Chapter

Practical and Optimal Crossover Designs for Clinical Trials

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Abstract

Crossover designs have received great attention in clinical trials, as they allow subjects to serve as their own controls and gain such advantage as higher efficiency and smaller sample size over parallel designs, because the within-subject variability is in general smaller than between-subject variability. Response-adaptive crossover designs allow clinical trials to adapt and respond to the information acquired during the trials to achieve various objectives. Adaptive designs have been considered to allocate more subjects to superior treatments, improve statistical efficiency, reduce the sample size for cost savings, increase the sample size to maintain prespecified statistical power, or include auxiliary information. We focus on an adaptive allocation scheme to maximize the benefits from superior treatments, while maintaining a sufficiently high level of statistical efficiency, controlled by a suitable weight parameter. We review and discuss the strategy of incorporating multiple objectives, while advocating a regression type estimation approach via the Generalized Estimating Equations method. We show that the multiple objectives can be successfully incorporated to construct a spectrum of designs, ranging over various efficiencies and trial outcomes of success. Moreover, the adaptive allocation scheme successfully constructs designs with a desired efficiency, as illustrated by practical two- and three-period designs.

Keywords: crossover design, response adaptive allocation, optimal design, multiple objective function

1. Introduction

Crossover designs have enjoyed advantages over parallel designs, such as completely randomized design in terms of statistical efficiencies. Equal or balanced allocations play an important role in the construction of optimal designs under various model assumptions. However, equal allocations may pose ethical dilemma when researchers start to suspect that one treatment may be superior to the other. All trials start with the null hypothesis that the effects of a new treatment being tested are the same as comparators before we could prove its superiority. At some point in the trial, one may find an evidence indicating that the effects of treatments are notably different. Then, one may wonder whether to equally allocate remaining subjects to the treatments as per the protocol or to adapt to the findings and alter the allocation scheme to reflect the trial phenomena. Connor et al. [1] studied HIV treatment drug

named AZT. Among 477 pregnant mothers with HIV, 239 were assigned to a placebo, and 238 were assigned to the AZT. The trial resulted in 60 infants diagnosed with HIV from the placebo group and 20 infants diagnosed with HIV from the AZT group. A decade later, Tymofyeyev et al. [2] suggested that use of 50–50 allocation was ethically improper given the seriousness of the outcome of the study and recommended to use a response-adaptive allocation. Tymofyeyev et al. [2] utilized the Play the Winner Rule (PWR) allocation [3, 4] and simulated the trial in a way that 360 and 117 pregnant mothers were adaptively allocated to the AZT or the placebo, respectively. The results of simulation showed that 60 infants were expected to be diagnosed with HIV in two groups combined as opposed to 80 infants in 1994, which revealed some of the benefits of the adaptive allocations.

Response-adaptive designs may have several other goals. Many authors [3–6] aimed at allocating more subjects to a better treatment. Armitage [7] aimed at reducing the sample size, and Wang [8] aimed at increasing the sample size based on the prespecified statistical power and the data acquired. Furthermore, Bandyopadhyay and Biswas [9] introduced covariates in response-adaptive designs. Sorkness et al. [10] proposed designs that were adaptive to the prevalence of events, in which the sample size recalculation was done to remedy the loss of statistical power arising from the imbalance of the prevalence. However, these studies utilized the acquired information using only a single objective. Many authors proposed a multiple objective adaptive design for continuous responses where they defined an objective function with two components, controlled by a weight parameter [11–13].

Binary responses are modeled differently from continuous responses in a way that the information is a function of the outcome. Standard logistic regression assumes that the responses are independent although crossover trial data are dependent on each subject. We use the Generalized Estimating Equations (GEEs) method, which can incorporate a desired covariance structure of responses. Liang and Zeger [14] proposed the GEE, which takes into account for the time dependencies of the data by allowing correlations. The GEE method estimates parameters by solving the system of equations based on the Quasi-Likelihood function. The advantage of Quasi-Likelihood method is that it does not need to provide joint distribution of the data and only requires the marginal distribution and its mean and variance. GEE estimates are proven consistent under a mild regularity conditions [14]. Valois [15] utilized GEE in the analysis of crossover designs.

This chapter demonstrates how to construct multiple objective response-adaptive designs for two treatments with binary outcomes using the GEE. We first review the theoretical grounds for crossover designs with binary outcome and the GEE method. Adaptive designs are constructed using simulations, and some two- and three-period practical designs will be built for various weights of multiple objective functions. We also compare the GEE methods to the other approaches done by Li [13]. Lastly, we develop a new strategy for maximizing the success outcome, while maintaining certain level of prefixed desired statistical efficiency.

