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Bayesian methods to compare dose levels with placebo in a small n, sequential, multiple assignment, randomized trial

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Clinical trials studying treatments for rare diseases are challenging to design and conduct due to the limited number of patients eligible for the trial. One design used to address this challenge is the small n, sequential, multiple assignment, randomized trial (snSMART). We propose a new snSMART design that investigates the response rates of a drug tested at a low and high dose compared with placebo. Patients are randomized to an initial treatment (stage 1). In stage 2, patients are rerandomized, depending on their initial treatment and their response to that treatment in stage 1, to either the same or a different dose of treatment. Data from both stages are used to determine the efficacy of the active treatment. We present a Bayesian approach where information is borrowed between stage 1 and stage 2. We compare our approach to standard methods using only stage 1 data and a log-linear Poisson model that uses data from both stages where parameters are estimated using generalized estimating equations. We observe that the Bayesian method has smaller root-mean-square-error and 95% credible interval widths than standard methods in the tested scenarios. We conclude that it is advantageous to utilize data from both stages for a primary efficacy analysis and that the specific snSMART design shown here can be used in the registration of a drug for the treatment of rare diseases.

KEYWORDS
adaptive randomization, clinical trial, repeated measures

1 | INTRODUCTION

A rare disease is defined as a disease that affects fewer than 200 000 people in the United States.[1] Taken together, there are more than 8000 rare diseases that affect over 30 million people in the United States.[2] Unfortunately, only 289 (4%) of these rare diseases have an approved drug, leaving 96% of rare diseases without an approved treatment and considerable unmet need for many patients.[3] Because of the limited number of individuals affected by rare diseases, it is difficult to find effective treatments for these conditions.[4] Approval of any drug is based on the same requirements for evidence of effectiveness, regardless of the size of the diseased population. While randomized clinical trials (RCTs) are utilized to demonstrate the strongest scientific evidence of an effective treatment, these trials are often difficult or impossible in rare disease settings because they require a large number of subjects. As a result, many RCTs involving rare diseases often have reduced power when compared with studies of diseases that are not rare.[5] To combat these issues, Tamura et al[6]

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previously proposed a small n, sequential, multiple assignment, randomized trial (snSMART) design to investigate three active treatments for a rare disease. Here, we propose a variation of the snSMART design that focuses on a single drug and placebo.

In many situations, there is only a single, novel drug of interest and the objective of a clinical trial is to determine efficacy of that drug. As an example, the Vasculitis Clinical Research Consortium was recently interested in testing a novel drug for patients suffering from granulomatosis with polyangitis (GPA) or microscopic polyangitis (MPA), forms of vasculitis characterized by inflammation of the blood vessels. The binary endpoint of the study was remission after 3 weeks of therapy. It was assumed, however, that an effective drug would have to be taken for longer than 3 weeks in practice. The trial needed to be placebo controlled and the investigators were interested in novel designs that could potentially increase the power of detecting a drug effect. Given that vasculitis is a rare disease, it was also necessary that the trial design was appropriate for small sample sizes.

An snSMART is a variation of a SMART design[7,8] that is specifically intended for small samples. In a SMART, patients are randomized to at least two sequential interventions in such a way that the second intervention assignment depends on the patient's response to the first intervention. The goal of a SMART is often to develop effective dynamic treatment regimens (DTRs) that specify an initial treatment for a patient followed by subsequent treatment, that is tailored by response to the initial treatment.[9,10] In contrast, the stages in an snSMART are used to garner more information from a smaller set of subjects rather than to identify sequences of treatments tailored to an individual. In other words, snSMARTs are not designed with the goal of developing or estimating the effects of DTRs. Instead, the goal of an snSMART is to efficiently use data across the two stages of the trial to find a single superior treatment or dose of treatment in a small sample of individuals.

Indeed, there have been previous examples of repurposing well-developed trial designs to address novel goals. For example, randomized discontinuation trials have been studied as an alternative phase II design in oncology.[11] In addition, randomized discontinuation trials have been modified using SMART designs in order to answer a wider variety of clinical questions.[12] Researchers have also considered some enhanced crossover designs in the rare diseases spectrum to address the concerns about the unnecessary exposure to placebo or treatment of high toxicity. For example, Makubate and Senn[13] and Nason and Follmann[14] both discussed designs that allow for discontinuation from the study according to the absorbed binary endpoints after a subject receives the first treatment. Honkanen et al[15] introduced an alternative design that consists of an initial randomized placebo-controlled stage, a randomized withdrawal stage for subjects who responded, and a third randomized stage for placebo nonresponders who subsequently respond to treatment.

In the snSMART design of Tamura et al (2016), three unique, active experimental treatments were compared. We propose extending this design to a three-arm trial comparing placebo with low and high doses of one experimental treatment (Figure 1). In such a trial, patients are initially randomized at stage 1 to either receive placebo, low dose, or high dose with equal likelihood. Patients receive this treatment for a prespecified amount of time, at which time their binary response status is ascertained. In stage 2, patients are rerandomized to either the same or a different dose of treatment depending on their initial treatment and their response to that treatment. Specifically, patients who received placebo at stage 1 are rerandomized to receive either low dose or high dose at stage 2, regardless of their stage 1 response. This is advantageous for patients because it means that everyone enrolled in the trial will receive an active treatment by stage 2, even if they were initially randomized to placebo. All patients who initially received low dose, regardless of their response status, are rerandomized to either low dose or high dose. In the case of patients who responded to low dose, this rerandomization is appropriate because it allows patients to either receive a higher dose of the drug that is already effective for them or to continue receiving low dose. Receiving low dose again is advantageous for patients because they continue receiving a drug they respond to and advantageous for the trial because we gain more information about the response rate to low dose in stage 2 of the study. All patients who did not respond to high dose receive high dose again in stage 2, whereas patients who initially responded to high dose are rerandomized to receive either high dose again or low dose. In this design, the primary objective is to estimate the difference in the probability of response to treatment between low dose and placebo and between high dose and placebo.

Compared with other rare diseases and clinical trial designs, this snSMART design is advantageous for three reasons. First, this design allows for the comparison of treatment against placebo, which is necessary to demonstrate efficacy of an experimental treatment. Second, this design allows for the comparison of more than one dosage level of a drug, so that a lower, less toxic dose may be shown to be efficacious as opposed to investigating only a high dose. Third, individuals who respond to treatment in stage 1 may continue their original dose or may increase or decrease dose. All participants receive an active treatment at some point in the trial. In addition, those who receive a low dose or high dose of the drug will continue to receive the drug at some level in both stages because there are no participants randomized to placebo in

stage 2. These factors may improve patient engagement and recruitment, which is a challenge in the study of rare diseases. Wei et al[16] demonstrated efficiency gains of the previous snSMART design compared with a one stage design, but such advantages have not yet been confirmed for this setting.

