0.9)\big].\end{aligned}$$

The observed bias is calculated from the mean of the estimated response rate minus the true response rate. We carry out the simulations with 10,000 iterations.

4. RESULTS

Figures 1–4 demonstrate the bias approximated by theoretical derivation (solid lines) and estimated by simulation (dashed lines) for both $\hat{p}_1$ and $\hat{p}_2$, with sample sizes ranging from 20 to 100. The theoretical approximations for the bias of the response rate estimators are derived from the formulas in Table 1. The results manifest that both $\hat{p}_1$ and $\hat{p}_2$ always underestimate the true response rates. When sample sizes increase, the bias decreases and eventually converges to zero, and the approximated bias approaches the simulated bias. We notice different patterns of bias for $\hat{p}_1$ and $\hat{p}_2$, when the true values of p_1 and p_2 are different. In particular, when the target allocation proportion is set as $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$, $\hat{p}_1$ underestimates its true response rate more than $\hat{p}_2$ in all settings, as shown in Figures 1 and 2. With this target allocation proportion, the bias can be as large as 20% of the true response rates in some settings, when the sample size is small; the absolute value of bias, however, remains smalls, as shown in Supplemental Figures 14–15. We also observe that the derived formulas in Table 1 can approximate the simulated bias well in all settings when the sample size is more than 100, as shown in Supplemental Figures 6–9 in Appendix B.

As seen in Figures 1–4, patterns of bias are similar between the SMLE and DBCD procedures. However, the patterns of bias varied a lot when we applied different target allocation proportions. Setting the target allocation proportion as $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$, we observe wider gaps between the approximated and simulated bias, when the response rates are small, e.g., $p_1 = 0.1$ and sample size is small, e.g., 20–40, as shown in Figures 1 and 2. In addition, the bias of $\hat{p}_1$ is always larger than the bias of $\hat{p}_2$ when $p_1 < p_2$. Largest difference of the bias between the two treatments occurs when p_1 is small, sample size is small, and $p_2 - p_1$ is large. When setting $q_2/(q_1+q_2)$ as the target allocation proportion, we observed different bias patterns. In Figures 3 and 4, we observe that the bias of $\hat{p}_1$ is larger as p_1 becomes larger, particularly, for $p_1 \geq 0.5$. On the other hand, the bias of $\hat{p}_2$ is small and relatively stable. Largest difference of the bias between the two treatments occurs when p_1 is large, sample size is small, and $p_2 - p_1$ is large. Since we are dealing with randomized trials, the approximated and simulated bias in estimating the difference of the treatment effects (i.e., the difference of the response rates of two treatments) are shown in Figure 5. It shows that the bias can account for up to 10% of the true difference in the response rates in some settings. The difference in the treatment effects is always over estimated for the target allocation proportion of $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$ shown in red curves, and the bias decreases with the increase of samples sizes or true response

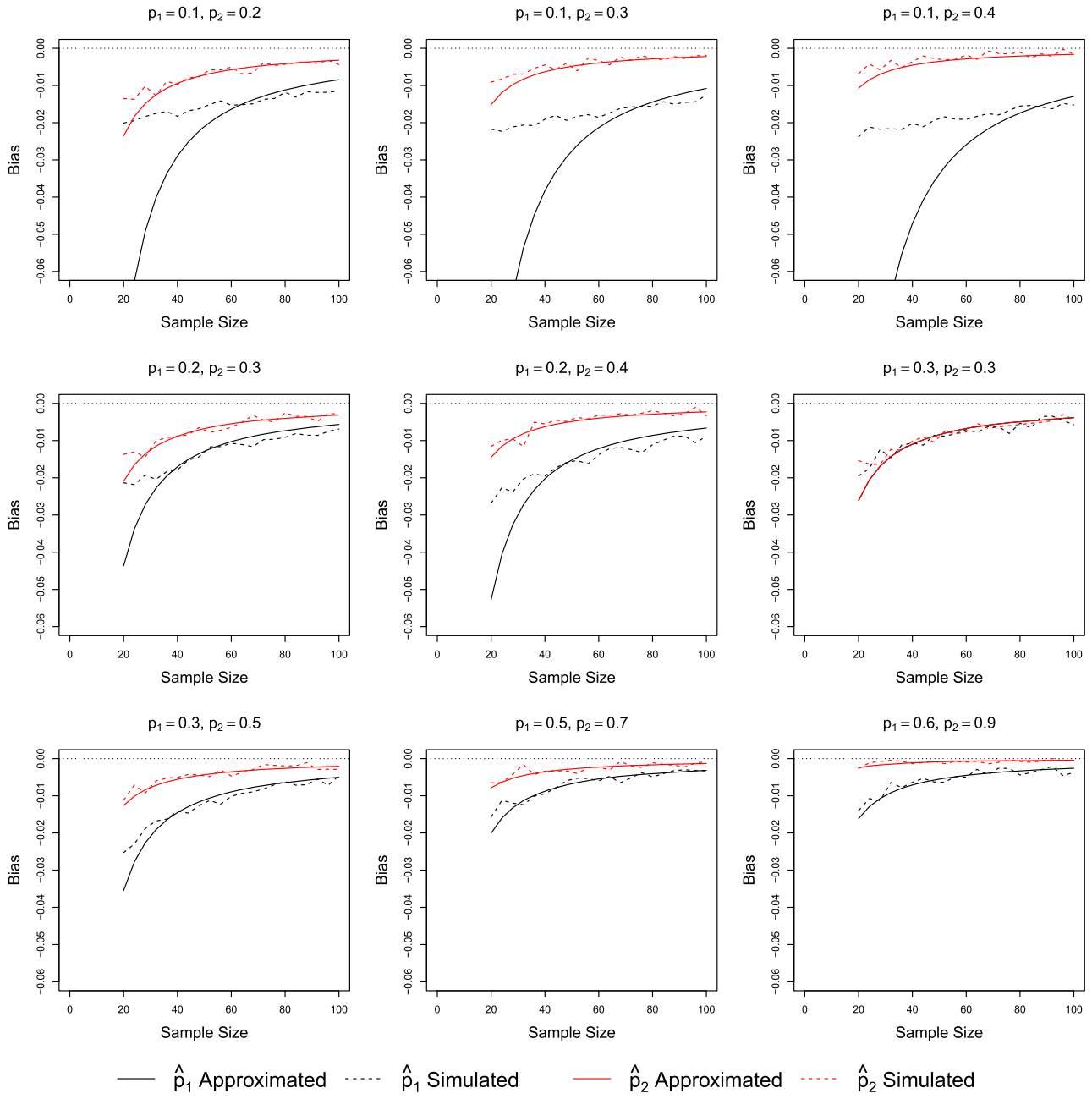

Figure 1. Bias of $\hat{p}_1$ and $\hat{p}_2$ using the SMLE procedure and varying the sample size from 20 *to* 100.
Target allocation proportion for arm 1 is $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$ and p_1 and p_2 are true response rates.

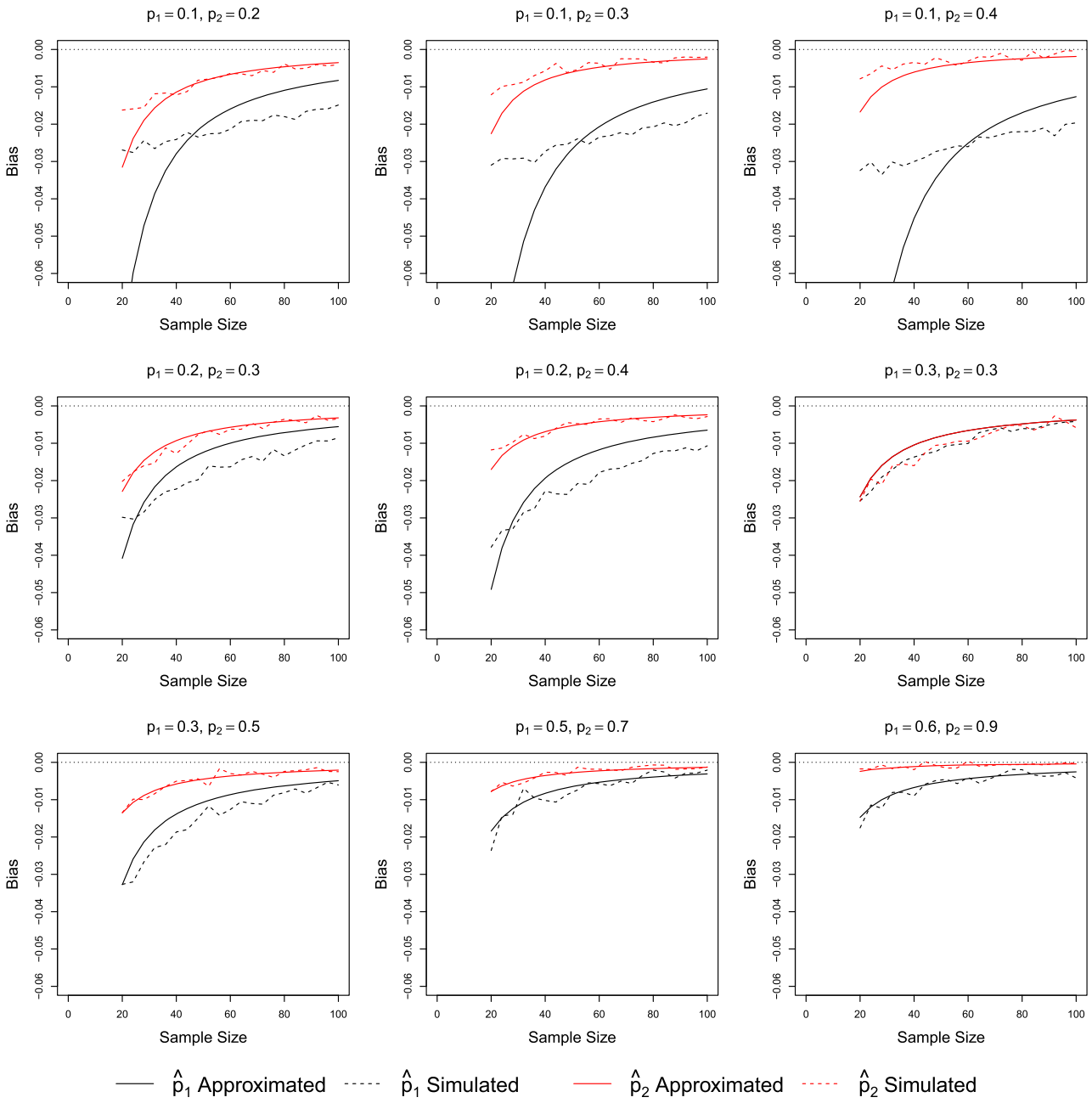

Figure 2. Bias of $\hat{p}_1$ and $\hat{p}_2$ using the DBCD procedure and varying the sample size from 20 *to* 100.
Target allocation proportion for arm 1 is $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$ and p_1 and p_2 are true response rates.

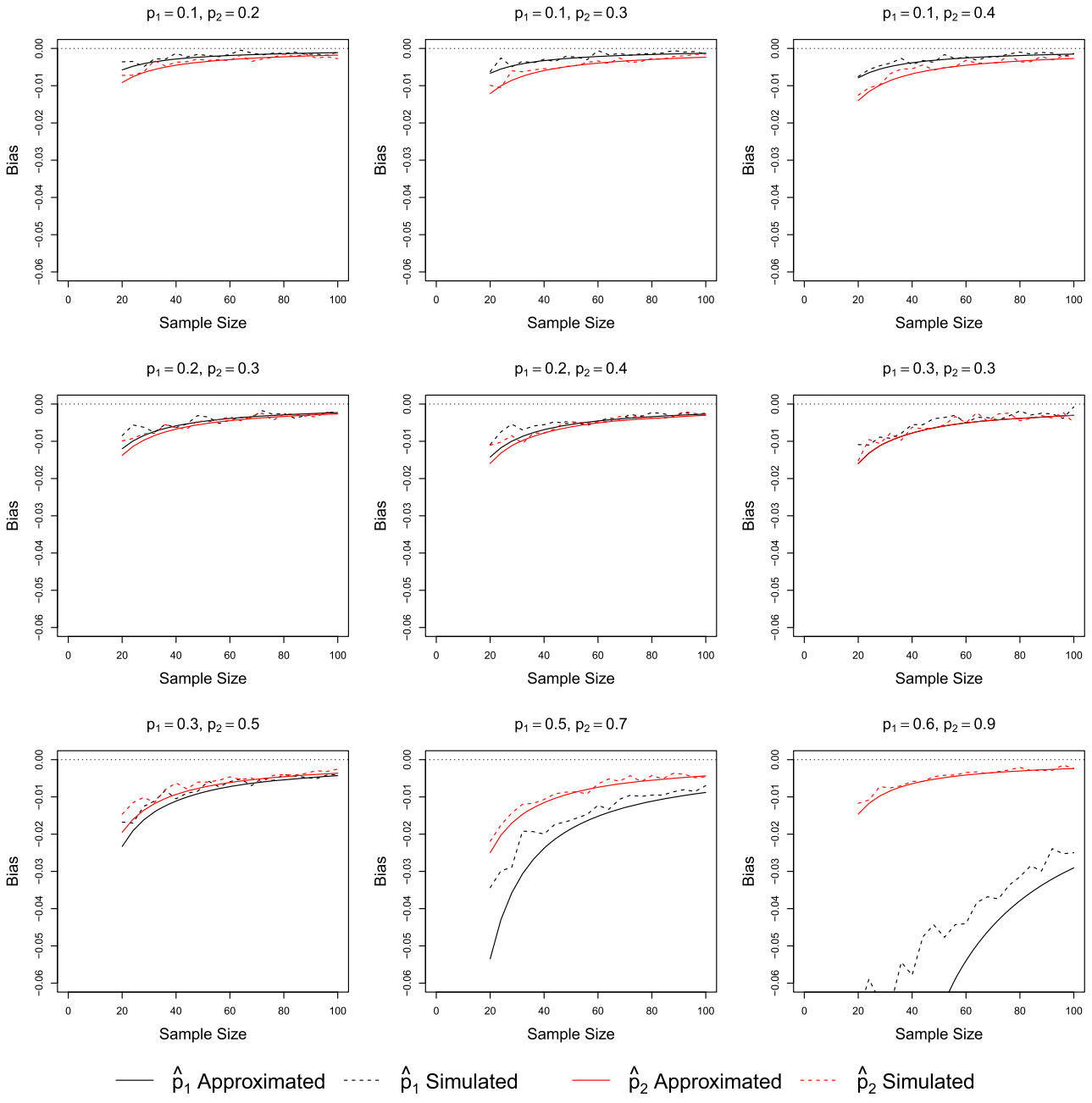

Figure 3. Bias of $\hat{p}_1$ and $\hat{p}_2$ using the SMLE procedure and varying the sample size from 20 *to* 100.
Target allocation proportion for arm 1 is $q_2/(q_1+q_2)$ and p_1 and p_2 are true response rates.

