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Adaptive clinical trial designs with pre-specified rules for modifying the sample size: understanding efficient types of adaptation

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Adaptive clinical trial design has been proposed as a promising new approach that may improve the drug discovery process. Proponents of adaptive sample size re-estimation promote its ability to avoid 'up-front' commitment of resources, better address the complicated decisions faced by data monitoring committees, and minimize accrual to studies having delayed ascertainment of outcomes. We investigate aspects of adaptation rules, such as timing of the adaptation analysis and magnitude of sample size adjustment, that lead to greater or lesser statistical efficiency. Owing in part to the recent Food and Drug Administration guidance that promotes the use of pre-specified sampling plans, we evaluate alternative approaches in the context of well-defined, pre-specified adaptation. We quantify the relative costs and benefits of fixed sample, group sequential, and pre-specified adaptive designs with respect to standard operating characteristics such as type I error, maximal sample size, power, and expected sample size under a range of alternatives. Our results build on others' prior research by demonstrating in realistic settings that simple and easily implemented pre-specified adaptive designs provide only very small efficiency gains over group sequential designs with the same number of analyses. In addition, we describe optimal rules for modifying the sample size, providing efficient adaptation boundaries on a variety of scales for the interim test statistic for adaptation analyses occurring at several different stages of the trial. We thus provide insight into what are good and bad choices of adaptive sampling plans when the added flexibility of adaptive designs is desired.

Keywords: adaptive designs; clinical trials; efficiency; group sequential tests; sample size modification; sufficiency

1. Introduction

Adaptive clinical trial design has been proposed as a promising new approach that may help improve the drug discovery process. A number of statistical papers have introduced methods to allow unplanned interim modifications to the study design while preserving the type I error rate of the clinical trial [1–5]. In particular, there is a large body of literature exploring designs with unplanned modifications to the sample size based on interim estimates of the treatment effect. Advantages perceived by proponents include the ability to avoid 'up-front' commitment of resources [6], improved handling of the complicated decisions faced by data monitoring committees in a statistically rigorous fashion [7], and more flexibility in minimizing accrual to studies having delayed ascertainment of primary outcomes [8]. On the other hand, Tsiatis and Mehta [9] and Jennison and Turnbull [10, 11] have demonstrated that methods allowing unplanned adaptations to the sample size do not base inference on the minimal sufficient statistic and come with costs in efficiency when compared with group sequential designs (GSDs).

It is possible, however, to completely pre-specify adaptive sampling plans at the design stage of the trial so that investigators can proceed with frequentist inference based on the minimal sufficient statistic at the analysis stage. Such designs are examples of the 'sequentially planned decision procedures'

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proposed by Schmitz [12]. We focus here on such pre-specified adaptation rules. An important reason to critically evaluate the class of pre-specified adaptive designs is the lack of regulatory support, in the setting of adequate and well-controlled phase III effectiveness trials, for designs allowing unplanned modifications to the sample size. The recent Food and Drug Administration draft guidance on adaptive trials discussed the interpretability challenges of approaches allowing unplanned design changes and asserted that ‘changes in study design occurring after an interim analysis of unblinded study data and that were not prospectively planned are not within the scope of this guidance’ [13]. Instead, the Food and Drug Administration guidance encourages the use of ‘well-understood’ methods, perhaps because the statistical community has not yet fully evaluated the potential for bias to be introduced unwittingly by a sponsor with a clear financial conflict of interest.

However, our greatest motivation in focusing on the class of pre-specified designs with inference based on the minimal sufficient statistic is to remove the violation of the sufficiency principle as a source of inefficiency. This allows differences in important operating characteristics between competing adaptive designs to be attributed solely to the contrasting boundaries and sample size rules rather than to the method of inference. As with GSDs, we would expect that a poor choice of adaptive sampling plan would lead to less desirable operating characteristics than might be obtained through a more careful evaluation of candidate designs. We thus provide insight into what are good and bad choices of adaptive sampling plans when the added flexibility of adaptive designs is desired in some particular setting.