In Section 2, we propose Bayesian and frequentist methods to analyze data for the primary efficacy analysis of the proposed snSMART design by borrowing information across patients and between trial stages. In the Bayesian model, we incorporate expert opinion and experience by using mildly informative prior distributions that are more flexible than those considered in Wei et al (2018). In Section 3, we assess the influence of the prior distributions through simulation. We compare the Bayesian model to a frequentist model that also jointly models the response rates across the two stages of the snSMART. Both models are compared with models using only stage 1 data to illustrate the potential efficiency gain of the two-stage design. In Section 4, we complete our article with a discussion.

2 | METHODS

2.1 | Bayesian joint stage model

For each subject $i = 1, \ldots, N$, stage of the snSMART j = 1, 2 and treatment k = P, L, H, where N denotes the sample size, P denotes placebo, L denotes low dose, and H denotes high dose, let Y_{ijk} be the observed binary response outcome where 1 corresponds to "response" and 0 corresponds to "no response" to treatment. The stage 1 outcome and the stage 2 outcome given the stage 1 outcome are each modeled as Bernoulli random variables. The stage 1 response rate for treatment k is denoted as π_k. The stage 2 response rate for stage 1 responders to treatment k who receive treatment k′ in stage 2 is equal to $\beta_{1k}\pi_{k'}$. For nonresponders to treatment k in stage 1 who receive treatment k* in stage 2, the stage 2 response rate is equal to $\beta_{0k}\pi_{k^*}$. Thus we have six unique linkage parameters that link stage 1 response to stage 2 response. Our proposed Bayesian joint stage model (BJSM) is as follows:

$$Y_{i1k}|\pi_k \sim Bernoulli(\pi_k), \tag{1}$$

$$Y_{i2k'}|\pi_k, \beta_{1k}, Y_{i1k} = 1 \sim Bernoulli(\beta_{1k}\pi_{k'}), \tag{2}$$

$$Y_{i2k^*}|\pi_k, \beta_{0k}, Y_{i1k} = 0 \sim Bernoulli(\beta_{0k}\pi_{k^*}). \tag{3}$$

Assumptions and prior distributions for the parameters are based on clinician input. Here, we incorporate prior knowledge about disease and current treatments and assume that an ineffective treatment has a response rate of 15% and thus use an informative prior Beta(3, 17) for π_P. It is a setting similar to the GPA/MPA example mentioned in the Introduction. For the effect of low and high dose, we allow for a weak tendency for the drug response rates to be greater than the effect of placebo and assume that the logarithm of treatment effect ratio follows a Gaussian prior distribution N(μ, σ^2), that is, $\log(\pi_L/\pi_P) \sim N(0.2,100)$ and $\log(\pi_H/\pi_P) \sim N(0.2,100)$. Note that $E(\pi_L/\pi_P) = e^{0.2} \approx 1.2$ under the proposed prior setting.

Wei et al (2018) assumed that the linkage parameters (i) did not depend on the initial treatment and that, (ii) $\beta_0 \leq 1$ and (iii) $\beta_1 > 1$. Here, since both responders and nonresponders are rerandomized and we are testing for a potential dose-response relationship between treatment arms, these previous assumptions are not appropriate. In our simulations, instead of assuming the Beta and Pareto priors used by Wei et al (2018), we consider Gamma priors so that the linkage parameters can span the positive real line.

2.2 | Log-linear Poisson joint stage model

The log-linear Poisson joint stage model (LPJSM) presented in Wei et al (2018) is slightly adjusted for our design. The LPJSM jointly models the stage 1 and stage 2 outcomes with a log link for interpretability. The LPJSM is shown below where there is a one-to-one correspondence to the parameters in the Bayesian model in Equations (1)-(3). Let Y_{ij} be the response of subject i in stage j ($j = 1, 2$), where $I(k_{ij} = k)$ is the indicator function for treatment k = P, L, H for subject i in stage j, then the LPJSM is as follows:

$$log(P(Y_{i1})) = \alpha_1 I(k_{i1} = P) + \alpha_2 I(k_{i1} = L) + \alpha_3 I(k_{i1} = H),$$

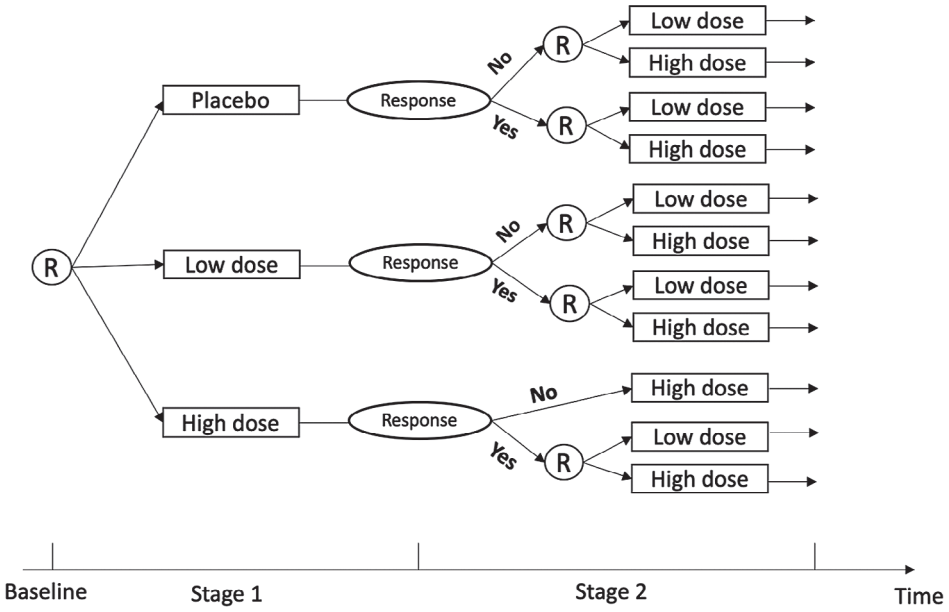

FIGURE 1 Study design of the proposed snSMART. Participants are randomized (R) to one of the first stage treatment arms, placebo, low dose or high dose equally (1:1:1). At the end of stage 1, patients are rerandomized to their second stage treatment based on their response status. Outcomes are collected at the end of stage 1 and stage 2

$$\begin{aligned} log(P(Y_{i2})) = {} & \alpha_1 I(k_{i2} = P) + \alpha_2 I(k_{i2} = L) + \alpha_3 I(k_{i2} = H) + \alpha_4 I(k_{i1} = P, Y_{i1} = 0) \\ & + \alpha_5 I(k_{i1} = P, Y_{i1} = 1) + \alpha_6 I(k_{i1} = L, Y_{i1} = 0) + \alpha_7 I(k_{i1} = L, Y_{i1} = 1) \\ & + \alpha_8 I(k_{i1} = H, Y_{i1} = 0) + \alpha_9 I(k_{i1} = H, Y_{i1} = 1). \end{aligned}$$