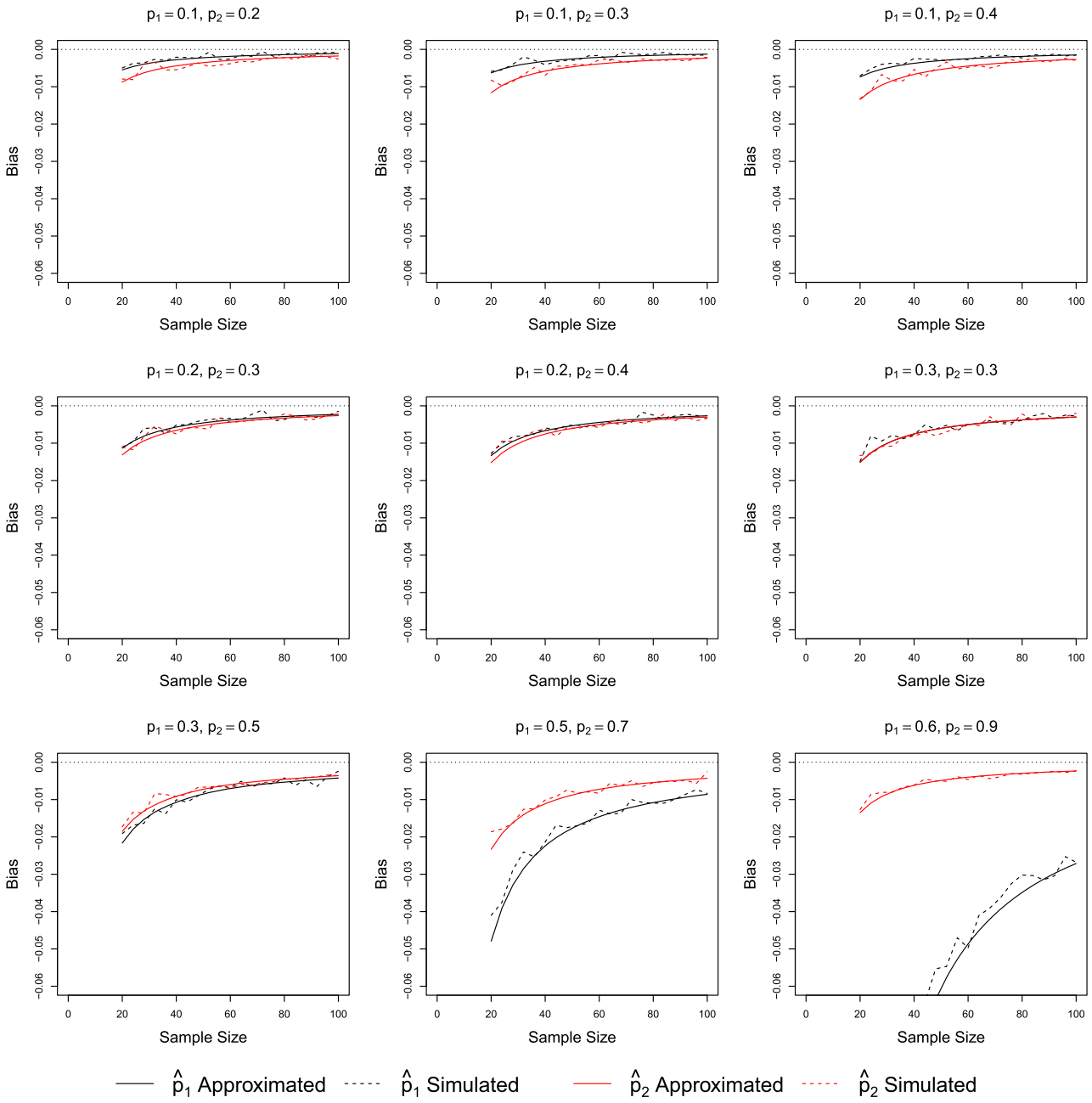

Figure 4. Bias of $\hat{p}_1$ and $\hat{p}_2$ using the DBCD procedure and varying the sample size from 20 *to* 100.
Target allocation proportion for arm 1 is $q_2/(q_1+q_2)$ and p_1 and p_2 are true response rates.

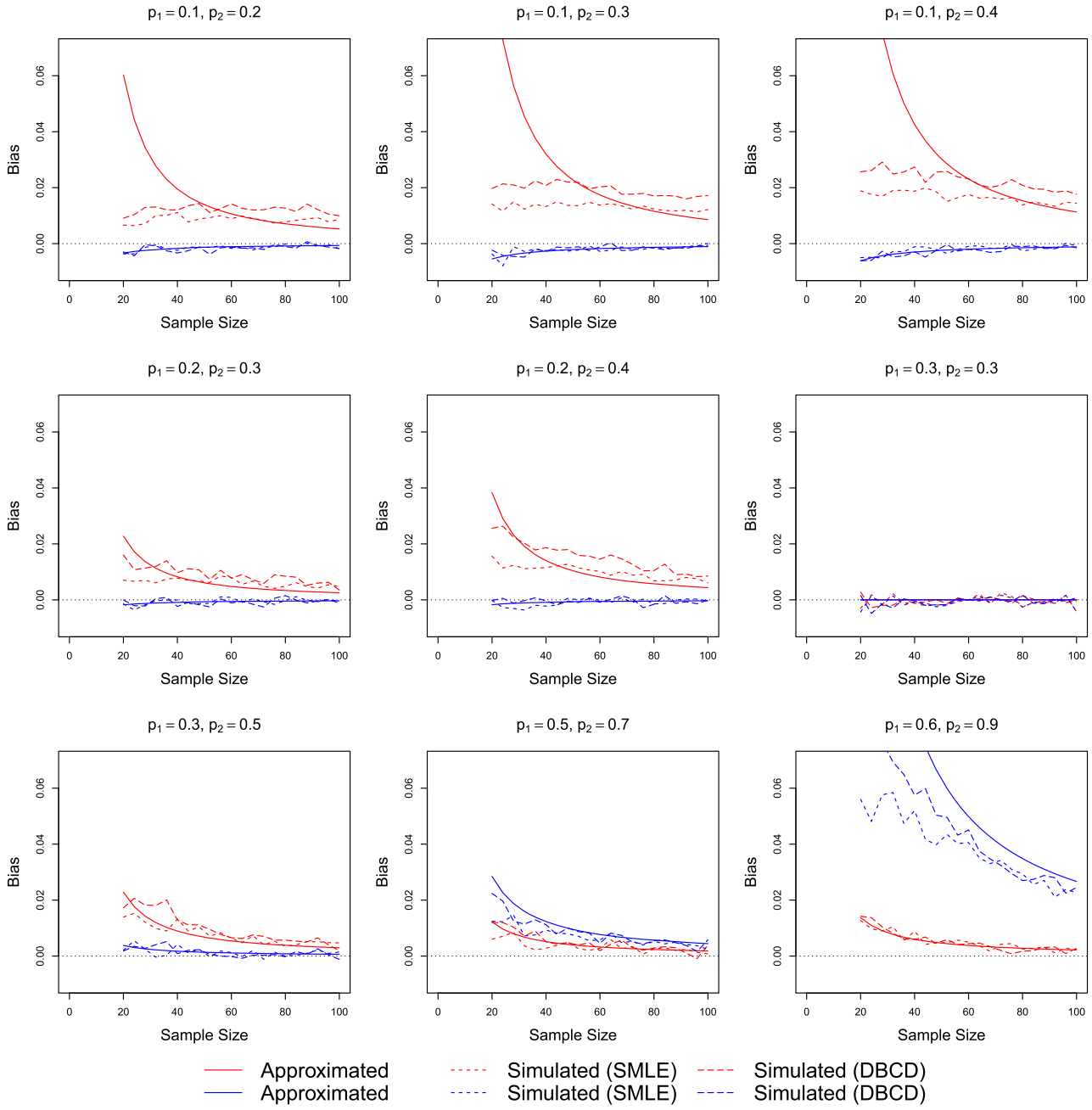

Figure 5. Bias of $\hat{p}_2 - \hat{p}_1$ using both procedures and varying the sample size from 20 *to* 100.
Target allocation proportion for arm 1 is $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$ and $q_2/(q_1+q_2)$ for red and blue lines respectively.

rates. When the target allocation proportion is $q_2/(q_1+q_2)$, the bias of the difference of the treatment effects is very small when both p_1 and p_2 are less than 0.5. It can be under estimated in some settings. For this target allocation setting, the largest over estimation of the treatment effects occurs when the true response rates are large for both p_1 and p_2, as shown in the last panel of Figure 5. This result suggests that when the response rates are less than 0.5, target allocation of $q_2/(q_1+q_2)$ is preferred while when the response rates are larger than 0.5, the target allocation of $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$ is preferred to reduce the bias for estimating the treatment difference. Same as the performance of the estimates for response rates, the bias for the treatment effect estimates converge to zero as sample size increases, as shown in Supplemental Figures 18.

To better evaluate the precision of the asymptotic bias approximation in Table 1, and to discover the performance of the OAR estimators in different settings, we fix the sample size to $n = 50$ to check the bias trend of $\hat{p}_1$ and $\hat{p}_2$ by varying the true values of p_1 or p_2. From Supplemental Figures 10–13 in Appendix B, we can see that both $\hat{p}_1$ and $\hat{p}_2$ underestimate their corresponding parameters, which are consistent with the results from Figures 1–4. In all figures, the bias of $\hat{p}_1$ and $\hat{p}_2$ are the same when p_1 equals to p_2 as it should be. The Supplemental Figure 19 shows that the bias for the difference of the response rates reach zero, when the true response rates are same. Furthermore, as the difference of p_1 and p_2 becomes larger, the bias grows larger as well. The bias patterns are different when different target allocation proportions are selected. When the target proportion of patients allocated to arm 1 is $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$, the approximated bias of $\hat{p}_2$ becomes worse in the scenarios with $p_2 < 0.3$. When the target proportion of patients allocated to arm 1 is $q_2/(q_1+q_2)$, the approximated bias for $\hat{p}_1$ gets worse in the scenarios with true response rates larger than 0.7. Both Supplemental Figures 10 and 11 show that, when p_1 is small and p_2 is large, bias of $\hat{p}_1$ is large, but bias of $\hat{p}_2$ is small. Likewise, when p_1 is large and p_2 is small, bias of $\hat{p}_1$ is small, but bias of $\hat{p}_2$ is large. These phenomenon can be proved by the derivation in Table 1, and the related proof is shown in Appendix A. In the up-left panels of Supplemental Figures 10 and 11, there are large gaps between the approximated and simulated bias for $\hat{p}_1$, which are shown as solid and dashed black lines. These gaps are consistent with those top panels in Figures 1 and 2. Since the formulas in Table 1 are approximated by omitting some high order terms, it may influence the performance of the approximation when p_1 or p_2 are extremely small. For example, if we use $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$ allocation proportion and SMLE procedure, the bias of $\hat{p}_1$ is approximated by the omitted terms with higher orders of p_1 in the denominators, accordingly the gaps between the approximated and simulated bias for $\hat{p}_1$ gets wider as p_2 increases.

Another interesting finding is that both Supplemental Figures 12 and 13 show that the red lines (bias of $\hat{p}_2$) have the parabola shape in the sense that when p_2 is very small or very big, the bias is small, but the bias is larger when p_2 is closer to 0.5. Note that the shape of the red lines can be derived from the formula in Table 1. In that the approximated bias of $\hat{p}_2$ for $q_2/(q_1+q_2)$ allocation proportion in SMLE procedure is

$$-p_2q_2\left[\frac{1}{nq_1}-\frac{q_1+2q_2-3}{n^2q_1^2}\right]$$

that is,

$$-p_2(1-p_2)\left[\frac{1}{n(1-p_1)}-\frac{(1-p_1)+2(1-p_2)-3}{n^2(1-p_1)^2}\right]$$

To find the p_2 which maximizes the bias, we obtain the following partial differentiation equation,

$$-\frac{\partial}{\partial p_2}p_2(1-p_2)\left[\frac{1}{n(1-p_1)}-\frac{(1-p_1)+2(1-p_2)-3}{n^2(1-p_1)^2}\right]=0$$

The maximized bias is reached when

$$\begin{aligned} p_2 \;=\; & \frac{1}{6}\Big[\sqrt{n^2(1-p_1)^2+2n(1-p_1^2)+(p_1+2)^2} \\ & -n(1-p_1)-p_1+2\Big] \end{aligned}$$

which are all around 0.5 when p_1 is from 0.1 to 0.9. The same steps can be used to explain the bias curve for $\hat{p}_2$ in DBCD procedure too. On the other hand, when p_2 is large, the bias of $\hat{p}_1$ can be very large, which are shown as black lines in Supplemental Figures 12 and 13. This can also be explained by the formula in 1. In that the approximated bias of $\hat{p}_1$ for $q_2/(q_1+q_2)$ allocation proportion in SMLE procedure is

$$-p_1q_1\left[\frac{1}{nq_2}-\frac{2q_1+q_2-3}{n^2q_2^2}\right]$$

that is,

$$-p_1(1-p_1)\left[\frac{1}{n(1-p_2)}-\frac{2(1-p_1)+(1-p_2)-3}{n^2(1-p_2)^2}\right]$$

To find the p_2 which maximizes the bias of $\hat{p}_1$, we obtain the following partial differential equation,

$$-\frac{\partial}{\partial p_2}p_1(1-p_1)\left[\frac{1}{n(1-p_2)}-\frac{2(1-p_1)+(1-p_2)-3}{n^2(1-p_2)^2}\right]=0$$

The maximized bias for $\hat{p}_1$ is reached when $p_2=(n+4p_1+1)/(n-1)$ which is larger than the upper bound of "[0,1]". Since the monotone of the partial differential equation, the bias of $\hat{p}_1$ get larger with the increase of p_2.

To explain the issue of bias in general and clear terms, we focused on the bias in each treatment parameter p_i. However, the difference in the treatment effects, p_2-p_1, is likely to be the primary outcome measure in a clinical trial. We also evaluated the performance of our bias approximation

strategy for treatment difference. From Supplemental Figure 18, we notice that the difference estimators tend to be over estimated, when the target allocation proportion for arm 1 is $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$. If we use $q_2/(q_1+q_2)$ allocation proportion, the bias can be either positive or negative, which depends what the true response rates are. The bias pattern are similar between SMLE and DBCD procedures. Our approximation strategy can estimate the bias well.

5. DISCUSSION

In this study, we evaluate and quantify the bias of the response rate estimators in outcome adaptive randomization designs. At first sight, it may seem odd that the response rate estimators are always underestimated in OAR designs, and we may wonder what is the cause of this underestimation.