2. Multiple objective response-adaptive designs with GEE

2.1 Model and information matrix

Agresti [16] discussed the Generalized Linear Model (GLM) for an exponential family of distributions. Suppose Y follows a distribution in an exponential family with parameters (θ, ϕ). Then the pdf of Y can be written as:

$$f(y|\theta,\phi) = \exp\left(y\theta - b(\theta)\right)/a(\phi) + c(y,\phi)). \tag{1}$$

Consider that the Y_{ijk} denotes the binary response of ith period of jth subject in kth treatment sequence, distributed as Bernoulli (p_{ijk}), and X is a design matrix for an overall mean effect (μ), period effects (α_i), direct treatment effects ($\tau_{d(i,j,k)}$), and carryover effects ($\gamma_{d(i-1,j,k)}$) with the corresponding vector of parameters β. By defining the relation $\theta = h(\eta), \eta = x'\beta$ and with a logit link function $g()$, we can entertain the following model:

$$\eta_{ijk} = g\left(E\left(Y_{ijk}\right)\right) = g\left(P\left(Y_{ijk}=1\right) = \text{logit}\left(P\left(Y_{ijk}=1\right)\right)\right) \tag{2}$$

$$= \log\left(\frac{P\left(Y_{ijk}=1\right)}{1-P\left(Y_{ijk}=1\right)}\right) = \mu + \alpha_i + \tau_{d(i,j,k)} + \gamma_{d(i-1,j,k)} = X'_{ijk}\beta_{ijk}. \tag{3}$$

It is easy to see that the mean and variance of Y_{ijk} are defined as

$$E\left(Y_{ijk}\right) = \mu_{ijk} = b'\left(\beta_{ijk}\right) = \frac{\exp\left(X'_{ijk}\beta_{ijk}\right)}{1-\exp\left(X'_{ijk}\beta_{ijk}\right)}, \tag{4}$$

$$\text{Var}\left(Y_{ijk}\right) = \sigma_{ijk} = b''\left(\beta_{ijk}\right) = \frac{\exp\left(X'_{ijk}\beta_{ijk}\right)}{\left(1-\exp\left(X'_{ijk}\beta_{ijk}\right)\right)^2}. \tag{5}$$

2.2 Generalized estimating equations

We use Generalized Estimating Equations to estimate the parameters of GLM with unknown correlation structure using the mean μ_{ijk} and unknown variance structure V_j^{-1}. The estimating equations can be shown as

$$\sum_{j=1}^{n}\frac{\partial\mu'_j}{\partial\beta}V_j^{-1}\left(Y_j-\mu_j\right) = 0, \tag{6}$$

where μ_j and Y_j are vector of means and responses for periods 1 to p.

The above estimating equation resembles that of GLM but does not require an exponential distribution assumption for Y, which is the strength of GEE. McCullaugh [17] showed that under the correct specification of mean and variance functions, the quasi-likelihood estimators demonstrate characteristics similar to MLE. The covariance matrix then can be written as:

$$\text{Var}(\beta) = \left[\sum_{j=1}^{n}\frac{\partial\mu'_j}{\partial\beta}V_j^{-1}\frac{\partial\mu_j}{\partial\beta}\right]^{-1} \tag{7}$$

Then, Bose and Dey [18] showed that the covariance matrix for parameters β can be defined with respect to k treatment sequences as follows:

$$\mathrm{Var}(\hat{\beta}) = \left(\sum_{k \in \Omega} n_k \frac{\partial \mu_k{}'}{\partial \beta} V_k^{-1} \frac{\partial \mu_k}{\partial \beta} \right)^{-1}, \tag{8}$$

where n_k denotes number of subjects allocated to kth sequence and the design matrices being identical for subjects in the same treatment sequence. However, when the specified covariance matrix V is not identical to the observed covariance matrix $\mathrm{Var}(Y)$, then the sandwich variance estimator is suggested:

$$\mathrm{Var}(\beta) = A \left(\sum_{k \in \Omega} n_k \frac{\partial \mu'_j}{\partial \beta} V_k^{-1} \mathrm{Var}(Y_k) V_k^{-1} \frac{\partial \mu_j}{\partial \beta} \right) A, \tag{9}$$

where A is the variance in Eq.(8). This sandwich variance estimator is shown to be consistent [14].

2.3 Multiple objective function

Liang and Carriere [11] proposed the following multiple objective function for the continuous responses:

$$\Phi_{j,k} = \lambda \frac{\Delta\left(\hat{I}^k_{j+1}(\beta)\right)}{\Delta\left(\hat{I}^{k'}_{j+1}(\beta)\right)} + (1-\lambda)\frac{f_{j,k}}{f_{j,k''}}, \tag{10}$$

where $\hat{I}^k_{j+1}(\beta)$ is the Fisher's Information matrix for subject $j+1$ allocated to treatment sequence k with Δ being an optimality criterion of choice and $f_{j,k}$ is an evaluation function for treatment sequence k based on the first j subjects in the trial. In this function, treatment sequence k' refers to the sequence with maximum $\hat{I}^k_{j+1}(\beta)$, and k'' refers to the sequence with maximum $f_{j,k}$, which may not necessarily be identical. Among the two terms in the objective function, the first term of the function investigates the efficiency of design with respect to the Fisher's information matrix given that subject $(j+1)$ is allocated to treatment sequence k. This is represented as a ratio over the sequence with maximum information so that the component may take value in $[0,1]$. The second term of the function is called the evaluation function that evaluates the total efficacy of treatment sequences based on the estimated treatment effects. When $\lambda = 0$, the objective function considers only the efficiency of the design and ignores any superiority/inferiority of the treatments being tested. On the other hand, the objective function with $\lambda = 1$ would construct adaptive designs based solely on the positive effects of treatments being tested.