Here we have nine estimated coefficients where α_1, α_2, and α_3 represent the log response rates of placebo, low, and high dose. Coefficients α_4-α_9 correspond to the six linkage parameters in the Bayesian model. The Poisson family is used to model the variance of the outcome to overcome convergence problems with log-binomial models in small samples.[17] The parameters are estimated via generalized estimating equations assuming an independent correlation structure. The variance of the LPJSM is corrected through robust sandwich estimators.

TABLE 1 Scenarios and priors for the simulation settings

BJSM prior for all scenarios	Response rates/linkage parameters	Scenarios			
		P = L = H	P < L < H	P < L = H	P = H < L
Beta(3,17)	π_P	0.15	0.15	0.15	0.15
$\log(\pi_L/\pi_P) \sim N(0.2,100)$	π_L	0.15	0.25	0.4	0.4
$\log(\pi_H/\pi_P) \sim N(0.2,100)$	π_H	0.15	0.35	0.4	0.15
Gamma(2,2)	β_{0P}	0.9	0.9	0.9	0.9
Gamma(2,2)	β_{1P}	1.3	1.3	1.3	1.3
Gamma(2,2)	β_{0L}	0.8	0.8	0.8	0.8
Gamma(2,2)	β_{1L}	1.2	1.2	1.2	1.2
Gamma(2,2)	β_{0H}	0.7	0.7	0.7	0.7
Gamma(2,2)	β_{1H}	1.1	1.1	1.1	1.1

Note: π_k is the first stage response rate for treatment k, $k = P, L, H$, where P = placebo, L = low dose, H = high dose. β_{1k} is the linkage parameter for first stage responders who receive treatment k in stage 1. β_{0k} is the linkage parameter for first stage nonresponders who receive treatment k in stage 1. Simulations are done under four scenarios: (i) P = L = H (low and high dose are both as effective as placebo), (ii) P < L < H (placebo is less effective than low dose, and low dose is less effective than high dose), (iii) P < L = H (low dose and high dose are equally effective, and they are more effective than placebo), and (iv) P = H < L (low dose is effective but high dose is not). BJSM prior setting (column 1) is where we use Gamma(2, 2) for all linkage parameters to relax the restriction of priors.

TABLE 2 Simulated bias and root-mean-square error (rMSE) for the estimators of π_k

		BJSM		LPJSM		BFSM		FSMLE	
Scenario		**Bias**	**rMSE**	**Bias**	**rMSE**	**Bias**	**rMSE**	**Bias**	**rMSE**
(1) P = L = H	π_P	−0.001	0.039	0.018	0.063	−0.001	0.039	−0.001	0.065
	π_L	−0.003	0.048	0.022	0.062	−0.005	0.062	0.000	0.064
	π_H	−0.007	0.043	0.020	0.062	−0.005	0.062	0.000	0.064
	π_L-π_P	−0.003	0.062	0.004	0.081	−0.005	0.073	0.001	0.091
	π_H-π_P	−0.006	0.058	0.002	0.087	−0.005	0.073	0.000	0.091
(2) P < L < H	π_P	0.000	0.039	0.009	0.063	0.000	0.039	0.000	0.065
	π_L	−0.005	0.057	0.014	0.068	−0.011	0.078	−0.003	0.080
	π_H	−0.013	0.064	−0.001	0.075	−0.013	0.084	−0.001	0.860
	π_L-π_P	−0.005	0.070	0.004	0.092	−0.011	0.087	−0.003	0.102
	π_H-π_P	−0.013	0.074	0.011	0.101	−0.012	0.093	−0.001	0.108
(3) P < L = H	π_P	0.000	0.040	0.007	0.064	0.000	0.040	−0.001	0.067
	π_L	−0.009	0.066	0.000	0.076	−0.013	0.087	0.000	0.089
	π_H	−0.012	0.065	0.000	0.074	−0.015	0.087	−0.003	0.089
	π_L-π_P	−0.009	0.077	−0.006	0.097	−0.013	0.096	0.001	0.112
	π_H-π_P	−0.012	0.076	−0.006	0.099	−0.015	0.096	−0.002	0.111
(4) P = H < L	π_P	−0.001	0.039	0.014	0.063	−0.001	0.039	−0.001	0.065
	π_L	−0.011	0.068	−0.023	0.081	−0.011	0.086	0.002	0.088
	π_H	−0.003	0.044	0.030	0.060	−0.004	0.063	0.001	0.065
	π_L-π_P	−0.010	0.078	−0.037	0.104	−0.010	0.094	0.002	0.109
	π_H-π_P	−0.003	0.059	0.016	0.083	−0.003	0.075	0.002	0.093

Note: π_k is the stage 1 response rate for treatment k, $k = P, L, H$, where P = placebo, L = low dose, and H = high dose. Scenarios are given in Table 1. Four modeling approaches: Bayesian joint stage modeling (BJSM), log-linear Poisson joint stage modeling (LPJSM), Bayesian first stage modeling (BFSM), and first stage maximum likelihood estimation (FSMLE) are compared. The sample size per treatment arm is 30.

3 | SIMULATIONS

In our simulations, we first assume that our drug of interest is ineffective and consider trials in the null scenario, that is, the response rate of placebo, low dose, and high dose are all equal (scenario 1, P = L = H). Under the assumption that the drug of interest is effective, we consider three additional scenarios. In scenario 2, a dose-response relationship occurs, that is, higher dose relates to higher treatment effect (response rates such that P < L < H). In scenario 3, no dose response occurs between low and high dose, so that the response rate of P < L = H. Lastly, we consider an unlikely, but possible setting in scenario 4 where no dose response occurs and low dose is effective but high dose is not, so that the response rate of P = H < L. We selected the Gamma(2, 2) prior for all linkage parameters, understanding this allows for positive probability for $\beta_{1k}\pi_{k'}$ and $\beta_{0k}\pi_{k*}$ to be greater than 1. We chose Gamma(2,2) as the prior for all $\beta_{1k}\pi_{k'}$ and $\beta_{0k}\pi_{k*}$ for three reasons: (i) simplicity, (ii) the distribution ranges from 0 to 3 for most of the random draws, which serves as a restriction to the prior distributions of the linkage parameters, and (iii) the distribution is centered at 1 with variance equal to 0.5, which allows for flexibility of the prior distribution of the linkage parameters to be below or above 1. This third property allows stage 1 responders the possibility to worsen in the second stage if they decrease dose and stage 1 nonresponders the possibility to respond if they increase dose. See Table 1 for the scenarios and priors we used in simulations.