Different from traditional ER trials, in which patients are assigned to each treatment arm with equal probability independently, in OAR trials, the randomization probability of the new incoming patient is dependent on the current observed data. The Supplemental Figure 20 shows that the ER is unbiased compared with OAR in different simulation scenarios. Under the standard assumption of random variables being identical and independent, such as in ER, the parameter can be consistently estimated. Under the OAR design, however, the random variables are still identical but no longer independent. Hence, the estimator may not be unbiased. When the sample size is small, the response rates tend to be underestimated.

It is reasonable to consider that the dependency structure of the OAR design affects the convergence of the allocation probability and the response rate estimators. We provide some heuristic explanation for the under-estimated bias below. Suppose that $p_1 = 0.2$ and $p_2 = 0.4$ are the true response rates. The target allocation proportion for arm 1 is $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$, as shown in the plots in the center panels of Figures 1 and 2. Assuming we have assigned 10 patients to treatment 1, it is not uncommon that we observe only 1 success. Then, depending on the current observation, $\hat{p}_1 = 0.1$, we may assign future patients to treatment 1 with a small probability that is smaller than the target allocation probability based on the true parameters. As a result, after 100 patients have been assigned to a treatment, at the end of the trial it is possible that $\hat{p}_1$ has not yet been restored from 0.1 to 0.2. That is, if the initial estimate of p_1 is smaller than the expected value, fewer patients will be assigned to that arm, and it is less likely that the trend of the underestimation can be recovered. The same problem exists for the treatment arm that has a higher response rate, if the initial estimated response rate is smaller than the expected value. On the other hand, when p_i (where $i \in \{1, 2\}$) is overestimated, patients have a greater chance of being assigned to that treatment. With more patients assigned to that treatment, the true response rate can be better estimated. Compared to the underestimating statistic $\hat{p}_i$, the overestimating statistic $\hat{p}_i$ is more likely to be restored to a value closer to the truth before the end of the trial. This occurs because the results are more likely to converge toward the truth as more patients are evaluated. As a result, both $\hat{p}_1$ and $\hat{p}_2$ tend to be underestimating the true parameters, but the one with a smaller true response rate tends to be underestimated more. As the sample size increases, the underestimated values are restored and approach the true values. A similar explanation can be applied to the scenario in which the target allocation proportion for arm 1 is $q_2/(q_1+q_2)$.

In addition to discovering the cause of the estimator bias in OAR, we also derived a practical approximation to adjust the bias for response rate estimator in the OAR design. Our derived formulas in Table 1 can approximate the bias well, even when the sample size is less than 100. Substituting p_1 and p_2 with estimated response rates, we can approximate the bias of these estimates, and provide a correction.

In general our approximation strategy provide good estimate of the bias. Nevertheless, some of the gaps between the approximated and simulated values cannot be ignored when the sample size is small. Setting $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$ as the target allocation proportion to arm 1, we find that the approximate bias curves of $\hat{p}_1$ differ a lot from the simulated curves when $p_1 = 0.1$, as shown in Figures 1 and 2. The bias can be as large as 20% of the true response rates, when the sample size is small. This is consistent with the up-left panel in Supplemental Figures 10 and 11 and the Supplemental Figures 14–15. We suggest future trial designer avoid the settings which may cause severe bias. For example, when $p_1 = 0.1$, we suggest to have a simple size greater than 500 to avoid severely under-estimating p_1, as shown in the Supplemental Figures 14–15. When setting the target allocation proportion to arm 1 as $q_2/(q_1+q_2)$, p_1 is severely underestimated, when $p_2 = 0.9$, as shown in Figures 3 and 4. This is consistent with Supplemental Figures 12 and 13. This result matches the one reported by [15], in which the limiting distribution of the proportions are unknown when $p_1 + p_2 > 3/2$. From both of the results of theory derivation and simulation, the bias is reduced and converges to zero, as the sample size increases. For cases with a small sample size and low response rate, we can consider applying some methods to alleviate the large underestimated bias. Among these strategies, we could choose to introduce ER in the first stage [14], threshold the randomization probability to avoid extreme allocation rates, or apply tuning parameters to determine the degree of imbalance (Lee and Chu, 2012). In our proposed two allocation proportion settings, when the assumed true response rates are small, we recommend choosing the target allocation proportion $q_2/(q_1+q_2)$ for treatment 1. On the other hand, the allocation proportion $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$ is recommended when the assumed response rates are large. We can also perform the Taylor's expansion to higher-order terms and propose corresponding estimators by plugging in the estimated response rate to reduce the bias. However, such estimators could be more

complicated as the number of higher order terms increase. Further improvements on the remedy of bias can be topics of future research.

Outcome adaptive randomization (OAR) in clinical trials uses observed outcomes of existing patients to compute randomization probabilities for newly accrued patients. It requires more resources to plan and implement. Except in early phase I cancer trials, adaptive designs have not been widely adopted [13]. However, with the "The 21st Century Cures Act" on its way, the future precision medicine development plan is integrating research with patient care, providing every individual patient with the best possible treatment based on the available information, and continuing to learn and improve the knowledge. Both I-SPY 2 and BATTLE are trials applying adaptive design trials in drug screening under the precision medicine structures [1, 10]. Some opinions emphasize efficiency above all other concerns to minimize research resources and expeditiously pass findings to the care delivery systems, which ER may perform better, but not always. However, when faced a life-threatening diseases, cancer for example, is there a single patient who does not want to benefit from participating in a clinical trial? Furthermore, physicians' mandate is to treat patients with the best treatment based on the current knowledge. Hence, it is reasonable to assign more patients to putatively better treatments with higher chance, in addition to have patients to contribute to generalizable knowledge in trials.

In summary, the OAR design is useful in many clinical trial settings to improve the overall response for patients in the trial. Although we have identified the estimation bias for OAR, the bias is relatively small in most cases. As the sample size increases, the bias is reduced and converges to zero. For cases with small sample sizes, the bias response rates estimator can not be neglected. Measure can be taken in implementing adaptive randomization to avoid extreme allocation proportion. In order to deal with unavoidable bias from the OAR design, the estimators can be adjusted by adding measures approximated from the methods we proposed, to improve the performance of the estimators from the OAR design.

APPENDIX A

A.1 Derivation of asymptotic bias

Suppose $Y_1(n) \sim Bin(N_1[n], p_1)$ and $Y_2(n) \sim Bin(N_2[n], p_2)$, where $Y_i(n)$ and $N_i(n)$ denote the respective number of responses and patients assigned to treatment i based on the first n patients for $i \in \{1, 2\}$. These random variables follow binomial distributions.

Let P_{p_1,p_2} denote the probability measure on the sequence of responses determined by p_1 and p_2, and E_{p_1,p_2} denote the expectation with respect to P_{p_1,p_2}. The likelihood ratio at stage n under P_{p_1,p_2} relative to $P_{\frac{1}{2},\frac{1}{2}}$ is given by

$$L_n(p_1, p_2) = \prod_{i=1}^{2} 2^{-N_i(n)} p_i^{Y_i(n)} q_i^{N_i(n)-Y_i(n)}.$$

Thus, the maximum likelihood estimator of p_i at stage n can be shown to be

$$\hat{p}_i = \frac{Y_i(n)}{N_i(n)}, \text{ where } i \in \{1, 2\}.$$

Suppose we use the sequential maximum likelihood procedure (SMLE) and set the allocation probability for treatment i as

$$\hat{\rho}_i(p_1, p_2) = \frac{\sqrt{\hat{p}_i}}{\sqrt{\hat{p}_1} + \sqrt{\hat{p}_2}}, \text{ where } i \in \{1, 2\}.$$

From (A.1), it then follows that

$$\begin{aligned}\frac{\partial}{\partial p_i} log L_n(p_1, p_2) &= \frac{1}{L_n(p_1, p_2)} \frac{\partial}{\partial p_i} L_n(p_1, p_2) \\ &= \left[\frac{Y_i(n)}{p_i} - \frac{N_i(n) - Y_i(n)}{q_i}\right], \\ &\quad \text{where } i \in \{1, 2\}.\end{aligned}$$

From the equation above, we can obtain

$$\begin{aligned}\frac{\partial}{\partial p_i} L_n(p_1, p_2) \quad &= \quad \left[\frac{Y_i(n)}{p_i} - \frac{N_i(n) - Y_i(n)}{q_i}\right] L_n(p_1, p_2), \\ &\quad \text{where } i \in \{1, 2\}.\end{aligned}$$

Then, by the fundamental identity of sequential analysis (Woodroofe, 1982), we can obtain

$$\begin{aligned}E_{p_1,p_2}\left[\frac{1}{N_i(n)}\right] &= \int \frac{1}{N_i(n)} dP_{p_1,p_2} \\ &= \int \frac{1}{N_i(n)} L_n(p_1, p_2) dP_{1/2,1/2}, \\ &\quad \text{where } i \in \{1, 2\}.\end{aligned}$$

Assuming that $E_{p_1,p_2}[N_i(n)]$ is continuous in p_i, we may differentiate within the integral sign to obtain

$$\begin{aligned}\frac{\partial}{\partial p_i} E_{p_1,p_2}\left[\frac{1}{N_i(n)}\right] &= \int \frac{1}{N_i(n)} \frac{\partial}{\partial p_i} L_n(p_1, p_2) dP_{1/2,1/2} \\ &= \int \frac{1}{N_i(n)} \left[\frac{Y_i(n)}{p_i} - \frac{N_i(n) - Y_i(n)}{q_i}\right] \\ &\quad L_n(p_1, p_2) dP_{1/2,1/2} \\ &= \frac{1}{p_i q_i} \int \frac{1}{N_i(n)} \left[Y_i(n) - p_i N_i(n)\right] \\ &\quad L_n(p_1, p_2) dP_{1/2,1/2} \\ &= \frac{1}{p_i q_i} \int \frac{1}{N_i(n)} [Y_i(n) - p_i N_i(n)] dP_{p_1,p_2} \\ &= \frac{1}{p_i q_i} E_{p_1,p_2}(\hat{p}_i - p_i), \text{ where } i \in \{1, 2\}.\end{aligned}$$

Hence, we have the relation

(1)
$$E_{p_1,p_2}(\hat{p}_i) = p_i + p_i q_i \frac{\partial}{\partial p_i} E_{p_1,p_2}\left[\frac{1}{N_i(n)}\right], \text{ where } i \in \{1,2\}.$$

Applying Taylor's expansion, we can obtain suitable approximations for $E_{p_1,p_2}\left[\frac{1}{N_i(n)}\right]$. In particular, we have the following steps:

(2)
$$\begin{aligned}\frac{1}{N_i(n)} =& \frac{1}{E_{p_1,p_2}[N_i(n)]} - \frac{N_i(n) - E_{p_1,p_2}[N_i(n)]}{(E_{p_1,p_2}[N_i(n)])^2} \\ &+ \frac{(N_i(n) - E_{p_1,p_2}[N_i(n)])^2}{(E_{p_1,p_2}[N_i(n)])^3} + \dots \\ E_{p_1,p_2}\left[\frac{1}{N_i(n)}\right] =& \frac{1}{E_{p_1,p_2}[N_i(n)]} + \frac{var_{p_1,p_2}[N_i(n)]}{(E_{p_1,p_2}[N_i(n)])^3} \\ &+ \dots, \text{ where } i \in \{1,2\}.\end{aligned}$$

Suppose we use the SMLE and set the allocation probability for treatment i as

$$\hat{\rho}_i(p_1,p_2) = \frac{\sqrt{\hat{p}_i}}{\sqrt{\hat{p}_1} + \sqrt{\hat{p}_2}}, \text{ where } i \in \{1,2\}.$$

From the results of Hu and Rosenberger (2003), we know that

$$\begin{aligned}E_{p_1,p_2}[N_i(n)] &= n \cdot \hat{\rho}_i(p_1,p_2) = \frac{n \cdot \sqrt{p_i}}{\sqrt{p_1} + \sqrt{p_2}}, \\ &\text{where } i \in \{1,2\} \\ var_{p_1,p_2}[N_i(n)] &= n \cdot \frac{p_1^{\frac{3}{2}}(p_2 + \frac{1}{2}q_2) + p_2^{\frac{3}{2}}(p_1 + \frac{1}{2}q_1)}{(\sqrt{p_1} + \sqrt{p_2})^3 \sqrt{p_1 p_2}}.\end{aligned}$$

Substituting the expectation and variance in Equation (2) with the results above, we obtain

$$\begin{aligned}&E_{p_1,p_2}\left[\frac{1}{N_1(n)}\right] \\ &\approx \frac{\sqrt{p_1} + \sqrt{p_2}}{n\sqrt{p_1}} + \frac{p_1^{\frac{3}{2}}(p_2 + \frac{1}{2}q_2) + p_2^{\frac{3}{2}}(p_1 + \frac{1}{2}q_1)}{n^2 p_1^2 \sqrt{p_2}} \\ &E_{p_1,p_2}\left[\frac{1}{N_2(n)}\right] \\ &\approx \frac{\sqrt{p_1} + \sqrt{p_2}}{n\sqrt{p_2}} + \frac{p_1^{\frac{3}{2}}(p_2 + \frac{1}{2}q_2) + p_2^{\frac{3}{2}}(p_1 + \frac{1}{2}q_1)}{n^2 p_2^2 \sqrt{p_1}}.\end{aligned}$$

Applying the above results to Equation (1), we obtain the approximation for the expectation of the response rate estimators as

$$\begin{aligned}&E_{p_1,p_2}(\hat{p}_1) \\ &\approx p_1 + p_1 q_1 \frac{\partial}{\partial p_1} E_{p_1,p_2}\left[\frac{1}{N_1(n)}\right] \\ &\approx p_1 - p_1 q_1 \left[\frac{\sqrt{p_2}}{2n p_1^{\frac{3}{2}}} + \frac{p_1^{\frac{3}{2}}(p_2+1) + 2p_1 p_2^{\frac{3}{2}} + 4p_2^{\frac{3}{2}}}{4n^2 p_1^3 \sqrt{p_2}}\right] \\ &E_{p_1,p_2}(\hat{p}_2) \\ &\approx p_2 + p_2 q_2 \frac{\partial}{\partial p_2} E_{p_1,p_2}\left[\frac{1}{N_2(n)}\right] \\ &\approx p_2 - p_2 q_2 \left[\frac{\sqrt{p_1}}{2n p_2^{\frac{3}{2}}} + \frac{p_2^{\frac{3}{2}}(p_1+1) + 2p_1^{\frac{3}{2}} p_2 + 4p_1^{\frac{3}{2}}}{4n^2 p_2^3 \sqrt{p_1}}\right].\end{aligned}$$