Liang et al. [12] and Li [13] extended their multiple objective function to binary responses and derived the information matrix for estimated success probabilities for binary responses. The observed number of successes for each treatment sequence was used for the evaluation function f. As the analysis of crossover trials mainly focuses on direct treatment effects, we choose the inverse of the variance of estimated treatment effects, $1/\mathrm{var}(\hat{\tau})$, as the criterion for comparing the efficiency of various treatment sequences. McCullagh [19] showed that quasi-likelihood estimates are invariant under a linear transformation. That is, $\hat{\mu}_k$ maximizes the quasi-likelihood function.

Throughout this chapter, we will refer to the Eq. (10) as the multiple objective function and choose the first term $\Delta\left(\hat{I}^{k}_{j+1}(\beta)\right)$ as the variance of the estimated treatment effects, $\text{var}\left(\hat{\tau}_{j+1,k}\right)$. The data acquired from the first j subjects are modeled using the GEE approach, and predictions for subject $j+1$ are made for all of the K treatment sequences. Then, we include the predicted responses of subject $j+1$ into the model and obtain the variance of an estimated treatment effects of each treatment sequence. Then, we evaluate the efficacy of each treatment sequence by using $\Sigma_{i=1}^{p}\hat{\eta}_{i,j,k}$. The $\eta's$ take any values in IR where large values correspond to a better treatment sequence. We transform these values to positive numbers so that a larger value indicates a better sequence and the ratios could be easily implemented. For this reason, we choose $f_{j,k} = \text{logit}\left(\Sigma_{i=1}^{p}\hat{\eta}_{i,j,k}\right)$, which falls in $(0,1)$ over all p periods.

3. Practical and nearly optimal designs

We apply the allocation method to construct some popular practical designs in clnical trials, two-treatment two-period designs and two-treatment three-period designs based on the parameter settings from Li [13], which are shown in **Table 1** with a slight modification on the values to incorporate the GEE modeling approach. Initially, one subject is assigned to each treatment sequence. Afterward, new subjects are introduced sequentially and are assigned to the treatment sequence with the highest Eq. (10). When all subjects are assigned, the variance of the estimated treatment effects, $\text{var}(\hat{\tau}_N)$, is computed and compared with the variance obtained from the optimal fixed designs suggested by Mukhopadhyay [20]. Mukhopadhyay [20] conducted simulation study for the optimal fixed crossover design with binary outcomes using the GEE method and showed that $AA/AB/BB/BA$ is optimal for $p = 2$ and

P	Parameters	Treatment sequences	Success probabilities	Expected success per period
2	$\mu = -0.22$	AA	(0.60, 0.70)	0.65
	$.\alpha_2 = 0.018$	AB	(0.60, 0.40)	0.50
	$.\tau = 0.63$	BA	(0.30, 0.50)	0.40
	$.\gamma = 0.42$	BB	(0.30, 0.22)	0.26
3	$\mu = -0.22$	AAA	(0.60, 0.70, 0.65)	0.65
	$.\alpha_2 = 0.018$	AAB	(0.60, 0.70, 0.35)	0.55
	$.\alpha_3 = -0.21$	ABA	(0.60, 0.40, 0.44)	0.48
	$.\tau = 0.63$	ABB	(0.60, 0.40, 0.19)	0.40
	$.\gamma = 0.4$	BAA	(0.30, 0.50, 0.65)	0.48
		BAB	(0.30, 0.50, 0.35)	0.38
		BBA	(0.30, 0.22, 0.44)	0.32
		BBB	(0.30, 0.22, 0.19)	0.23

Table 1.
Parameter values for simulation in construction of multiple-objective response-adaptive crossover design with binary outcomes.

$ABB/AAB/BAA/BBA$ is optimal for $p = 3$ under the compound symmetric covariance structure with binary outcomes.

3.1 Two-period design

There are four possible treatment sequences for two-treatment two-period crossover trials. Carriere and Reinsel [21] showed that an equal allocation on all sequences AA/BB/AB/BA, denoted as $d_{\text{opt},p2}$, is universally optimal for a continuous response, and Mukhopadhyay [20] confirmed that it is also numerically optimal even when responses are binary. We assign a subject to each of the four sequences and allocate the rest based on the objective function in Eq. (10). The following tables show the allocations of the adaptive designs, their efficiency compared with the fixed optimal design, and their success outcome ratio for various values of λ and N.