In the data generating process, we simulated 2000 realizations per scenario under the four settings in Table 1. For each realization, $N/3$ subjects were assigned to each treatment arm in stage 1, with a total sample size N. Responses to stage 1 were computed as random Bernoulli variables with the proposed response rates under different scenarios (Table 1,

columns 3-6). Subjects were then rerandomized equally to their stage 2 treatment based on their stage 1 treatment and stage 1 response. Stage 2 responses were computed using formulas (2) and (3) under the different scenarios. We compared bias, root mean-square error (rMSE), coverage rates, and widths of the 95% credible/confidence intervals (CIs) between the proposed BJSM, LPJSM, a Bayesian method using only the first stage data (BFSM), and a maximum likelihood method (FSMLE) using only the first stage data.

The 95% CI for BJSM and BFSM are the narrowest intervals that include 95% of the posterior distribution of π_k, while the 95% CI for LPJSM and FSMLE are the asymptotic, normal-approximation 95% confidence intervals. The R package rjags was used to generate the posterior distributions of π_k, β_{1k}, and β_{0k}, and the R package gee was used to estimate the parameters defined in LPJSM.

3.1 | Results

In this section, we present simulation results for the snSMART design in Figure 1 with sample sizes of N = 90. Results for N = 300 and N = 45 can be found in Table A1 through A3 in the Appendix.

For all scenarios, Table 2 gives the bias and rMSE for estimators of the stage 1 response rates for placebo, low dose, and high dose. In the null scenario (scenario 1, P = L = H), we note that BJSM, BFSM, and FSMLE provide estimators of the difference in response rates and of individual response rates with small bias. While the estimators for the difference in response rates in LPJSM is comparable with the other methods, we see that the bias in the point estimates of π_P, π_L, and π_H is much larger than the other methods. This is likely because there are few patients that respond to treatment in the trial. We also note that BJSM estimators have the smallest rMSEs out of all methods.

For scenario 2 (P < L < H), there is, on average, low to no bias for the response rate estimators for each dose level. Looking specifically at the estimation of the placebo response rate, we see that there is no bias, on average, for BJSM, BFSM, and FSMLE. In the LPJSM method, the smallest bias is in the estimator of π_H. This is likely due to the large number of participants in the trial that receive high dose. The estimators of π_P and π_L likely have higher bias in the LPJSM because there are fewer patients that receive placebo and low dose in the trial. The estimator of π_H, however, has the largest bias in the Bayesian methods (BJSM and BFSM). The bias of the high dose response rate estimate is likely large because the true value of π_H in scenario 2 is 0.35, which is relatively far from the prior mean (0.183) for stage 1 response rates. In comparison, in BJSM and BFSM the estimator of π_L has less bias than that of π_H, presumably because the true value of π_L is 0.25, which is closer to 0.183. Looking at rMSE, we observe that the BJSM method estimators of π_P, π_L, and π_H have the lowest rMSE out of the estimators we compared. While the FSMLE approach has very low bias, it tends to have the largest rMSE out of the compared methods because it only models first-stage outcomes. When we consider the estimators for the difference between placebo and low and high dose response rates, we see that all methods provide estimators with small bias. The estimators for the difference in response rates for placebo vs low and high dose of the BJSM have the smallest rMSEs out of all methods.

In scenario 3 (P < L = H), we see small bias for the response rate estimators, specifically for the LPJSM and FSMLE methods. Looking at the BJSM and BFSM results, we see that the bias is negligible for the estimators of π_P, but slightly larger for estimators of π_L and π_H. In contrast, the LPJSM estimators of π_L and π_H have negligible bias, but the estimator of π_P is slightly higher. As in scenario 2, the bias in the Bayesian methods is due to the difference between the true value of the parameters (0.40) and the prior mean (0.183). We expect to see larger bias in the estimation of π_P from the LPJSM because few patients are randomized to placebo. The BJSM provides response rate estimators for placebo, low dose, and high dose with the smallest rMSEs out of all methods. Again, we see that BFSM and FSMLE have larger rMSE than the joint stage modeling procedures. The results of scenario 3 for the bias and rMSE of the estimators of response rate differences are similar to that of scenario 2.

In scenario 4 (P = H < L), we once again see similar patterns in bias and rMSE of response rate estimators to scenarios 2 and 3. Again, estimators for the difference in response rate estimators generally have small bias, and the BJSM estimators have the smallest rMSE out of all methods.

It should be noted that across all four scenarios, the efficiency gain observed using joint stage modeling approaches, compared with BFSM and FSMLE, is not large for the estimators of π_P. We see little efficiency gain using joint stage approaches because no one is randomized to placebo treatment in stage 2 of the design. As such, first stage methods are comparable with joint stage methods in estimating π_P. We do, however, see modest efficiency gains using joint stage modeling approaches for the estimators of π_L-π_P and π_H-π_P. Since the estimation of π_L-π_P and π_H-π_P is typically of greater interest than the estimation of π_P, the efficiency gains we observe represent an advantage of using BJSM procedures.