From the above derivation, the bias of $\hat{p}_1$ and $\hat{p}_2$ can be respectively approximated by

$$\begin{aligned}&-p_1 q_1 \left[\frac{\sqrt{p_2}}{2n p_1^{\frac{3}{2}}} + \frac{p_1^{\frac{3}{2}}(p_2+1) + 2p_1 p_2^{\frac{3}{2}} + 4p_2^{\frac{3}{2}}}{4n^2 p_1^3 \sqrt{p_2}}\right] \\ &-p_2 q_2 \left[\frac{\sqrt{p_1}}{2n p_2^{\frac{3}{2}}} + \frac{p_2^{\frac{3}{2}}(p_1+1) + 2p_1^{\frac{3}{2}} p_2 + 4p_1^{\frac{3}{2}}}{4n^2 p_2^3 \sqrt{p_1}}\right]\end{aligned}$$

In the SMLE randomization procedure, if we choose the allocation probability for treatment 1 as

$$\hat{\rho}_1 = \frac{q_2}{q_1 + q_2}, \text{ where } i \in \{1,2\},$$

then from the results of Hu and Rosenberger (2003), we know that

$$\begin{aligned}E_{p_1,p_2}[N_1(n)] &= \frac{n \cdot q_2}{q_1 + q_2}, \quad E_{p_1,p_2}[N_2(n)] = \frac{n \cdot q_1}{q_1 + q_2}, \\ &\text{where } i \in \{1,2\}, \\ var_{p_1,p_2}[N_i(n)] &= \frac{n q_1 q_2 (3 - q_1 - q_2)}{(q_1 + q_2)^3}.\end{aligned}$$

Thus we obtain

$$\begin{aligned}E_{p_1,p_2}\left[\frac{1}{N_1(n)}\right] &\approx \frac{q_1 + q_2}{n q_2} + \frac{n q_1 q_2 (3 - q_1 - q_2)}{(n q_2)^3} \\ E_{p_1,p_2}\left[\frac{1}{N_2(n)}\right] &\approx \frac{q_1 + q_2}{n q_1} + \frac{n q_1 q_2 (3 - q_1 - q_2)}{(n q_1)^3}.\end{aligned}$$

and

$$\begin{aligned}E_{p_1,p_2}(\hat{p}_1) &\approx p_1 + p_1 q_1 \frac{\partial}{\partial p_1} E_{p_1,p_2}\left[\frac{1}{N_1(n)}\right] \\ &\approx p_1 - p_1 q_1 \left[\frac{1}{n q_2} - \frac{2q_1 + q_2 - 3}{(n q_2)^2}\right] \\ E_{p_1,p_2}(\hat{p}_2) &\approx p_2 + p_2 q_2 \frac{\partial}{\partial p_2} E_{p_1,p_2}\left[\frac{1}{N_2(n)}\right] \\ &\approx p_2 - p_2 q_2 \left[\frac{1}{n q_1} - \frac{q_1 + 2q_2 - 3}{(n q_1)^2}\right].\end{aligned}$$

From the above derivation, the bias of $\hat{p}_1$ and $\hat{p}_2$ can be respectively approximated by

$$\begin{aligned}&-p_1 q_1 \left[\frac{1}{n q_2} - \frac{2q_1 + q_2 - 3}{(n q_2)^2}\right] \\ &-p_2 q_2 \left[\frac{1}{n q_1} - \frac{q_1 + 2q_2 - 3}{(n q_1)^2}\right]\end{aligned}$$

Using the DBCD randomization procedure, when we choose the allocation probability for treatment 1 as

$$\hat{\rho}_1(p_1,p_2)=\frac{\sqrt{\hat{p}_1}}{\sqrt{\hat{p}_1}+\sqrt{\hat{p}_2}}.$$

From the results of Hu and Rosenberger (2003), we know that

$$E_{p_1,p_2}[N_i(n)]=n\cdot\hat{\rho}_i(p_1,p_2)=\frac{n\cdot\sqrt{p_i}}{\sqrt{p_1}+\sqrt{p_2}},$$
$$\text{where } i\in\{1,2\},$$
$$var_{p_1,p_2}[N_i(n)]=n\cdot\frac{p_1^{\frac{3}{2}}(p_2+\frac{3}{2}q_2)+p_2^{\frac{3}{2}}(p_1+\frac{3}{2}q_1)}{3(\sqrt{p_1}+\sqrt{p_2})^3\sqrt{p_1p_2}}.$$

Hence, we obtain

$$E_{p_1,p_2}\left[\frac{1}{N_1(n)}\right]\approx\frac{\sqrt{p_1}+\sqrt{p_2}}{n\sqrt{p_1}}+\frac{p_1^{\frac{3}{2}}(p_2+\frac{3}{2}q_2)+p_2^{\frac{3}{2}}(p_1+\frac{3}{2}q_1)}{3n^2p_1^2\sqrt{p_2}}$$
$$E_{p_1,p_2}\left[\frac{1}{N_2(n)}\right]\approx\frac{\sqrt{p_1}+\sqrt{p_2}}{n\sqrt{p_2}}+\frac{p_1^{\frac{3}{2}}(p_2+\frac{3}{2}q_2)+p_2^{\frac{3}{2}}(p_1+\frac{3}{2}q_1)}{3n^2p_2^2\sqrt{p_1}},$$

and thus we obtain

$$E_{p_1,p_2}(\hat{p}_1)\approx p_1+p_1q_1\frac{\partial}{\partial p_1}E_{p_1,p_2}\left[\frac{1}{N_1(n)}\right]\approx p_1-p_1q_1\left[\frac{\sqrt{p_2}}{2np_1^{\frac{3}{2}}}-\frac{p_1^{\frac{3}{2}}(p_2-3)+2p_1p_2^{\frac{3}{2}}-12p_2^{\frac{3}{2}}}{12n^2p_1^3\sqrt{p_2}}\right]$$
$$E_{p_1,p_2}(\hat{p}_2)\approx p_2+p_2q_2\frac{\partial}{\partial p_2}E_{p_1,p_2}\left[\frac{1}{N_2(n)}\right]\approx p_2-p_2q_2\left[\frac{\sqrt{p_1}}{2np_2^{\frac{3}{2}}}-\frac{2p_1^{\frac{3}{2}}(p_2-6)+p_1p_2^{\frac{3}{2}}-3p_2^{\frac{3}{2}}}{12n^2p_2^3\sqrt{p_1}}\right]$$

From the above derivation, the bias of $\hat{p}_1$ and $\hat{p}_2$ can be respectively approximated by

$$-p_1q_1\left[\frac{\sqrt{p_2}}{2np_1^{\frac{3}{2}}}-\frac{p_1^{\frac{3}{2}}(p_2-3)+2p_1p_2^{\frac{3}{2}}-12p_2^{\frac{3}{2}}}{12n^2p_1^3\sqrt{p_2}}\right]$$
$$-p_2q_2\left[\frac{\sqrt{p_1}}{2np_2^{\frac{3}{2}}}-\frac{p_2^{\frac{3}{2}}(p_1-3)+2p_1^{\frac{3}{2}}p_2-12p_1^{\frac{3}{2}}}{12n^2p_2^3\sqrt{p_1}}\right]$$

Using the DBCD as the randomization procedure, when we choose the allocation probability for treatment 1 as

$$\hat{\rho}_1=\frac{q_2}{q_1+q_2},\text{ where } i\in\{1,2\},$$

from the results of Hu and Rosenberger (2003), we know that

$$E_{p_1,p_2}[N_1(n)]=\frac{n\cdot q_2}{q_1+q_2},\quad E_{p_1,p_2}[N_2(n)]=\frac{n\cdot q_1}{q_1+q_2},$$
$$\text{where } i\in\{1,2\},$$
$$var_{p_1,p_2}[N_i(n)]=\frac{nq_1q_2(11-5q_1-5q_2)}{5(q_1+q_2)^3}.$$

Hence, we obtain

$$E_{p_1,p_2}\left[\frac{1}{N_1(n)}\right]\approx\frac{q_1+q_2}{nq_2}+\frac{nq_1q_2(11-5q_1-5q_2)}{5(nq_2)^3}$$
$$E_{p_1,p_2}\left[\frac{1}{N_2(n)}\right]\approx\frac{q_1+q_2}{nq_1}+\frac{nq_1q_2(11-5q_1-5q_2)}{5(nq_1)^3},$$

and

$$E_{p_1,p_2}(\hat{p}_1)\approx p_1+p_1q_1\frac{\partial}{\partial p_1}E_{p_1,p_2}\left[\frac{1}{N_1(n)}\right]\approx p_1-p_1q_1\left[\frac{1}{nq_2}-\frac{10q_1+5q_2-11}{5(nq_2)^2}\right]$$
$$E_{p_1,p_2}(\hat{p}_2)\approx p_2+p_2q_2\frac{\partial}{\partial p_2}E_{p_1,p_2}\left[\frac{1}{N_2(n)}\right]\approx p_2-p_2q_2\left[\frac{1}{nq_1}-\frac{5q_1+10q_2-11}{5(nq_1)^2}\right].$$

From the above derivation, the bias of $\hat{p}_1$ and $\hat{p}_2$ can be respectively approximated by

$$-p_1q_1\left[\frac{1}{nq_2}-\frac{2q_1+q_2-3}{(nq_2)^2}\right]$$
$$-p_2q_2\left[\frac{1}{nq_1}-\frac{q_1+2q_2-3}{(nq_1)^2}\right]$$

In the SMLE randomization procedure, if we choose the allocation probability for treatment 1 as

$$\hat{\rho}_1(p_1,p_2)=\frac{\sqrt{\hat{p}_1}}{\sqrt{\hat{p}_1}+\sqrt{\hat{p}_2}},$$

we can easily prove,

$$p_1q_1\left[\frac{\sqrt{p_2}}{2np_1^{\frac{3}{2}}}+\frac{p_1^{\frac{3}{2}}(p_2+1)+2p_1p_2^{\frac{3}{2}}+4p_2^{\frac{3}{2}}}{4n^2p_1^3\sqrt{p_2}}\right]>p_2q_2\left[\frac{\sqrt{p_1}}{2np_2^{\frac{3}{2}}}+\frac{p_2^{\frac{3}{2}}(p_1+1)+2p_1^{\frac{3}{2}}p_2+4p_1^{\frac{3}{2}}}{4n^2p_2^3\sqrt{p_1}}\right]$$

Since

$$p_1q_1\cdot\frac{\sqrt{p_2}}{2np_1^{\frac{3}{2}}}>p_2q_2\cdot\frac{\sqrt{p_1}}{2np_2^{\frac{3}{2}}},$$
$$p_1q_1\cdot\frac{p_1^{\frac{3}{2}}(p_2+1)+2p_1p_2^{\frac{3}{2}}+4p_2^{\frac{3}{2}}}{4n^2p_1^3\sqrt{p_2}}>p_2q_2\cdot\frac{p_2^{\frac{3}{2}}(p_1+1)+2p_1^{\frac{3}{2}}p_2+4p_1^{\frac{3}{2}}}{4n^2p_2^3\sqrt{p_1}}$$

Similarly, from Table 1, when $p_1 < p_2$, we can also prove

$$p_1 q_1 \left[\frac{1}{nq_2} - \frac{2q_1 + q_2 - 3}{(nq_2)^2}\right] > p_2 q_2 \left[\frac{1}{nq_1} - \frac{q_1 + 2q_2 - 3}{(nq_1)^2}\right]$$

$$p_1 q_1 \left[\frac{\sqrt{p_2}}{2np_1^{\frac{3}{2}}} - \frac{p_1^{\frac{3}{2}}(p_2 - 3) + 2p_1 p_2^{\frac{3}{2}} - 12p_2^{\frac{3}{2}}}{12n^2 p_1^3 \sqrt{p_2}}\right]$$

$$> p_2 q_2 \left[\frac{\sqrt{p_1}}{2np_2^{\frac{3}{2}}} - \frac{p_2^{\frac{3}{2}}(p_1 - 3) + 2p_1^{\frac{3}{2}} p_2 - 12p_1^{\frac{3}{2}}}{12n^2 p_2^3 \sqrt{p_1}}\right]$$

$$p_1 q_1 \left[\frac{1}{nq_2} - \frac{2q_1 + q_2 - 3}{(nq_2)^2}\right] > p_2 q_2 \left[\frac{1}{nq_1} - \frac{q_1 + 2q_2 - 3}{(nq_1)^2}\right]$$

Hence, when $p_1 < p_2$, the bias of $\hat{p}_1$ is larger than the bias of $\hat{p}_2$.

APPENDIX B. SUPPLEMENTAL FIGURES

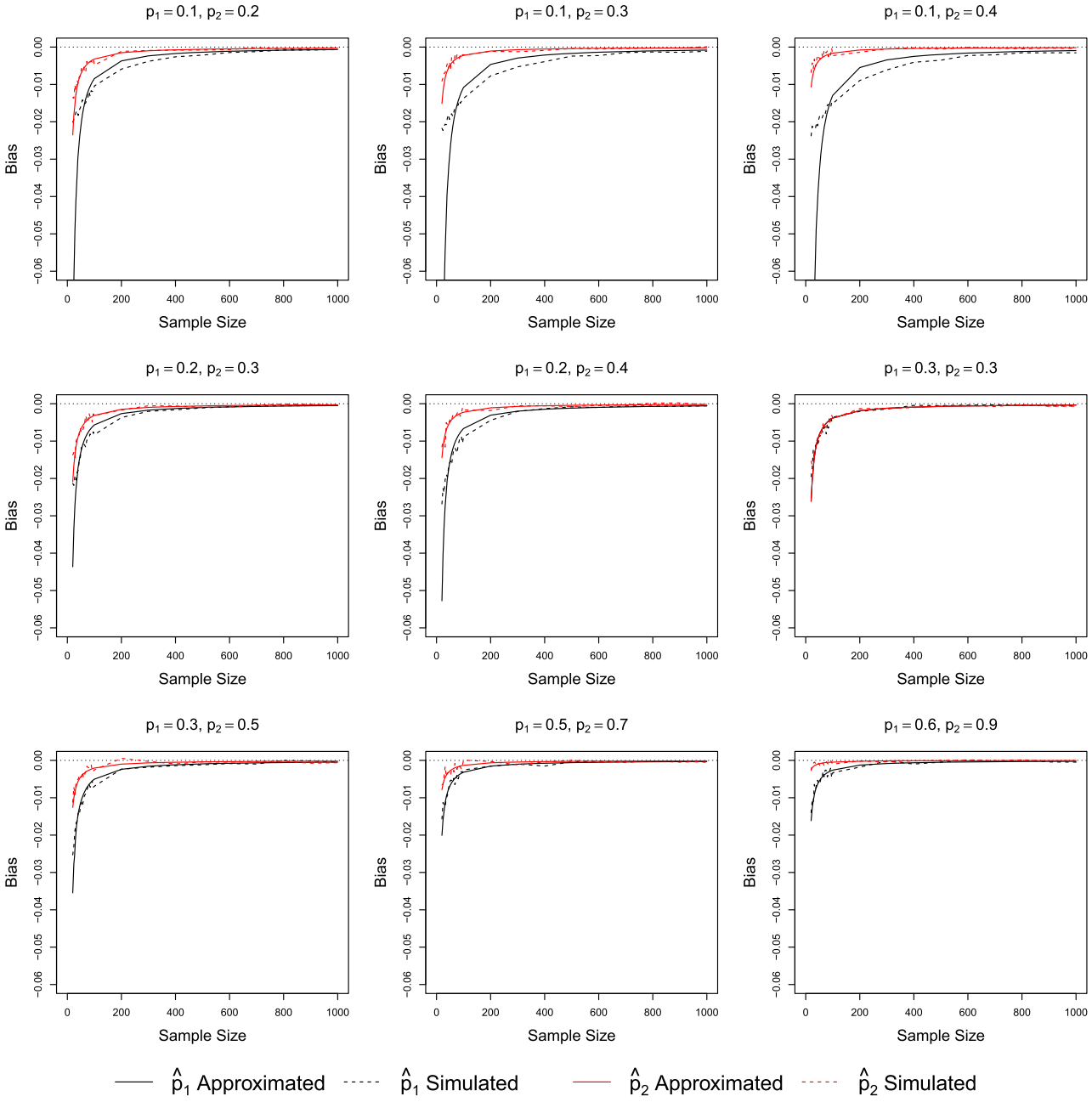

Figure 6. Bias of $\hat{p}_1$ and $\hat{p}_2$ using the SMLE procedure and varying the sample size from 20 *to* 1000.
Target allocation proportion for arm 1 is $\sqrt{p_1}/(\sqrt{p_1} + \sqrt{p_2})$ and p_1 and p_2 are settings of true response rates.