When $\lambda = 0$, the resulting allocation focuses on the treatment sequence AA with very few assigned to the rest of the sequences due to randomness during the initial stage of the trial. We can see that the allocation to the sequence AA decreases as λ increases. The allocations move toward a dual balanced design $d_{\text{opt},p2}$, which assigns equal allocations to all four sequences. The relative efficiency, which is defined as the ratio of variance of estimated treatment effects of $d_{\text{opt},p2}$ over the proposed multiple objective adaptive design, is low for $\lambda = 0$ and approaches 1 as λ increases to 1. The success ratio is close to the expected success shown in **Table 1** when $\lambda = 0$ and decreases as λ increases. Therefore, we must find a reasonable compromise between efficiency and a success ratio. For $n = 40$, $\lambda \in (0.85, 0.9)$ would construct an efficient design (efficiency > 0.8) with a sufficiently higher success ratio (5–8% increased) than $\lambda = 1$. For $n = 80$, $\lambda \in (0.9, 0.95)$ would construct a similar design (efficiency > 0.8 and success ratio improved by 5–8%). For $n = 100$, we note a drastic result around $\lambda \in (0.9, 0.95)$ where efficiency changes from 0.8957 to 0.7096, while the success ratio changes from 0.5168 to 0.5638, showing that the choice of suitable λ may vary significantly by the sample size n.

The consistent estimates for the above terms can be obtained by replacing the parameters with their GEE estimates. Also, the variance of the estimated β's can easily be computed using the sandwich covariance matrix from GEE. The treatment sequences with a smaller variance do not necessarily improve efficiency in this case, and the efficiency depends on the covariance matrix of the estimates of parameters. This covariance matrix, in turn, does not have a closed form, unlike in the continuous response case.

3.2 Three-period design

Three-period two-treatment crossover designs constructed from the multiple objective response-adaptive approach behave similarly as the two-period two-treatment designs. When $\lambda = 0$, the majority of the subjects are allocated to the treatment sequence AAA, which has the highest success ratio per period. For small sample size, $n = 40$, the efficiencies remain high and the success ratios are improved for any values of $\lambda < 1$. This is largely due to the conditions of the design, where $3 \times 8 = 24$ subjects out of 40 are assigned evenly to all eight sequences and thus only 16 subjects are allocated based on the multiple objective response-adaptive schemes. Therefore, the relative efficiency, which is computed based on the optimal design [20], remains high and the success ratio is improved only to a degree.

However, in the case of $n = 80$, the success ratio increases from 0.4323 to 0.5647 and the efficiency decreases from 1.0370 to 0.5793 as λ changes from 1 to 0. It is notable that the relative efficiencies of multiple objective response-adaptive designs for $\lambda = 1$ are greater than 1, indicating that these designs are slightly better than the optimal design [20] for the given set of parameters. The design with $\lambda = 0.95$ is as efficient as the optimal design, with a relative efficiency of 1.0055, and yet shows a higher success ratio (0.4708 compared with 0.4323), with an expected success ratio of 0.4696 (compared with 0.4375). In the case of $\lambda = 0.9$, the relative efficiency decreases to 0.9220 while the success ratio increases to 0.5050 from 0.4323. Looking at the design with $\lambda = 0.85$, we see that the relative efficiency decreases to 0.8133 while the success ratio increases to 0.5290. These two designs with $\lambda = 0.9$ and $\lambda = 0.85$ indicate that we could improve the success ratio of the design by 7–10% at the cost of relative efficiency between 0.1 and 0.2.

When $n = 100$, the designs show a similar performance to the case of $n = 80$ with respect to efficiency and the success ratio, except that efficiencies drop sharply, as we give attention to beneficial treatment effects with $\lambda < 1$.

In summary, the above tables show that adaptive schemes could benefit more subjects without much loss of efficiency for the given set of parameters. But it is important to find an appropriate λ to improve the success ratios while maintaining a sufficient level of statistical efficiency. In this case, $\lambda \in (0.85, 0.9)$ is recommended for both $n = 80$ and $n = 100$. However, we can see that the decrease in efficiency is more evident for $n = 100$ than that of $n = 80$, indicating that sample size N is another player determining the balance parameter λ. The resulting designs would have success ratios increased by 9–12% when compared with the optimal fixed design ($\lambda = 1$). Taking a smaller value of λ can benefit further, but the gain in success ratio decreases marginally as the λ decreases.

4. Comparison with other approaches

Bandyopadhyay [22] utilized an example of a three-period crossover trial of two treatments for hypertension. In this trial, 68 subjects were equally assigned to the treatment sequences $ABB/BAA/ABA/BAB$. Li [13] used the last two periods of this trial to obtain a crossover design with $AA/BB/AB/BA$. The response variable was continuous measurements of systolic blood pressure. Binary response variables were computed by dichotomizing the blood pressures at "135 or more" and "140 or more" and denoting the responses as failures. Two corresponding sets of success probabilities were estimated from this data. $(\hat{v}_{A1}, \hat{v}_{A2}, \hat{v}_{B1}, \hat{v}_{B2}) = (0.24, 0.24, 0.24, 0.35)$ and $(\hat{v}_{A1}, \hat{v}_{A2}, \hat{v}_{B1}, \hat{v}_{B2}) = (0.35, 0.5, 0.35, 0.53)$ where v is the probability of success with the letters denoting treatments and numbers denoting periods.