TABLE 3 Simulated width and 95% coverage rate (CR) for the estimators of π_k

		BJSM		LPJSM		BFSM		FSMLE	
Scenario		**CR**	**Width**	**CR**	**Width**	**CR**	**Width**	**CR**	**Width**
(1) P = L = H	π_P	0.98	0.187	0.97	0.261	0.99	0.187	0.94	0.245
	π_L	0.93	0.183	0.95	0.229	0.87	0.221	0.95	0.246
	π_H	0.93	0.171	0.95	0.228	0.87	0.221	0.95	0.246
(2) P < L < H	π_P	0.98	0.187	0.96	0.254	0.99	0.187	0.94	0.246
	π_L	0.94	0.225	0.94	0.263	0.88	0.280	0.94	0.304
	π_H	0.94	0.256	0.94	0.298	0.92	0.317	0.91	0.335
(3) P < L = H	π_P	0.98	0.186	0.96	0.252	0.98	0.187	0.94	0.245
	π_L	0.95	0.267	0.94	0.296	0.94	0.327	0.93	0.346
	π_H	0.94	0.261	0.95	0.296	0.94	0.327	0.94	0.344
(4) P = H < L	π_P	0.99	0.187	0.98	0.258	0.99	0.187	0.94	0.245
	π_L	0.96	0.282	0.92	0.301	0.94	0.328	0.94	0.336
	π_H	0.93	0.169	0.96	0.213	0.88	0.222	0.94	0.247

Note: π_k is the true stage 1 response rate for the treatment k, $k = P, L, H$, where P = placebo, L = low dose, and H = high dose. Scenarios are given in Table 1. Four modeling approaches: Bayesian joint stage modeling (BJSM), log-linear Poisson joint stage modeling (LPJSM), Bayesian first stage modeling (BFSM), and first stage maximum likelihood estimation (FSMLE) are compared. The sample size per treatment arm is 30.

Across all scenarios, we see that the bias of LPJSM estimators of π_P is large compared with the other LPJSM response rate estimators, and compared with the estimators of π_P for other methods. This increased bias likely stems from the low number of patients receiving placebo. Since there are few people in the placebo treatment arm, and none in stage 2 of the study, there is less information to estimate π_P, leading to more bias. In larger samples (see Appendix), we see negligible bias for the LPJSM estimator of π_P, which supports our explanation that the bias observed in Table 2 is due to a low sample size.

Table 3 presents the 95% CI width and coverage rates (CR). Here, we see that the BJSM methods has smaller average 95% CI width than the LPJSM, BFSM, and FSMLE methods. In addition, the CR is around the target 95% for the BJSM in all tested scenarios.

When a sample size of N = 300 is used, we see similar results (Appendix). Overall, we observe smaller bias across all settings when N = 100 in each arm. Interestingly, there is still an efficiency gain when using BJSM methods in larger sample sizes, as the BJSM response rate estimators have smaller rMSEs than the response rate estimators from the LPJSM approach. In addition, for small samples, N = 45, under the null setting where we assume a spontaneous response rate of 30% or 40% for placebo, low, and high doses of the experimental therapy, we again observe efficiency gains when using BJSM methods (Appendix). The BJSM response rate estimators also have smaller bias than the LPJSM and BFSM methods.

3.2 | Sensitivity to priors

In addition to the prior setting presented in Section 3.1, we also explored other prior settings to evaluate the robustness of the BJSM method. First, we adjusted the mean of the prior distribution for $\log(\pi_L/\pi_P)$ and $\log(\pi_H/\pi_P)$. While we settled on a mean of 0.2 to be conservative, we also tested mean values of 0.3, 0.4, and 0.5, and found that our results were largely unchanged in the null and dose-response scenarios (see Table A4 and Table A6 in the Appendix). Second, we adjusted the center of the prior distribution for π_P. In our presented results, the mean of the prior distribution for π_P was equal to the true value of π_P in all scenarios. We present simulations for the null and dose-response scenarios with prior distributions of Beta(2, 18) and Beta(4, 16), and means of 0.10 and 0.20, respectively, for π_P. While in these simulations, we did find that our estimates of the placebo response rate were more biased than in the results in Section 3.1, our estimation of response

rates for low and high doses were unchanged. Coverage rate and credible interval width estimates were also unchanged in our sensitivity analyses (data not shown). Additionally, even when the mean of our prior distribution for the placebo response rate did not match the true value of π_P, BJSM was still more efficient than the LPJSM and first-stage methods (see Table A5 and A7 in the Appendix). Based on these additional analyses, we conclude that our method is generally robust to the choice of mean for all prior distributions of π_P, $\log(\pi_L/\pi_P)$, and $\log(\pi_H/\pi_P)$. We drew the same conclusions after adjusting the priors for scenarios 3 and 4 (data not shown).

4 | DISCUSSION

In this article, we adapted the Bayesian method (BJSM) for use in a different snSMART design where low and high doses of a single experimental therapy are compared with placebo. Due to dose comparison and the stage 2 rerandomization strategy, our design required novel methods that use six linkage parameters to share information on the response rates from both stages of the trial. In this setting, the BJSM yields accurate estimators that are easy to interpret in a clinical setting. Our proposed method was compared with three other methods via simulation. Through simulation, we demonstrated that BJSM estimators are the most efficient of the methods presented.

An advantage of the BJSM method is that it provides estimates of π_P, π_L, and π_H, even when the true response rates were low. In our simulation scenarios, we noted convergence issues for the LPJSM method, specifically under scenario 1, where all treatments have true response rates of 0.15. In this scenario, there were instances where no response outcomes were observed for a given stage 1 treatment. Thus, there would be no responders to rerandomize in stage 2; all stage 2 rerandomization would occur through the nonresponder arm of that treatment. This low probability of response caused failures in convergence for the LPJSM method, but good estimation with low bias was still possible using the BJSM.

Interestingly, in simulations with large true response rates or large sample size, LPJSM performs better than BFSM (smaller rMSE) in terms of the estimation of each individual response rate. However, LPJSM performs worse than BFSM in many scenarios in terms of the difference between the response rates of different dosage levels. This is likely due to our assumption of a prior distribution on the ratio of response rates in the Bayesian methods, which implicitly places correlation among response rates. No such correlation structure is assumed with LPJSM.

Another strength of the BJSM method is its robustness under different prior settings. As discussed in Section 3.2, the BJSM method remained efficient regardless of the center of the response rate estimator prior distributions. Additionally, the bias of the response rate estimators for low and high dose remained low in all tested scenarios for the BJSM, even when the mean of the prior distribution for π_P no longer matched the true mean in the simulation scenarios. This robustness is particularly important for trials investigating drugs in rare diseases, as there may be little previous data to guide prior distribution selection.

Our first formulation of the BJSM model had 11, rather than six, linkage parameters. These parameters corresponded to the 11 unique paths through which a participant could follow in the trial. We found that, while this model still produced response rate estimators with small bias and with increased efficiency compared with other tested methods, these advantages were not substantial. By limiting the model to only six linkage parameters, we were able to retain small bias and gains in efficiency, while using a simpler model. These efficiency gains were present for estimators of π_L-π_P and π_H-π_P. These difference estimators are generally of greater interest than individual response rates in clinical trials. As such, the efficiency gains we observe represent an advantage of using Bayesian joint stage modeling procedures. This model could be expanded if investigators wanted a different bias-variance trade-off than shown here.