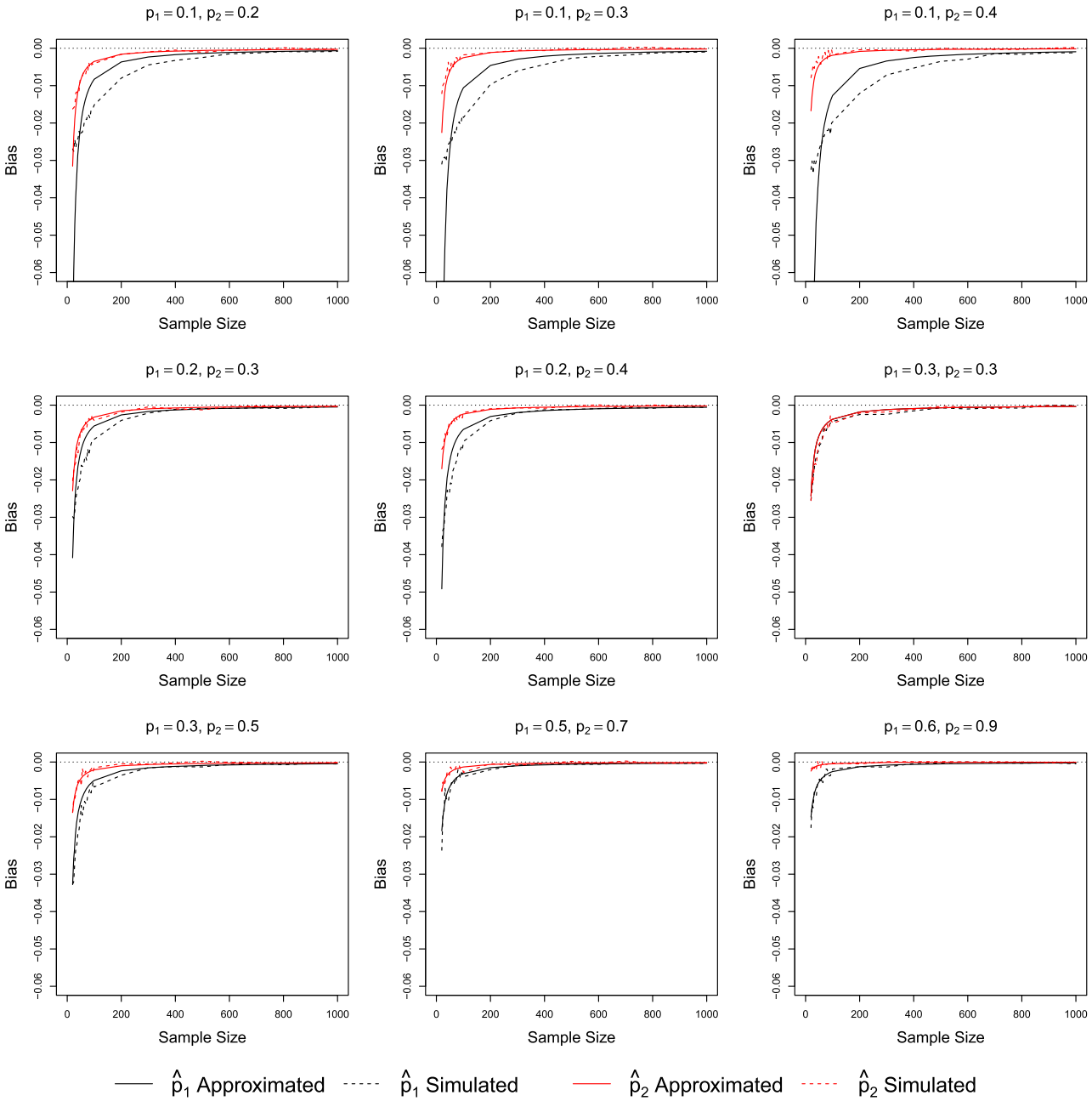

Figure 7. Bias of $\hat{p}_1$ and $\hat{p}_2$ using the DBCD procedure and varying the sample size from 20 *to* 1000.
Target allocation proportion for arm 1 is $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$ and p_1 and p_2 are settings of true response rates.

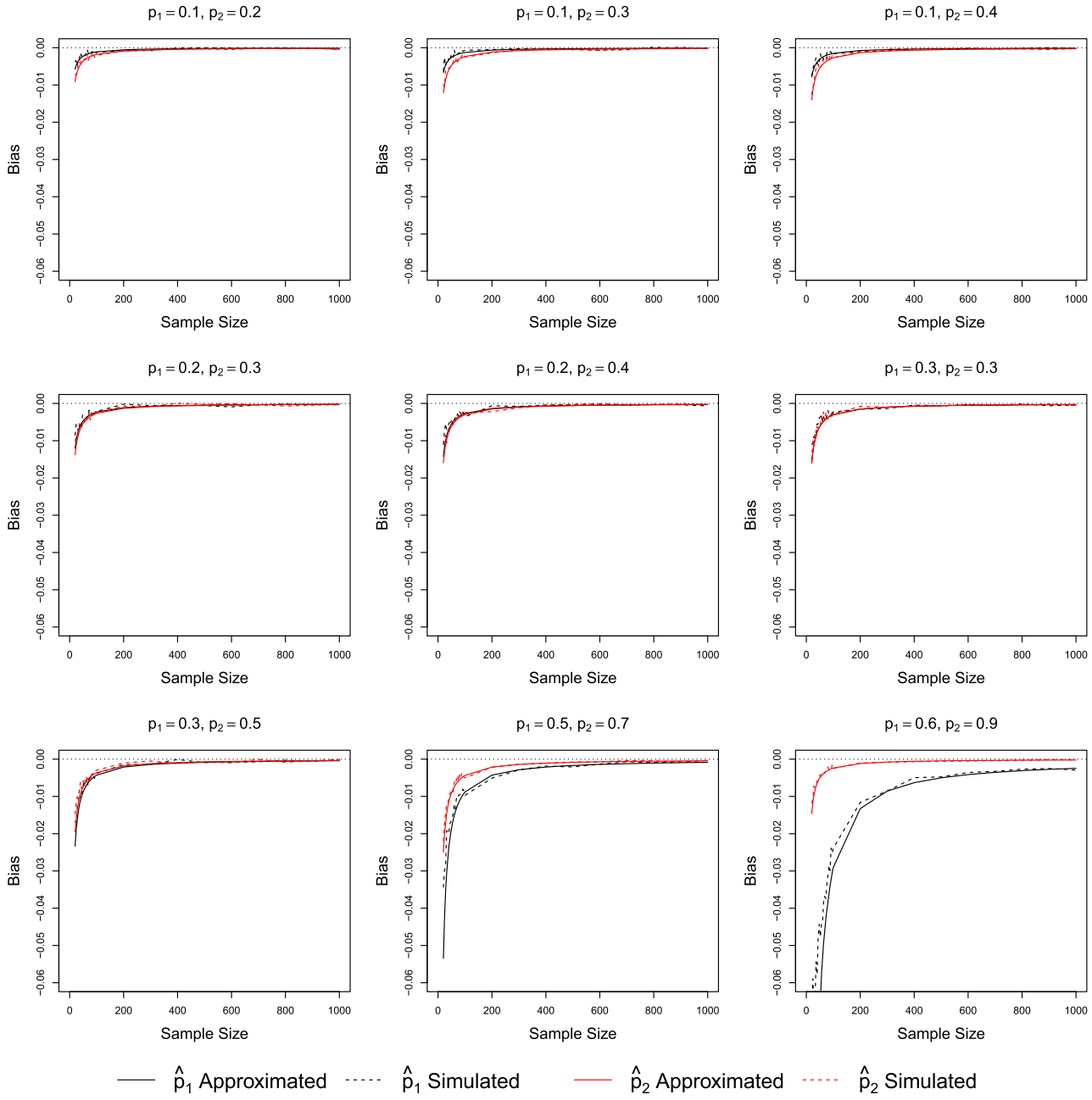

Figure 8. Bias of $\hat{p}_1$ and $\hat{p}_2$ using the SMLE procedure and varying the sample size from 20 *to* 1000.
Target allocation proportion for arm 1 is $q_2/(q_1+q_2)$ and p_1 and p_2 are settings of true response rates.

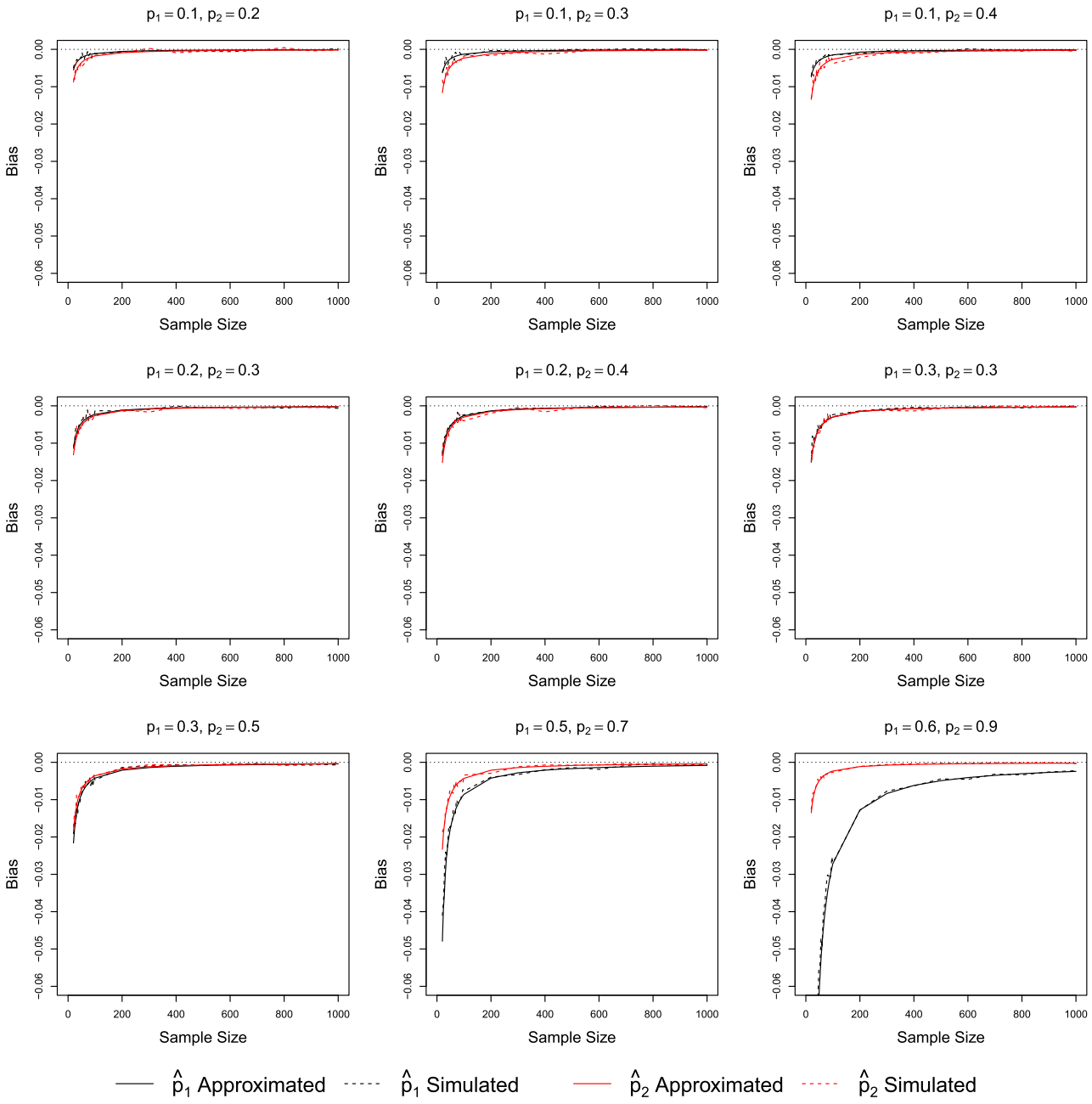

Figure 9. Bias of $\hat{p}_1$ and $\hat{p}_2$ using the DBCD procedure and varying the sample size from 20 *to* 1000.
Target allocation proportion for arm 1 is $q_2/(q_1+q_2)$ and p_1 and p_2 are settings of true response rates.