These estimated probabilities were considered as actual success probabilities, and the multiple objective response-adaptive technique was applied with $\lambda = 1$ and $\lambda = 0.9$. A comparison of allocations, efficiencies, and success ratios of the three methods (B, L, K proposed by [20, 13, 23], respectively) is provided below. We included fixed group effects, β_k, to the model in Eq. (2) to incorporate success probabilities. The parameters and other settings are provided in **Table 2**, and the results of simulations are found in **Tables 3** and **4**.

The efficiencies in **Table 3** were computed against the equal allocation design, which are nonadaptive but optimal for two-period and two-treatment designs. First, we examine multiple objective response-adaptive designs with $\lambda = 1$. We see that when the

Probabilities	Parameters	Treatment sequences	Success probabilities	Expected success per period
$\hat{v}_{A1} = 0.24$	$\mu = -1.89, \beta_1 = 1$	AA	$(0.24, 0.24)$	0.240
$\hat{v}_{A2} = 0.24$	$\alpha_2 = 0.27, \beta_2 = 1$	AB	$(0.24, 0.35)$	0.295
$\hat{v}_{B1} = 0.24$	$\tau = -0.27, \beta_3 = 0.47$	BA	$(0.24, 0.24)$	0.240
$\hat{v}_{B2} = 0.35$	$\gamma = -0.27, \beta_4 = 0.47$	BB	$(0.24, 0.35)$	0.295
$\hat{v}_{A1} = 0.35$	$\mu = -1.56, \beta_1 = 1$	AA	$(0.35, 0.50)$	0.425
$\hat{v}_{A2} = 0.5$	$\alpha_2 = 0.68, \beta_2 = 1$	AB	$(0.35, 0.53)$	0.440
$\hat{v}_{B1} = 0.35$	$\tau = -0.06, \beta_3 = 0.88$	BA	$(0.35, 0.50)$	0.425
$\hat{v}_{B2} = 0.53$	$\gamma = -0.06, \beta_4 = 0.88$	BB	$(0.35, 0.53)$	0.440

Table 2.
Parameter values and expected success probabilities based on the crossover trial of [22].

Parameters	Design	λ	AA	AB	BA	BB	Efficiency	Expected success
$(\hat{v}_{A1}, \hat{v}_{A2}, \hat{v}_{B1}, \hat{v}_{B2})$ $(0.24, 0.24, 0.24, 0.35)$	d_1^B		15.75	16.92	17.01	18.32	0.9912	0.2685
	d_2^L	1	13.13	21.03	13.03	20.80	0.9143	0.2738
	d_3^L	0.1	14.69	19.06	13.64	20.62	0.9522	0.2729
	d_4^K	1	12.81	20.85	12.49	21.85	0.8913	0.2745
	d_5^K	0.1	15.22	19.58	14.19	19.01	0.9829	0.2713
	d_6^E		17.00	17.00	17.00	17.00	1.0000	0.2675
$(0.35, 0.50, 0.35, 0.53)$	d_7^B		13.00	16.42	16.46	22.12	0.9769	0.4335
	d_8^L	1	7.32	16.35	14.88	29.46	0.8376	0.4352
	d_9^L	0.1	12.38	16.71	15.80	23.11	0.9627	0.4338
	d_{10}^K	1	16.22	17.89	15.40	18.49	0.9970	0.4330
	d_{11}^K	0.1	16.76	17.53	16.80	16.91	0.9983	0.4326
	d_6^E		17.00	17.00	17.00	17.00	1.0000	0.4325

[B] [22]; [L] [13]; [K] [23]; [E] Equal allocation design.

Table 3.
Allocation, efficiency, and success ratio for two-period designs.

difference of the expected success probabilities between the sequences is small (0.425 vs. 0.44, second example in **Table 2**), [13]'s strategy allocates an extensive number of the subjects to the treatment sequences AB/BB and results in a substantial loss of efficiency. Moreover, the gain in the expected success over an equal allocation design is minimal (0.4352 vs. 0.4325). The simulations confirm this observation, and d_8 has relative efficiency of 0.8376 without much gain as a result. On the other hand, d_{10} adapts to the small differences in the sequences in a careful manner, and it assigns about three more subjects to better treatment sequences AB/BB without losing efficiency (0.9970). d_{10} allocates fewer subjects to AB/BB compared with d_7, d_8, and d_9.