The efficiency gains of the BJSM are still relevant for clinical trials with larger sample sizes (Appendix). A trial design that reduces rMSE would also reduce the total number of patients that need to enroll in the trial, and therefore results in a shorter duration of the trial. As such, this snSMART design may be appropriate not just in rare disease research, but also in time-sensitive research like emerging infectious diseases. Similarly, efficiency gains of the BJSM remain for clinical trials with even smaller sample size. Simulations with only N = 45 patients (N = 15 per arm) showed that the BJSM remains efficient and estimates response rates with low bias, even as sample size decreases (Appendix).

A limitation that results from the proposed prior distribution settings and model assumptions is that the posterior distributions for the linkage parameters and π_k allow for $\beta_{1k}\pi_{k'} > 1$. However, we did not draw any samples where $\beta_{1k}\pi_{k'} > 1$ in our simulations. Thus, it is unlikely that this limitation would be a problem in clinical settings, unless the treatment under consideration has a high response rate. Another limitation of our design is we assume there are no carryover effects of the stage 1 treatment in stage 2 of the study. We note, however, that our trial design allows for investigators to implement

a washout period between stage 1 and stage 2 of the study if there was concern with carryover effects. Our future work will include modifications to our method to account for carryover effects.

Future directions for this work include adapting the BJSM to continuous outcomes. We are also examining models with fewer unique linkage parameters to see if we can improve efficiency of the BJSM method without much increased bias. In addition, future work can construct sample size calculations based on the BJSM for snSMART designs. These sample size calculations will aid in the extension of snSMART designs for primary efficacy analysis when more than two dose levels of a drug are compared. We note that our study design allows for a customizable randomization scheme in stage 2. While balanced rerandomization was applied in our simulations, future work could consider unbalanced or/and stratified randomization in stage 2 within responders and nonresponders.

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DATA AVAILABILITY STATEMENT

The author will provide any code used to generate the simulation results presented in this manuscript upon request.

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REFERENCES

1. 107th Congress rare diseases act of 2002. *Pub Law*; 2002:107-280.
2. Griggs RC, Batshaw M, Dunkle M, et al. Clinical research for rare disease: opportunities, challenges and solutions. *Mol Genet Metab*. 2009;96(1):20-26.
3. FDA guidance for industry (Draft). Rare diseases: common issues in drug development; 2015.
4. Levin KA. Study design VII. Randomised controlled trials. *Evidence-Based Dentistry*. 2007;8(1):22.
5. Gupta S, Faughnan ME, Tomlinson GA, Bayoumi AM. A framework for applying unfamiliar trial designs in studies of rare diseases. *J Clin Epidemiol*. 2011;64(10):1085-1094.
6. Tamura RN, Krischer JP, Pagnoux C, et al. A small n sequential multiple assignment randomized trial design for use in rare disease research. *Contemp Clin Trials*. 2016;46:48-51.
7. Lavori PW, Dawson R. A design for testing clinical strategies: biased adaptive within-subject randomization. *J Royal Stat Soc Ser A (Stat Soc)*. 2000;163(1):29-38.
8. Murphy SA. An experimental design for the development of adaptive treatment strategies. *Stat Medic*. 2005;24(10):1455-1481.
9. Robins J. A new approach to causal inference in mortality studies with a sustained exposure period–application to control of the healthy worker survivor effect. *Math Modell*. 1986;7(9-12):1393-1512.
10. Murphy SA. Optimal dynamic treatment regimes. *J Royal Stat Soc Ser B (Stat Methodol)*. 2003;65(2):331-355.
11. Rosner GL, Stadler W, Ratain MJ. Randomized discontinuation design: application to cytostatic antineoplastic agents. *J Clin Oncol*. 2002;20(22):4478-4484.
12. Almirall D, Compton SN, Rynn MA, Walkup JT, Murphy SA. SMARTer discontinuation trial designs for developing an adaptive treatment strategy. *J Child Adolescent Psychopharmacol*. 2012;22(5):364-374.
13. Makubate B, Senn S. Planning and analysis of cross-over trials in infertility. *Stat Medic*. 2010;29(30):3203-3210.
14. Nason M, Follmann D. Design and analysis of crossover trials for absorbing binary endpoints. *Biometrics*. 2010;66(3):958-965.
15. Honkanen VEA, Siegel AF, Szalai JP, Berger V, Feldman BM, Siegel JN. A three-stage clinical trial design for rare disorders. *Stat Medic*. 2001;20(20):3009-3021.
16. Wei B, Braun TM, Tamura RN, Kidwell KM. A Bayesian analysis of small n sequential multiple assignment randomized trials (snSMARTs). *Stat Medic*. 2018;37(26):3723-3732.
17. Williamson T, Eliasziw M, Fick GH. Log-binomial models: exploring failed convergence. *Emerg Themes Epidemiol*. 2013;10(1):14.

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APPENDIX

Simulation results with N = 300

TABLE A1 Simulated bias and root-mean-square error (rMSE) for the estimators of π_k

		BJSM		LPJSM		BFSM		FSMLE	
Scenario		**Bias**	**rMSE**	**Bias**	**rMSE**	**Bias**	**rMSE**	**Bias**	**rMSE**
(1) P = L = H	π_P	0.000	0.030	0.001	0.035	0.000	0.030	0.000	0.035
	π_L	0.000	0.028	0.002	0.030	0.000	0.035	0.001	0.036
	π_H	−0.002	0.026	0.001	0.031	−0.002	0.034	0.000	0.035
	π_L-π_P	0.000	0.041	0.001	0.045	0.000	0.046	0.002	0.051
	π_H-π_P	−0.002	0.040	0.000	0.046	−0.002	0.045	0.000	0.049
(2) P < L < H	π_P	0.000	0.031	0.000	0.360	0.001	0.030	0.001	0.037
	π_L	−0.001	0.033	0.007	0.038	−0.002	0.042	0.000	0.042
	π_H	−0.004	0.039	−0.007	0.043	−0.005	0.048	−0.001	0.048
	π_L-π_P	−0.002	0.046	0.008	0.051	−0.003	0.053	0.000	0.057
	π_H-π_P	−0.005	0.049	−0.007	0.056	−0.005	0.056	−0.002	0.059
(3) P < L = H	π_P	0.000	0.030	0.000	0.036	0.000	0.300	0.000	0.036
	π_L	−0.002	0.040	0.000	0.042	−0.003	0.049	0.001	0.050
	π_H	−0.004	0.040	0.000	0.042	−0.005	0.050	−0.001	0.050
	π_L-π_P	−0.002	0.050	0.000	0.054	−0.003	0.058	0.001	0.062
	π_H-π_P	−0.004	0.051	0.001	0.055	−0.005	0.059	−0.001	0.062
(4) P = H < L	π_P	0.001	0.030	0.000	0.035	0.001	0.030	0.001	0.036
	π_L	−0.002	0.043	−0.026	0.049	−0.003	0.050	0.001	0.050
	π_H	−0.002	0.026	0.026	0.039	−0.002	0.036	0.000	0.036
	π_L-π_P	−0.003	0.053	−0.026	0.060	−0.004	0.058	0.000	0.062
	π_H-π_P	−0.003	0.040	0.026	0.052	−0.003	0.047	−0.001	0.051