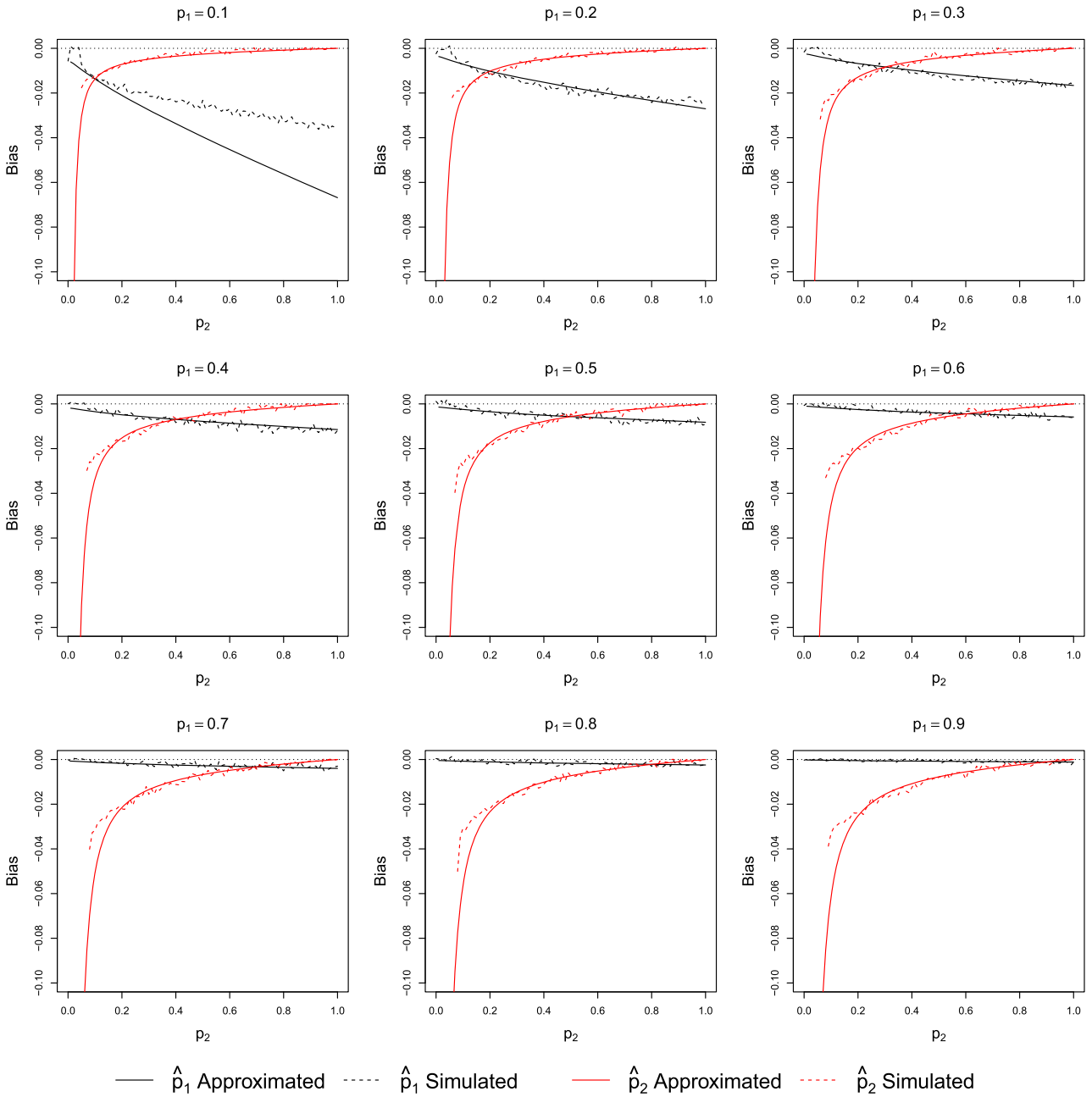

Figure 10. Bias of $\hat{p}_1$ and $\hat{p}_2$ using the SMLE procedure and varying p_1 and p_2.
Target allocation proportion for arm 1 is $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$ and $n = 50$.

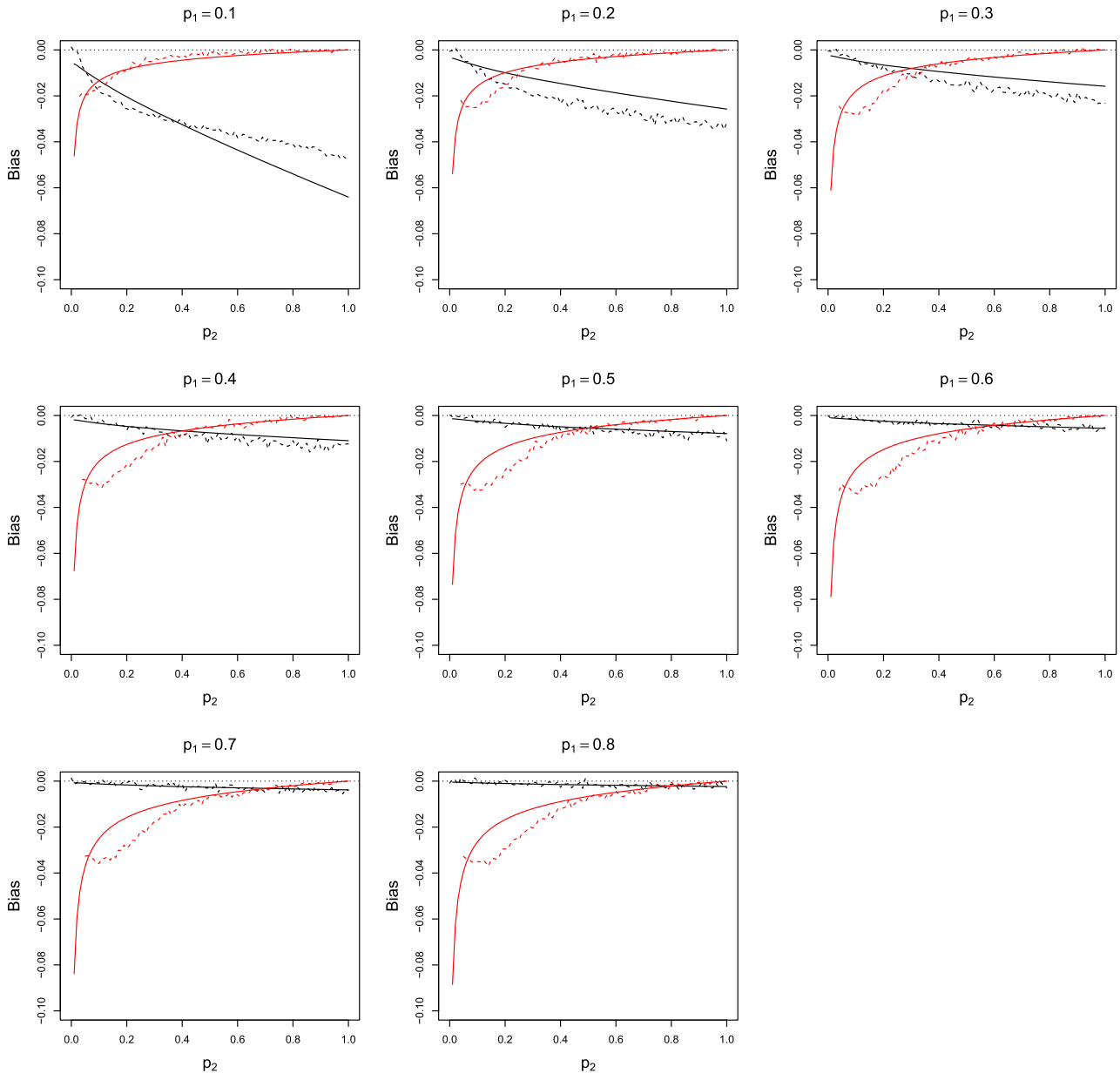

Figure 11. Bias of $\hat{p}_1$ and $\hat{p}_2$ using the DBCD procedure and varying p_1 and p_2.
Target allocation proportion for arm 1 is $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$ and $n = 50$.

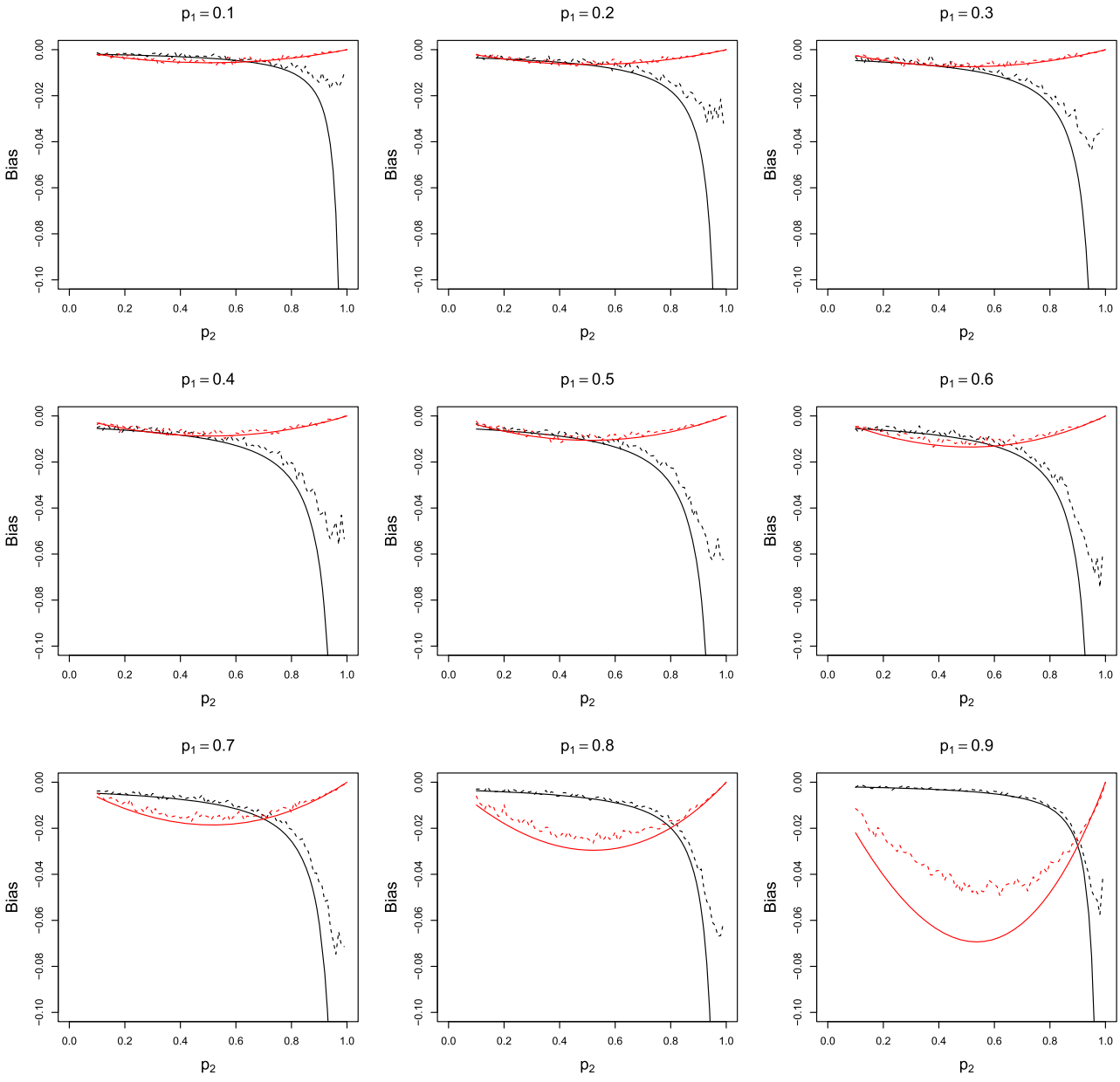

Figure 12. Bias of $\hat{p}_1$ and $\hat{p}_2$ using the SMLE procedure and varying p_1 and p_2.
Target allocation proportion for arm 1 is $q_2/(q_1+q_2)$ and $n = 50$.

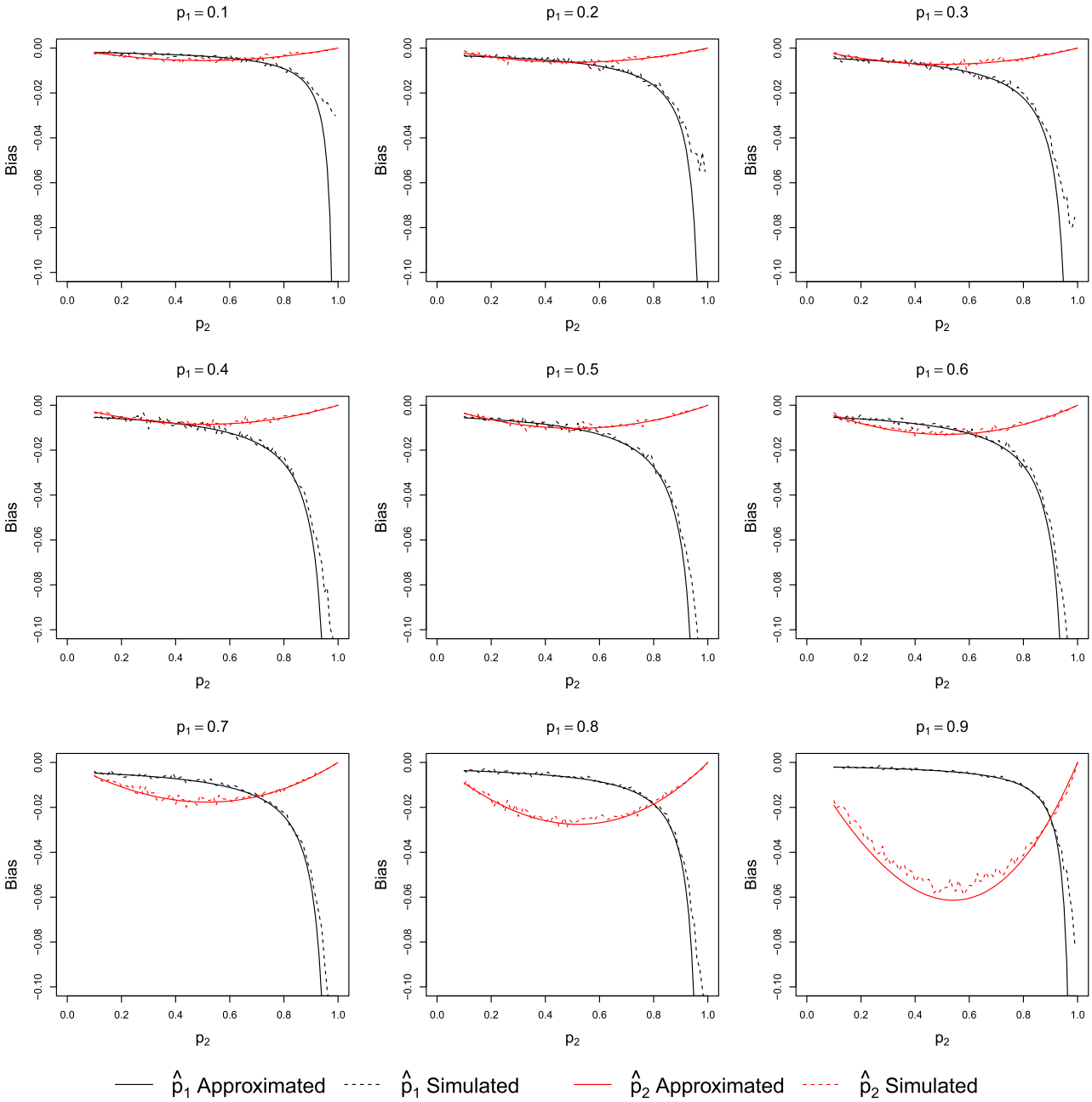

Figure 13. Bias of $\hat{p}_1$ and $\hat{p}_2$ using the DBCD procedure and varying p_1 and p_2.
Target allocation proportion for arm 1 is $q_2/(q_1 + q_2)$ and $n = 50$.