It is noticeable that the pattern is not the same when there is some difference in the expected success probabilities between the treatment sequences (0.24 vs. 0.295). Design d_2 allocates 41.83 subjects to better sequences AB/BB, whereas d_4 allocates 42.7

N	Designs	AA	AB	BA	BB	Efficiency	Success ratio
40	$d_{(0.8)}$	22.22	7.60	5.63	4.55	0.7615	0.5420
	$d_{(0.9)}$	16.63	9.49	7.28	6.60	0.9152	0.5042
	$d_{(1)}$	10.20	10.01	9.66	10.13	1.0141	0.4534
	$d_{Adaptive}$	21.75	6.11	6.21	5.94	0.8465	0.5319
80	$d_{(0.9)}$	45.08	16.64	10.56	7.72	0.7582	0.5507
	$d_{(0.95)}$	33.68	18.98	13.95	13.39	0.9368	0.5048
	$d_{(1)}$	20.35	19.81	18.96	20.88	1.0076	0.4532
	$d_{Adaptive}$	43.58	12.35	12.24	11.83	0.8430	0.5309
100	$d_{(0.9)}$	61.75	19.36	11.01	7.89	0.7096	0.5638
	$d_{(0.95)}$	45.77	23.49	16.30	14.44	0.8957	0.5168
	$d_{(1)}$	25.41	24.40	23.66	26.54	1.0258	0.4525
	$d_{Adaptive}$	57.09	14.42	14.12	14.37	0.7972	0.5391

Table 4.
Comparison of new revised response-adaptive two-period design with the results from ***Table 5****.*

subjects. The designs allocate more subjects to better treatment sequences than d_1 while maintaining a high level of efficiency.

The designs constructed using the multiple objective response-adaptive method with GEE are more responsive to the differences in treatments better than Bandyopadhyay [22] and Li [13], while maintaining a high level of efficiency when there is a large difference in the treatment effects. The method by Kim [23] assigns more subjects to the better treatment sequence when the treatment differences are large. Moreover, the resulting designs are close to the optimal design with an equal allocations on all four sequences, when the treatment differences are negligible. This assures that even if the treatment difference is not as large as expected, the multiple objective response-adaptive method is robust and creates an efficient design.

5. Implementing the adaptive allocations

In **Tables 5** and **6**, we observed that the decrease in efficiency following the decrease in λ is not consistent for differing sample sizes. That is, if we wish to maintain some level of relative efficiency with respect to a known fixed optimal design while applying the multiple objective adaptive allocation scheme, we must fully understand the behaviors of this adaptive allocation scheme and find the suitable λ, which is determined by the true parameters as well as the sample size. The simulations on this scheme may help suggest some λ's, but is limited to the specific scenarios being studied. Therefore, we implement a sensible strategy of the multiple-objective-based allocation scheme without having to precisely know which λ to use.

The multiple-objective function as in Eq. (10) is now split into two objective functions:

$$H_{1,j,k} = \frac{\Delta\left(\hat{I}^{k}_{j+1}(\beta)\right)}{\Delta\left(\hat{I}^{k'}_{j+1}(\beta)\right)}, \tag{11}$$

N	λ	AA	AB	BA	BB	Efficiency	Success ratio
40	0	26.97	4.37	4.51	4.15	0.5679	0.5635
	0.3	26.46	4.40	4.94	4.20	0.5696	0.5596
	0.7	25.42	5.46	4.89	4.23	0.6378	0.5576
	0.8	22.22	7.60	5.63	4.55	0.7615	0.5420
	0.9	16.63	9.49	7.28	6.60	0.9152	0.5042
	1	10.20	10.01	9.66	10.13	1.0141	0.4534
80	0	65.81	4.53	5.46	4.20	0.2998	0.6046
	0.3	66.05	4.65	5.13	4.17	0.3012	0.6055
	0.7	64.37	5.95	5.43	4.26	0.3554	0.6020
	0.8	59.16	9.95	6.28	4.60	0.4844	0.5896
	0.9	45.08	16.64	10.56	7.72	0.7582	0.5507
	0.95	33.68	18.98	13.95	13.39	0.9368	0.5048
	1	20.35	19.81	18.96	20.88	1.0076	0.4532
100	0	85.14	4.71	5.85	4.31	0.2859	0.6126
	0.3	85.84	4.56	5.45	4.15	0.2773	0.6136
	0.7	84.57	6.03	5.25	4.16	0.3184	0.6114
	0.9	61.75	19.36	11.01	7.89	0.7096	0.5638
	0.95	45.77	23.49	16.30	14.44	0.8957	0.5168
	1	25.41	24.40	23.66	26.54	1.0258	0.4525

Table 5.
Allocation, efficiency, and success ratio for two-period designs using the multiple objective criteria in Eq. (10).

$$H_{2,j,k} = \frac{f_{j,k}}{f_{j,k''}}, \tag{12}$$

which are the first and second terms of the Eq. (10). The allocation scheme takes the following steps.

1. Determine a desirable relative efficiency r^*, e.g., 80%.

2. Acquire a small number of subjects to each sequence and obtain the quasi-likelihood estimates of the parameters, μ, π_i's, τ, γ from a logistic model.

3. Generate another set of data with the same number of total subjects as the current dataset with allocations according to the optimal design $d_{\text{opt},p2}$. Obtain estimates of the parameters and sandwich covariance matrices of the estimated parameters from the new data and compare the efficiencies of two designs, $r = \text{var}\left(\hat{\tau}_{\text{opt}}\right)/\text{var}\left(\hat{\tau}_{\text{Adaptive}}\right)$.