Note: π_k is the stage 1 response rate for treatment k, $k = P, L, H$, where P = placebo, L = low dose, and H = high dose. Scenarios are given in Table 1. Four modeling approaches: Bayesian joint stage modeling (BJSM), log-linear Poisson joint stage modeling (LPJSM), Bayesian first stage modeling (BFSM), and first stage maximum likelihood estimation (FSMLE) are compared. The sample size per treatment arm is 100.

TABLE A2 Simulated width and 95% coverage rate (CR) for the estimators of π_k

		BJSM		LPJSM		BFSM		FSMLE	
Scenario		**CR**	**Width**	**CR**	**Width**	**CR**	**Width**	**CR**	**Width**
(1) P = L = H	π_P	0.96	0.124	0.94	0.139	0.96	0.124	0.93	0.138
	π_L	0.94	0.112	0.95	0.121	0.93	0.135	0.93	0.139
	π_H	0.95	0.108	0.95	0.121	0.94	0.134	0.94	0.138
(2) P < L < H	π_P	0.95	0.125	0.94	0.138	0.95	0.125	0.93	0.139
	π_L	0.95	0.133	0.95	0.144	0.95	0.165	0.95	0.170
	π_H	0.95	0.156	0.93	0.164	0.95	0.182	0.94	0.186
(3) P < L = H	π_P	0.96	0.124	0.94	0.138	0.96	0.124	0.94	0.139
	π_L	0.95	0.157	0.94	0.163	0.94	0.188	0.94	0.191
	π_H	0.95	0.156	0.94	0.163	0.93	0.188	0.94	0.191
(4) P = H < L	π_P	0.96	0.125	0.94	0.139	0.96	0.125	0.93	0.139
	π_L	0.95	0.170	0.90	0.166	0.94	0.188	0.93	0.186
	π_H	0.94	0.101	0.90	0.117	0.93	0.134	0.93	0.138

Note: π_k is the true stage 1 response rate for the treatment k, $k = P, L, H$, where P = placebo, L = low dose, and H = high dose. Scenarios are given in Table 1. Four modeling approaches: Bayesian joint stage modeling (BJSM), log-linear Poisson joint stage modeling (LPJSM), Bayesian first stage modeling (BFSM), and first stage maximum likelihood estimation (FSMLE) are compared. The sample size per treatment arm is 100.

Simulation results with N = 45

TABLE A3 Simulated bias and root-mean-square error (rMSE) for the estimators of π_k under null scenarios with different spontaneous response rate

		BJSM		LPJSM		BFSM		FSMLE	
Scenario		**Bias**	**rMSE**	**Bias**	**rMSE**	**Bias**	**rMSE**	**Bias**	**rMSE**
(1) P = L = H	π_P	−0.002	0.047	0.012	0.116	−0.084	0.098	0.001	0.120
$\pi = 0.3$	π_L	−0.010	0.086	0.031	0.108	−0.021	0.110	0.003	0.121
	π_H	−0.015	0.075	0.018	0.100	−0.018	0.111	0.002	0.120
	π_L-π_P	−0.008	0.098	0.019	0.157	0.062	0.135	0.002	0.175
	π_H-π_P	−0.012	0.085	0.006	0.152	0.066	0.138	0.002	0.168
(2) P = L = H	π_P	0.000	0.053	0.007	0.123	−0.141	0.151	0.004	0.128
$\pi = 0.4$	π_L	−0.015	0.087	0.012	0.107	−0.027	0.119	−0.003	0.130
	π_H	−0.018	0.084	0.006	0.105	−0.023	0.120	−0.001	0.124
	π_L-π_P	−0.015	0.100	0.005	0.162	0.114	0.172	−0.007	0.182
	π_H-π_P	−0.018	0.100	−0.001	0.158	0.118	0.176	−0.005	0.175

Note: π_k is the true stage 1 response rate for the treatment k, $k = P, L, H$, where P = placebo, L = low dose, and H = high dose. Under null scenario, we assume $\pi_P = \pi_L = \pi_H = \pi$. Four modeling approaches: Bayesian joint stage modeling (BJSM), log-linear Poisson joint stage modeling (LPJSM), Bayesian first stage modeling (BFSM), and first stage maximum likelihood estimation (FSMLE) are compared. The sample size per treatment arm is 15.

Simulation results with different prior settings

TABLE A4 Simulated bias and root-mean-square error (rMSE) under the null scenario for the estimators when assuming different prior mean for $log(\pi_L/\pi_P)$ and $log(\pi_H/\pi_P)$, that is, $E(log(\pi_L/\pi_P)) = \mu$, given $\mu = 0.2, 0.3, 0.4, 0.5$

		BJSM		BFSM	
Scenario		**Bias**	**rMSE**	**Bias**	**rMSE**
(1) P = L = H	π_P	−0.001	0.039	−0.001	0.039
$\mu = 0.2$	π_L	−0.003	0.048	−0.005	0.062
	π_H	−0.007	0.043	−0.005	0.062
	π_L-π_P	−0.003	0.062	−0.005	0.073
	π_H-π_P	−0.006	0.058	−0.005	0.073
(2) P = L = H	π_P	−0.001	0.039	−0.001	0.039
$\mu = 0.3$	π_L	−0.003	0.048	−0.005	0.062
	π_H	−0.007	0.043	−0.005	0.062
	π_L-π_P	−0.003	0.062	−0.005	0.073
	π_H-π_P	−0.006	0.058	−0.005	0.073
(3) P = L = H	π_P	−0.001	0.039	−0.001	0.039
$\mu = 0.4$	π_L	−0.003	0.048	−0.005	0.062
	π_H	−0.007	0.043	−0.005	0.062
	π_L-π_P	−0.003	0.062	−0.005	0.073
	π_H-π_P	−0.006	0.058	−0.005	0.073
(4) P = L = H	π_P	−0.001	0.039	−0.001	0.039
$\mu = 0.5$	π_L	−0.003	0.048	−0.005	0.062
	π_H	−0.007	0.043	−0.005	0.062
	π_L-π_P	−0.003	0.062	−0.005	0.073
	π_H-π_P	−0.006	0.058	−0.005	0.073

Note: Results are presented for two modeling approaches: Bayesian joint stage model (BJSM) and Bayesian first stage modeling (BFSM). π_k is the true stage 1 response rate for the treatment k, $k = P, L, H$, where P = placebo, L = low dose, and H = high dose. The sample size per treatment arm is 30.