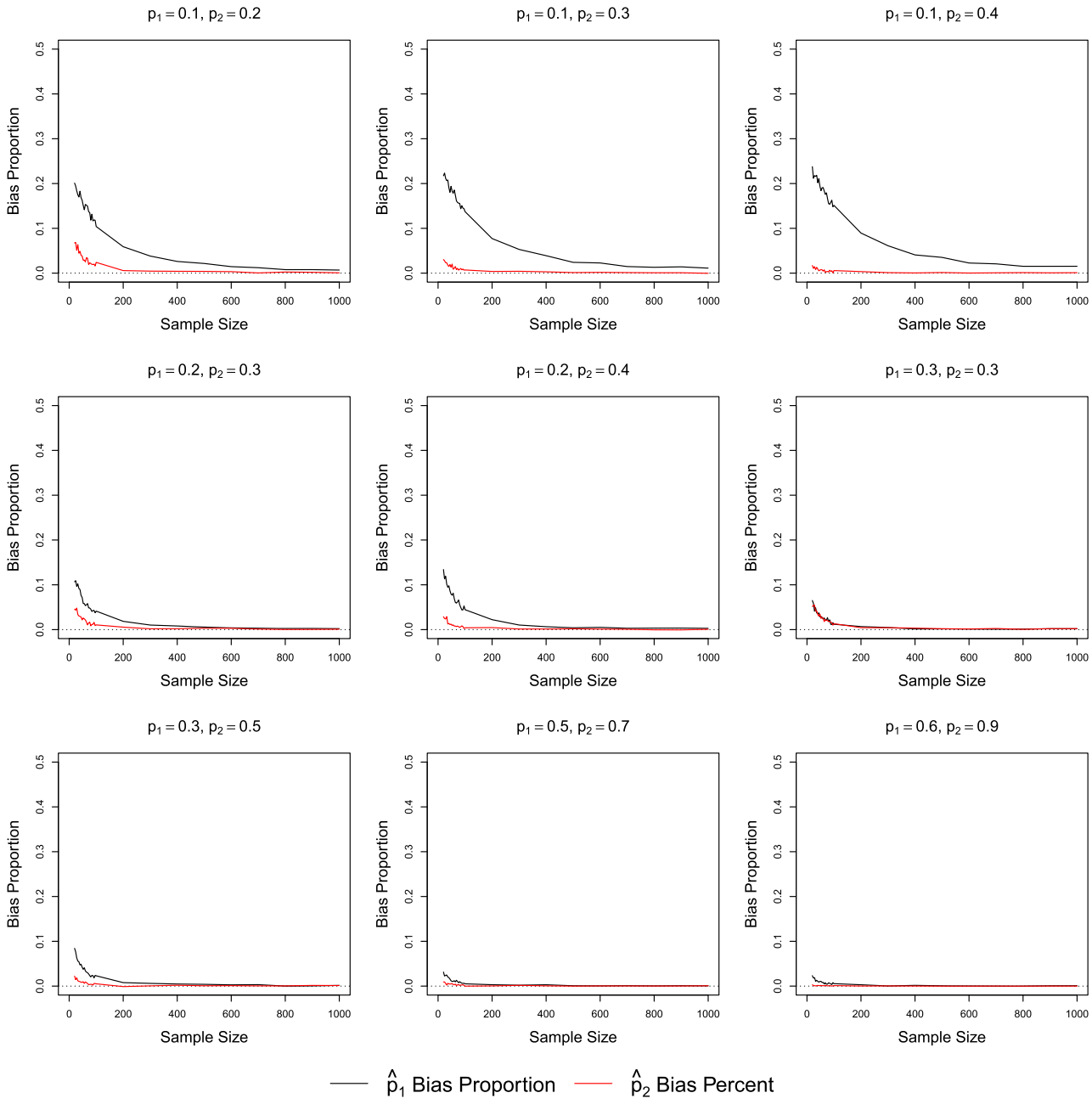

Figure 14. Bias proportion of $\hat{p}_1$ and $\hat{p}_2$ using the SMLE procedure and varying the sample size from 20 *to* 1000. Target allocation proportion for arm 1 is $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$ and p_1 and p_2 are settings of true response rates.

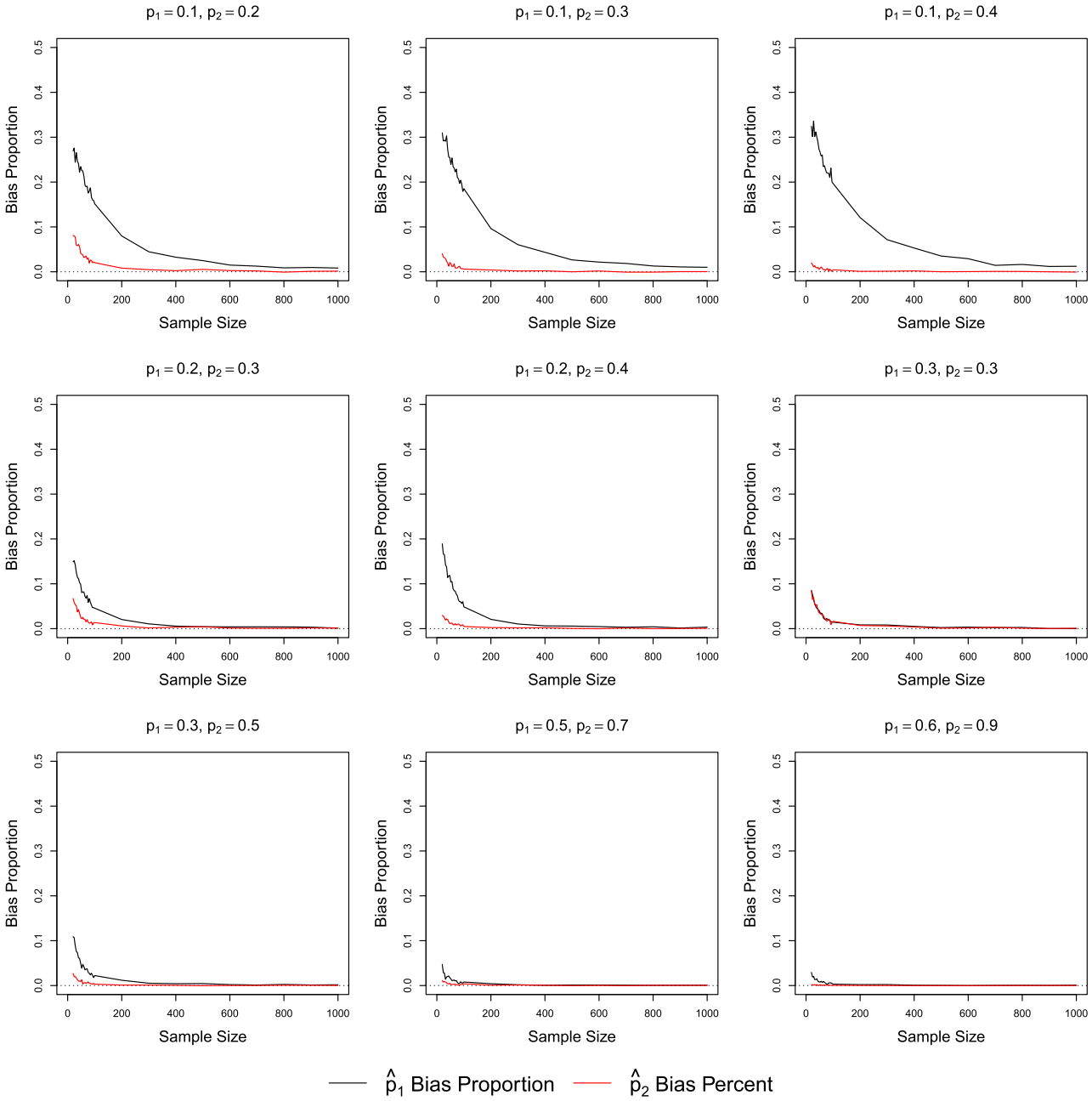

Figure 15. Bias proportion of $\hat{p}_1$ and $\hat{p}_2$ using the DBCD procedure and varying the sample size from 20 *to* 1000.
Target allocation proportion for arm 1 is $\sqrt{p_1}/(\sqrt{p_1}+\sqrt{p_2})$ and p_1 and p_2 are settings of true response rates.

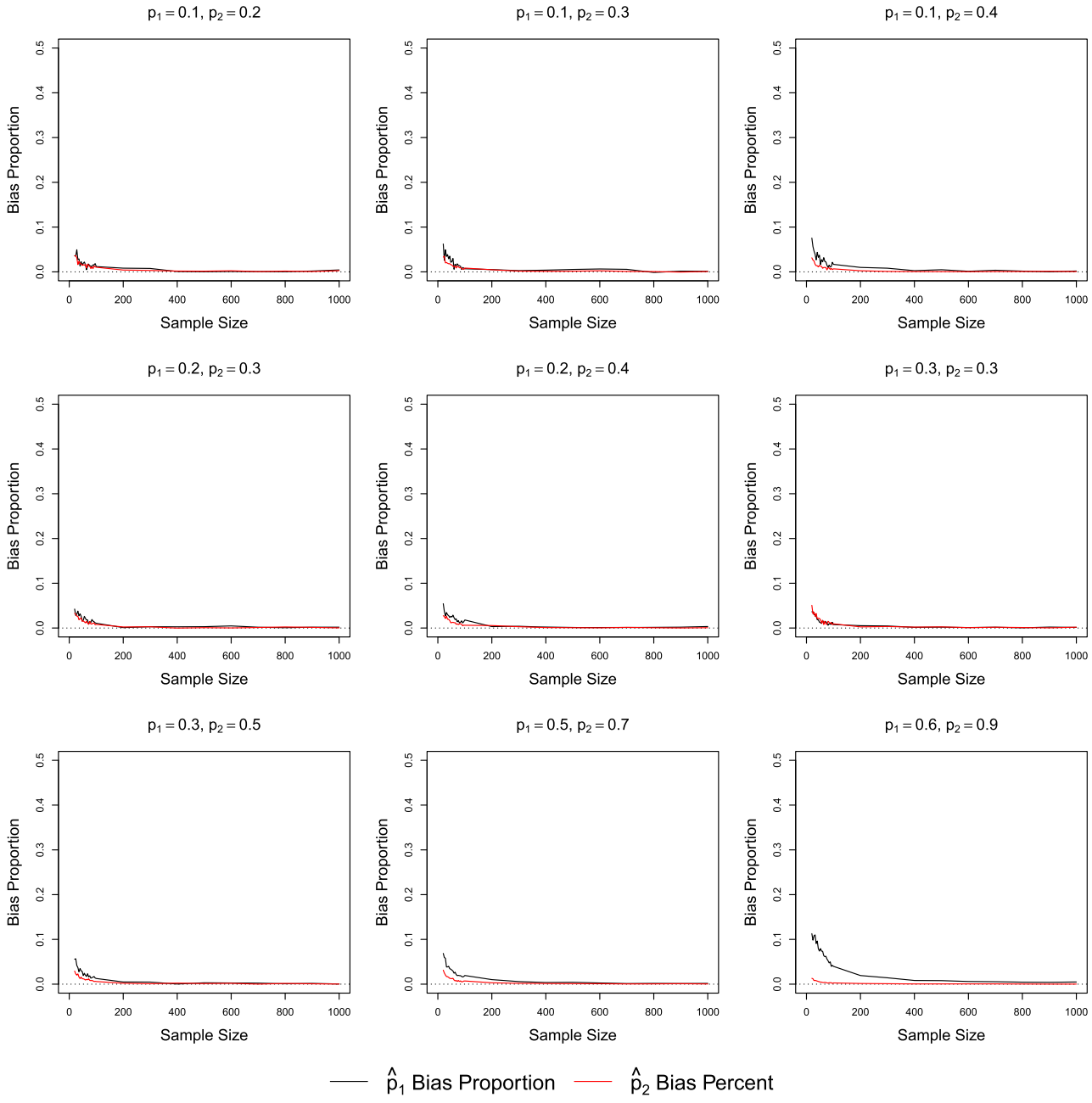

Figure 16. Bias proportion of $\hat{p}_1$ and $\hat{p}_2$ using the SMLE procedure and varying the sample size from 20 *to* 1000.
Target allocation proportion for arm 1 is $q_2/(q_1 + q_2)$ and p_1 and p_2 are settings of true response rates.