4. If $r < r^*$, then use $H_{1,j,k}$ as the allocation function for subject $j+1$, otherwise use $H_{2,j,k}$ as the allocation function for subject $j+1$.

5. Return to step 2 until all subjects are allocated.

N	λ	AAA	AAB	ABA	ABB	BAA	BAB	BBA	BBB	Efficiency	Success ratio
40	0	11.98	4.00	4.01	4.00	4.00	4.00	4.01	4.00	0.9603	0.4797
	0.3	11.95	4.02	4.00	4.00	4.01	4.00	4.02	4.00	0.9631	0.4785
	0.7	10.97	4.77	4.12	4.12	4.11	4.01	4.00	4.00	0.9891	0.4767
	0.8	9.24	5.62	4.73	4.56	5.01	4.55	4.36	4.23	0.9931	0.4678
	0.9	6.94	5.62	4.73	4.56	5.01	4.55	4.36	4.23	1.0075	0.4566
	1	5.04	5.03	4.73	4.96	4.98	4.93	4.97	5.36	1.0302	0.4377
80	0	51.98	4.01	4.00	4.00	4.00	4.00	4.01	4.00	0.5793	0.5647
	0.3	51.95	4.00	4.01	4.00	4.01	4.00	4.00	4.00	0.5848	0.5656
	0.7	49.58	5.91	4.24	4.01	4.23	4.01	4.02	4.00	0.6043	0.5619
	0.8	41.09	10.41	6.07	4.24	5.89	4.24	4.06	4.00	0.7223	0.5458
	0.85	33.85	12.40	7.48	5.14	7.47	5.20	4.39	4.07	0.8133	0.5290
	0.9	25.20	13.16	8.67	6.74	9.10	6.94	5.63	4.56	0.9220	0.5050
	0.95	16.76	12.06	9.02	8.48	10.27	8.61	7.94	6.86	1.0055	0.4708
	1	10.09	9.97	8.58	9.95	9.83	9.75	9.91	11.92	1.0370	0.4323
100	0	71.97	4.01	4.00	4.00	4.00	4.00	4.02	4.00	0.4972	0.5817
	0.3	71.98	4.01	4.00	4.00	4.01	4.00	4.00	4.01	0.5081	0.5805
	0.7	69.41	6.03	4.28	4.02	4.25	4.01	4.00	4.00	0.5379	0.5812
	0.8	57.12	6.09	5.56	6.20	6.01	5.95	6.18	6.90	0.6345	0.5445
	0.85	54.13	12.65	7.646	4.94	7.32	5.00	4.28	4.05	0.6951	0.5553
	0.9	37.37	16.65	10.20	7.39	10.46	7.62	5.80	4.50	0.8696	0.5231
	0.95	23.93	15.91	10.85	10.17	12.35	10.44	9.17	7.19	0.9858	0.4794
	1	12.45	12.50	10.38	12.57	12.10	12.18	12.49	15.32	1.0435	0.4315

Table 6.
Allocation, efficiency, and success ratio for three-period design using the multiple objective criteria in Eq. (10).

To illustrate, we apply the above strategy to the parameters in **Table 1** with the aim of constructing a response-adaptive design with a relative efficiency around $r^* > 0.8$. First, we construct two-period two-treatment response-adaptive designs with $n = 40$, 80, and 100. We present the results for three-period two-treatment designs with $n =$ 80 and 100. The case for $n = 40$ was excluded as all adaptive designs constructed using Eq. (10) with any λ have relative efficiencies > 0.9.

From **Table 4**, we can see that the designs constructed using the adaptive allocation method by Kim [23], denoted as d_{Adaptive}, have relative efficiencies close to 0.8 or slightly larger than that while the success ratios are increased by 9% compared with the designs for $\lambda = 1$. For $n = 40$, the adaptive design follows the pattern of changes in the allocations, efficiency, and success ratio so that we can find one between $d_{(0.8)}$ and $d_{(0.9)}$. For example, the allocation to the treatment sequence AA is 21.75 (d_{Adaptive}), which is between 16.63 ($d_{(0.8)}$) and 22.22 ($d_{(0.9)}$). This pattern is also the case for all other columns in the table for $n = 80$ and 100. Our adaptive designs appear to be constructed in a similar manner as the multiple objective response-adaptive designs as if they were constructed with the λ in the suggested range of