TABLE A5 Simulated bias and root-mean-square error (rMSE) under the null scenario for the estimators when assuming different shape and scale parameter values for the placebo prior distributions

		BJSM		BFSM	
Scenario		**Bias**	**rMSE**	**Bias**	**rMSE**
(1) P = L = H	π_P	−0.001	0.039	−0.001	0.039
$E(\pi_P) = 0.15$	π_L	−0.003	0.048	−0.005	0.062
	π_H	−0.007	0.043	−0.005	0.062
	π_L-π_P	−0.003	0.062	−0.005	0.073
	π_H-π_P	−0.006	0.058	−0.005	0.073
(2) P = L = H	π_P	−0.021	0.044	−0.021	0.044
$E(\pi_P) = 0.1$	π_L	−0.003	0.048	−0.005	0.062
	π_H	−0.007	0.043	−0.005	0.062
	π_L-π_P	0.017	0.064	0.015	0.075
	π_H-π_P	0.014	0.059	0.015	0.075
(3) P = L = H	π_P	0.019	0.043	0.019	0.043
$E(\pi_P) = 0.2$	π_L	−0.003	0.048	−0.005	0.062
	π_H	−0.007	0.043	−0.005	0.062
	π_L-π_P	−0.023	0.066	−0.025	0.077
	π_H-π_P	−0.026	0.063	−0.025	0.077

Note: Three different prior settings are presented: $\pi_P \sim Beta(3, 17)$, $\pi_P \sim Beta(2, 18)$ and $\pi_P \sim Beta(4, 16)$, corresponding to the placebo prior mean $E(\pi_P) = (0.15, 0.1, 0.2)$, respectively. Results are presented for two modeling approaches: Bayesian joint stage model (BJSM) and Bayesian first stage modeling (BFSM). π_k is the true stage 1 response rate for the treatment k, $k = P, L, H$, where P = placebo, L = low dose, and H = high dose. The sample size per treatment arm is 30.

TABLE A6 Simulated bias and root-mean-square error (rMSE) under the dose-response scenario for the estimators when assuming different prior mean for $log(\pi_L/\pi_P)$ and $log(\pi_H/\pi_P)$, that is, $E(log(\pi_L/\pi_P)) = \mu$, given $\mu = 0.2, 0.3, 0.4, 0.5$

		BJSM		BFSM	
Scenario		**Bias**	**rMSE**	**Bias**	**rMSE**
(1) P < L < H	π_P	0.000	0.039	0.000	0.039
$\mu = 0.2$	π_L	−0.005	0.057	−0.011	0.078
	π_H	−0.013	0.064	−0.013	0.084
	π_L-π_P	−0.005	0.069	−0.011	0.087
	π_H-π_P	−0.013	0.074	−0.012	0.093
(2) P < L < H	π_P	0.000	0.039	0.000	0.039
$\mu = 0.3$	π_L	−0.005	0.057	−0.011	0.078
	π_H	−0.013	0.064	−0.013	0.084
	π_L-π_P	−0.005	0.069	−0.011	0.087
	π_H-π_P	−0.013	0.074	−0.012	0.093
(3) P < L < H	π_P	0.000	0.039	0.000	0.039
$\mu = 0.4$	π_L	−0.005	0.057	−0.011	0.078
	π_H	−0.013	0.064	−0.013	0.084
	π_L-π_P	−0.005	0.070	−0.011	0.087
	π_H-π_P	−0.013	0.074	−0.012	0.093
(4) P < L < H	π_P	0.000	0.039	0.000	0.039
$\mu = 0.5$	π_L	−0.005	0.057	−0.011	0.078
	π_H	−0.013	0.064	−0.013	0.084
	π_L-π_P	−0.005	0.070	−0.011	0.087
	π_H-π_P	−0.013	0.074	−0.012	0.093

Note: Results are presented for two modeling approaches: Bayesian joint stage model (BJSM) and Bayesian first stage modeling (BFSM). π_k is the true stage 1 response rate for the treatment k, $k = P, L, H$, where P = placebo, L = low dose, and H = high dose. The sample size per treatment arm is 30.

TABLE A7 Simulated bias and root-mean-square error (rMSE) under the dose-response scenario for the estimators when assuming different shape and scale parameter values for the placebo prior distributions

		BJSM		BFSM	
Scenario		**Bias**	**rMSE**	**Bias**	**rMSE**
(1) P < L < H	π_P	0.000	0.039	0.000	0.039
$E(\pi_P) = 0.15$	π_L	−0.005	0.057	−0.011	0.078
	π_H	−0.013	0.064	−0.013	0.084
	π_L-π_P	−0.005	0.069	−0.011	0.087
	π_H-π_P	−0.013	0.074	−0.012	0.093
(2) P < L < H	π_P	−0.020	0.044	−0.020	0.044
$E(\pi_P) = 0.1$	π_L	−0.005	0.057	−0.011	0.078
	π_H	−0.013	0.064	−0.013	0.084
	π_L-π_P	0.015	0.071	0.009	0.087
	π_H-π_P	0.007	0.073	0.008	0.092
(3) P < L < H	π_P	0.020	0.044	0.020	0.044
$E(\pi_P) = 0.2$	π_L	−0.005	0.057	−0.011	0.078
	π_H	−0.013	0.064	−0.013	0.084
	π_L-π_P	−0.025	0.074	−0.031	0.091
	π_H-π_P	−0.033	0.080	−0.032	0.098

Note: Three different prior settings are presented: $\pi_P \sim Beta(3, 17)$, $\pi_P \sim Beta(2, 18)$ and $\pi_P \sim Beta(4, 16)$, corresponding to the placebo prior mean $E(\pi_P) = (0.15, 0.1, 0.2)$, respectively. Results are presented for two modeling approaches: Bayesian joint stage model (BJSM) and Bayesian first stage modeling (BFSM). π_k is the true stage 1 response rate for the treatment k, $k = P, L, H$, where P = placebo, L = low dose, and H = high dose. The sample size per treatment arm is 30.