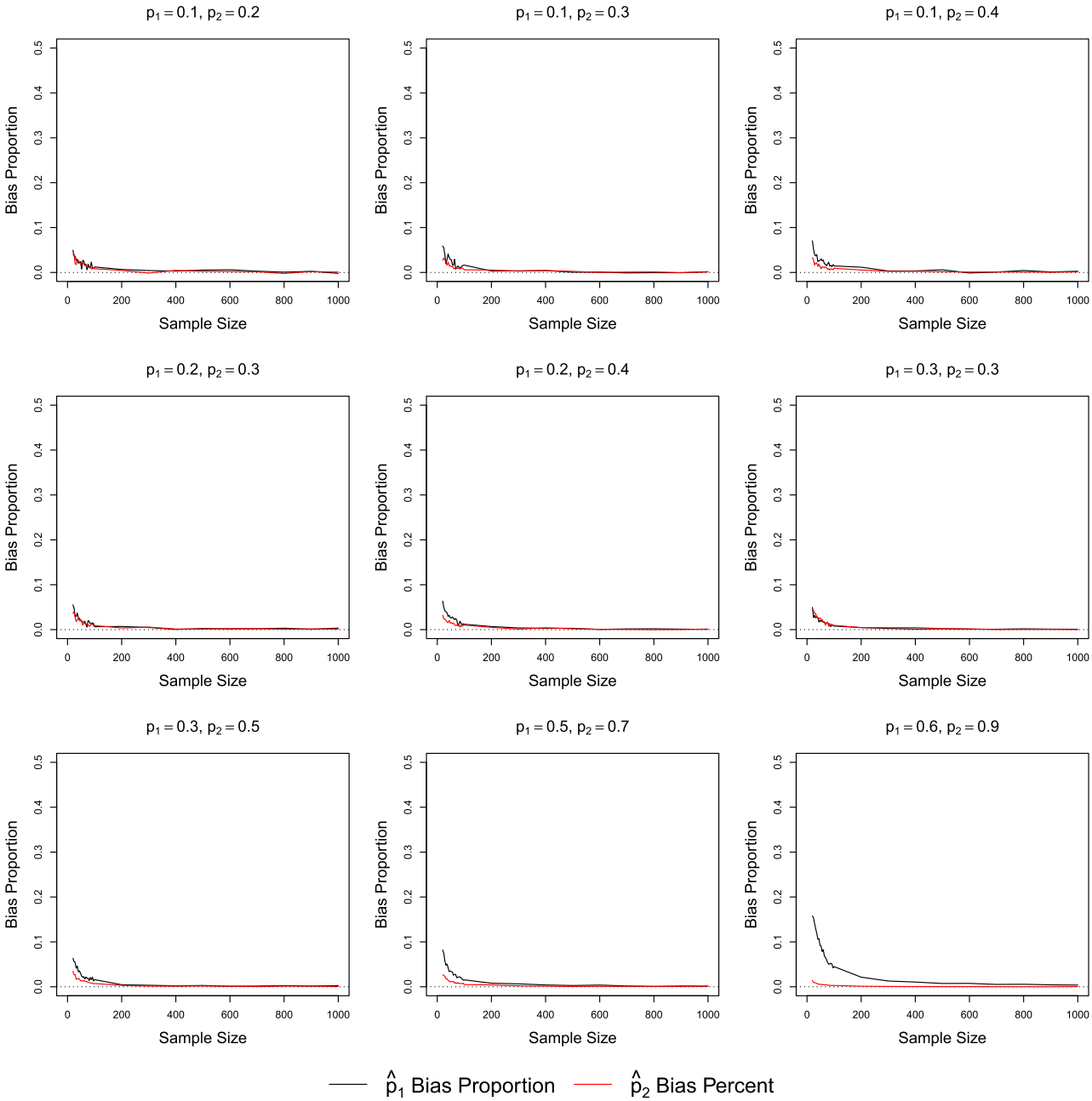

Figure 17. Bias proportion of $\hat{p}_1$ and $\hat{p}_2$ using the DBCD procedure and varying the sample size from 20 *to* 1000.
Target allocation proportion for arm 1 is $q_2/(q_1+q_2)$ and p_1 and p_2 are settings of true response rates.

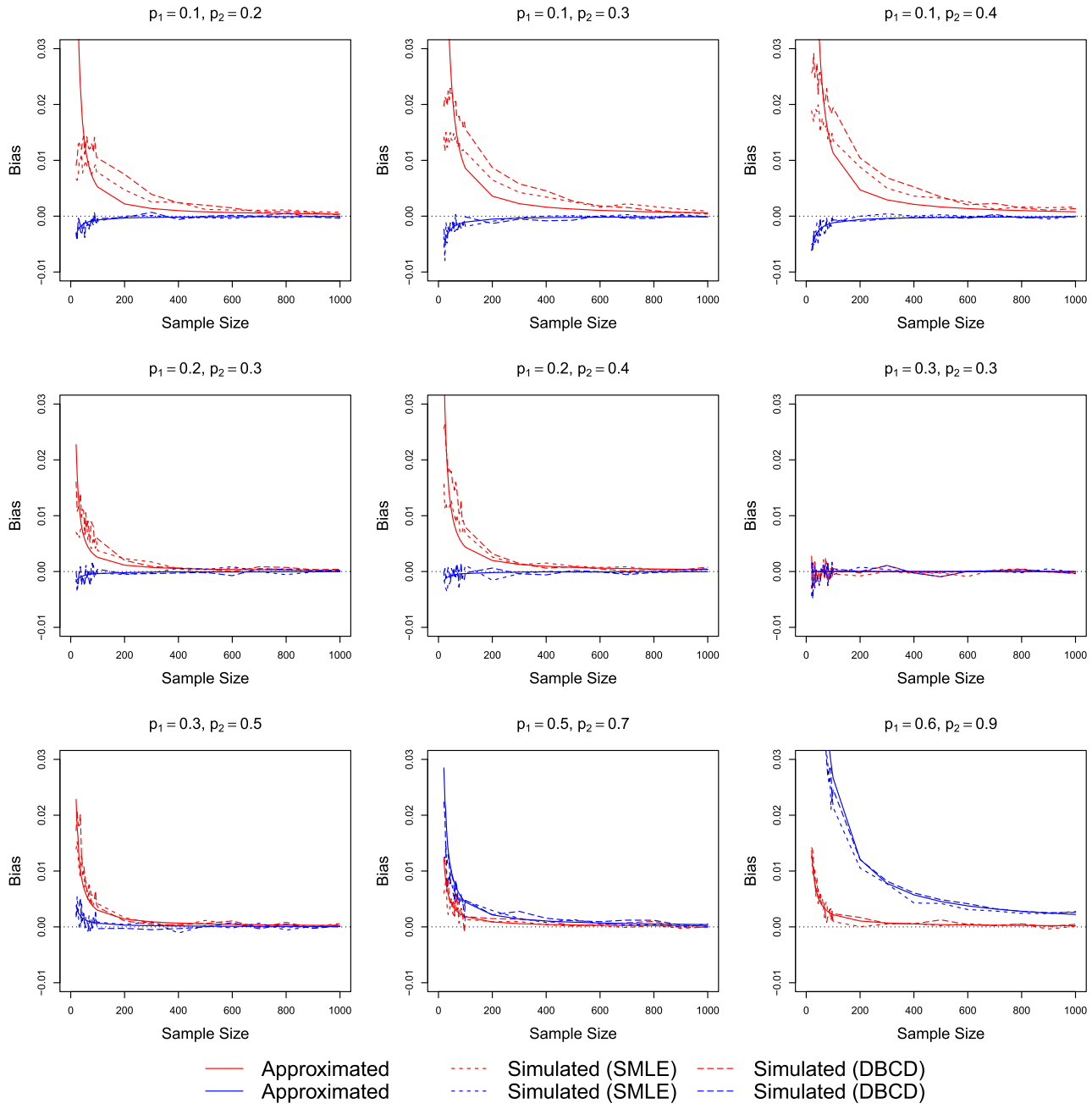

Figure 18. Bias of $\hat{p}_2 - \hat{p}_1$ using both procedures and varying the sample size from 20 *to* 1000.
Target allocation proportion for arm 1 is $\sqrt{p_1}/(\sqrt{p_1} + \sqrt{p_2})$ and $q_2/(q_1 + q_2)$ for red and blue lines respectively.

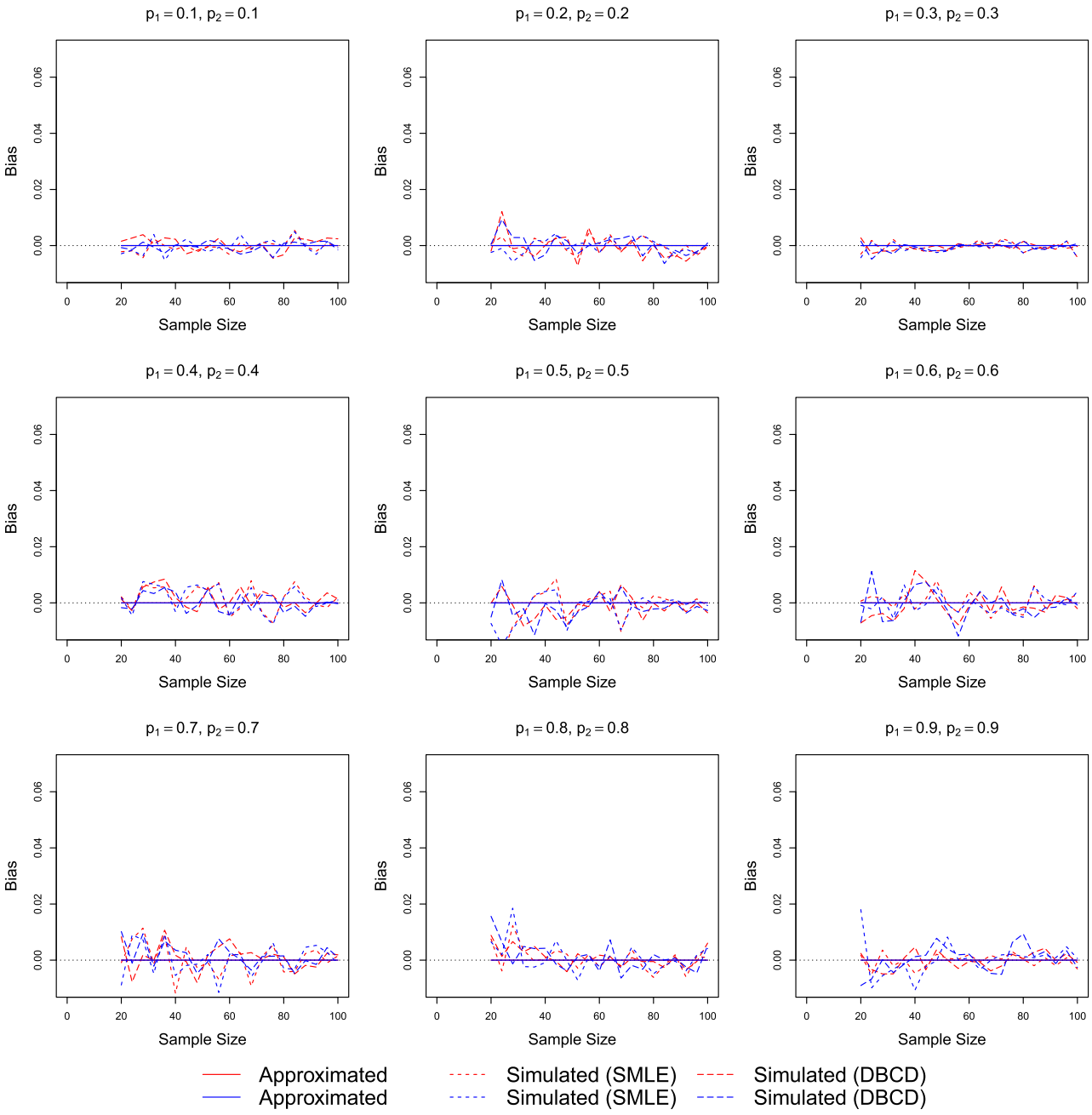

Figure 19. Bias of $\hat{p}_2 - \hat{p}_1$ using both procedures with $p_1 = p_2$.
Target allocation proportion for arm 1 is $\sqrt{p_1}/(\sqrt{p_1} + \sqrt{p_2})$ and $q_2/(q_1 + q_2)$ for red and blue lines respectively.

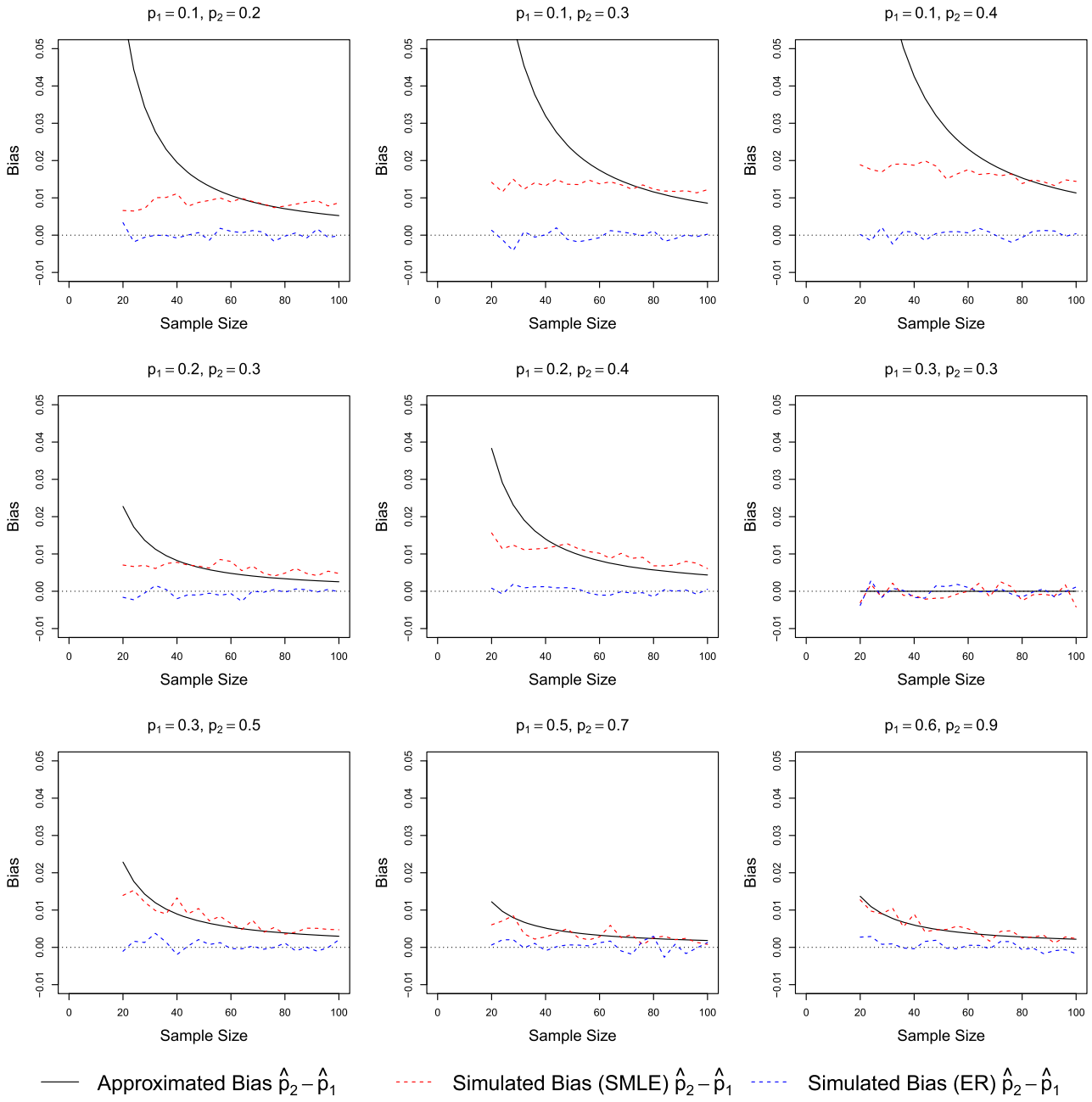

Figure 20. Bias of $\hat{p}_2 - \hat{p}_1$ using both ER and OAR (SMLE) and varying p_1 and p_2.

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CONFLICT OF INTEREST

This article reflects the views of the author and should not be construed to represent the FDA's views or policies. This work was completed outside of FDA.

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