N	Designs	AAA	AAB	ABA	ABB	BAA	BAB	BBA	BBB	Efficiency	Success ratio
80	$d_{(0.8)}$	41.09	10.41	6.07	4.24	5.89	4.24	4.06	4.00	0.7223	0.5458
	$d_{(0.9)}$	25.20	13.16	8.67	6.74	9.10	6.94	5.63	4.56	0.9220	0.5050
	$d_{(0.95)}$	16.76	12.06	9.02	8.48	10.27	8.61	7.94	6.86	1.0055	0.4708
	$d_{(1)}$	10.09	9.97	8.58	9.95	9.83	9.75	9.91	11.92	1.0370	0.4323
	$d_{Adaptive}$	39.49	5.25	7.35	5.42	4.98	5.02	6.88	5.61	0.7999	0.5267
100	$d_{(0.7)}$	69.41	6.03	4.28	4.02	4.25	4.01	4.00	4.00	0.5379	0.5812
	$d_{(0.8)}$	57.12	6.09	5.56	6.20	6.01	5.95	6.18	6.90	0.6345	0.5445
	$d_{(0.9)}$	37.37	16.65	10.20	7.39	10.46	7.62	5.80	4.50	0.8696	0.5231
	$d_{(0.95)}$	23.93	15.91	10.85	10.17	12.35	10.44	9.17	7.19	0.9858	0.4794
	$d_{(1)}$	12.45	12.50	10.38	12.57	12.10	12.18	12.49	15.32	1.0435	0.4315
	$d_{Adaptive}$	50.48	5.93	9.52	6.45	5.65	5.78	9.11	7.08	0.7854	0.5278

Table 7.
Comparison of our new revised response-adaptive three-period design with the results from ***Table 6****.*

$(0.8, 0.9)$. Similarly, the d_{Adaptive} designs for $n = 80$ and $n = 100$ fall right in between $d_{(0.9)}$ and $d_{(0.95)}$.

From **Table 7**, the relative efficiencies of our adaptive three-period designs are 0.7999 and 0.7854 for $n = 80$ and $n = 100$, respectively. These efficiencies are very close to our target $r^* = 0.8$ while the success ratios are improved by approximately 9%. We can see that the allocation for treatment sequence AAA, relative efficiency, and the success ratio for the new adaptive designs d_{Adaptive} follow the same pattern as the multiple objective response-adaptive designs. The allocations to the other sequences are relatively small and do not seem to affect the efficiency much as long as the allocation to AAA is well controlled. The above strategy successfully leads us to obtain desired success ratios and maintain efficiency to a prespecified level without having to determine what the ideal λ is.

6. Conclusion

This chapter discussed practical and nearly optimal designs for clinical trials. One of the major concerns is that response-adaptive designs have so much potential to complement the traditional experimental designs. The use of the data acquired during the trial may benefit the trial in numerous ways such as improving the statistical power, reducing the cost of the trial by recalculating the required sample size, assigning more subjects to a better treatment or treatment sequences, or utilizing the information acquired from the covariates to improve efficiency. The multiple objective criteria may incorporate more components or select various other sets of components such as cost efficiency versus statistical efficiency and many others.

To achieve any efficiency in trials with binary responses, we start by recognizing that they have distinct properties that are different from continuous responses in that their means and variances are functions of the outcomes. As a result, binary response designs are response-dependent. Due to this characteristic, the construction of

optimal designs for binary responses requires special attention. Due in part to these difficulty, there are limited studies on response-adaptive designs and optimal designs in the literature for binary outcome data. In this chapter, we compared approaches of constructing response-adaptive designs. Also, we conducted a simulation study based on an actual data example to investigate the performance of the multiple objective response-adaptive designs using the GEE over the other two methods.

We demonstrated by constructing response-adaptive designs using an objective function, namely the multiple objective function. The designs constructed using the multiple objective function were highly efficient, successful with respect to desirable or beneficial treatment outcomes. In **Tables 5** and **6**, we observed that the choice of λ for an efficient and successful design would depend on the sample size and the true values of μ, $\pi_i's$, τ, and γ. The efficiencies drop significantly when n increases or λ decreases. These designs may have significantly higher success ratios but may also have significantly low efficiency (<0.6), which is undesirable.

We then compared the approach by Kim [23] to other multiple objective adaptive designs using the GEE to the response-adaptive design by Mukhopadhyay [20] and multiple objective adaptive designs using binary probability modeling approach by Li [13] for two-period two-treatment crossover designs. The proposed designs responded to the differences in the treatment effects in a rather robust manner. When the treatment difference is very small, the proposed designs were very close to the optimal design with an equal allocation on four treatment sequences, $AA/AB/BA/BB$, as expected. On the other hand, the other two methods assign too large a proportion of subjects to treatment sequences BB and lose efficiencies for very small gain in successful outcome ratios. When the treatment difference is large, the design with $\lambda = 1$ assigns more subjects to a better treatment sequences compared with the other two designs considered by Bandyopadhyay et al. [5] and Li [13].

We observed that the choice of λ was very important in finding a balance between the relative efficiency and a success ratio. One may suggest some appropriate range of λ, but it is valid for only a certain set of parameters and sample size, and the true parameters are usually unknown. To overcome this challenge, Kim [23] devised a multiple objective response-adaptive scheme, which utilizes all of the two components of Eq. (10), not simultaneously but in a sequential manner. The simulation results show that this adaptive scheme can construct designs with desired relative ratios without having to select the weight parameter λ. The scheme by Kim [23] allows researchers to run an adaptive trial knowing that their design would find the balance between two important components of the trial—statistically efficiency and higher allocation to a beneficial treatment.

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