Because GSDs are just one subgroup of the more flexible broader class of pre-specified adaptive designs, one would expect that some efficiency gains can be made by incorporating the opportunity for sample size adaptations into the sampling plan. A few recent papers have derived optimal pre-specified adaptive designs under a Bayesian framework and then shown that these adaptive designs can attain only minor efficiency gains over alternative GSDs [10, 14–16]. In particular, Jennison and Turnbull concluded that standard GSDs are nearly as efficient as any optimized adaptive design. They also noted that ‘it will be quite a challenge to find simply defined adaptive procedures with such robustly efficient performance’ and that they have ‘observed the sampling rules of optimal adaptive tests to be qualitatively different from rules based on conditional power commonly used in adaptive designs’ [14]. It is these two comments that we hope to illuminate clearly and build on in this paper.

There is a need for studies that exactly quantify and discuss the relative costs and benefits of simple and easily implemented pre-specified adaptive designs as compared with alternative designs in realistic settings. This includes settings in which efficiency is the primary concern and also settings in which other scientific issues govern the choice of clinical trial design. In addition, because adaptive trials are being proposed and carried out in actual clinical research, there is a need for a detailed description of the sampling rules that lead to desirable operating characteristics. It is not clear what are good and bad choices of rules for modifying the sample size on different scales for the interim test statistic, nor is it well-understood at what time it is best to perform such an adaptation. We find that many of the adaptive designs proposed in the literature consist of suboptimal modification rules based on poorly understood scales (such as conditional power) and carried out at poorly chosen stages of the trial. We believe that a proper evaluation of any adaptive design should compare it with alternative sequential sampling plans with respect to unconditional operating characteristics such as power and aspects of the sample size distribution under a range of clinically meaningful treatment effects. Our goal is to help trial investigators better understand different types of adaptation rules and what to expect with respect to their impact on standard operating characteristics. We also hope that our findings suggest where it may be best to dedicate future research efforts in the study of adaptive trial designs.

We first describe some notation and a general setting for our comparisons. We write out the sampling density for a completely pre-specified adaptive design and show that inference can be based on the minimal sufficient statistic. We then clearly define the optimality criteria governing the choice of randomized clinical trial (RCT) design in two simple, realistic settings, describe in detail the sampling plan of the optimal adaptive designs, and compare the operating characteristics of these adaptive designs with those of alternative group sequential and fixed sample designs in these scenarios. In the final sections, we discuss the implications of our results and other issues inherent in adaptive design. We performed all computations using the R package RCTdesign built from the S-Plus module S+SeqTrial [17].

2. Setting and notation

Consider the following simple setting of a balanced two-sample comparison, which is easily generalized [18]. Potential observations X_{Ai} on treatment A and X_{Bi} on treatment B, for $i = 1, 2, \ldots,$ are independently distributed, with means μ_A and μ_B, respectively, and common variance σ^2. The parameter of interest is the difference in mean treatment effects, $\theta = \mu_A - \mu_B$. We assume that the variance is known, and without loss of generality, let $\sigma^2 = 0.5$. There will be up to J interim analyses conducted with sample sizes $N_1, N_2, N_3, ..., N_J$ accrued on each arm (both J and the $N_j s$ may be random variables). At the jth analysis, let $S_j = \sum_{i=1}^{N_j}(X_{Ai} - X_{Bi})$ denote the partial sum of the first N_j paired observations, and define

$$\hat{\theta}_j = \frac{1}{N_j} S_j = \overline{X}_{A,j} - \overline{X}_{B,j}$$

as the estimate of the treatment effect of interest θ based on the cumulative data available at that time. The normalized Z statistic and upper one-sided fixed sample P-value are transformations of that statistic: $Z_j = \sqrt{N_j}\left(\hat{\theta}_j - \theta_0\right)$ and $P_j = 1 - \Phi(Z_j)$. We represent any random variable (e.g., N_j) with an upper-case letter and any realized value of a random variable (e.g., $N_j = n_j$) or fixed quantity with a lower-case letter. We additionally use a * to denote incremental data. We define N_j^* as the sample size accrued between the $(j-1)$th and jth analyses, with $N_0 = 0$ and $N_j^* = N_j - N_{j-1}$. Similarly, the partial sum statistic and estimate of treatment effect based on the incremental data accrued between the $(j-1)$th and jth analyses are $S_j^* = \sum_{i=N_{j-1}+1}^{N_j}(X_{Ai} - X_{Bi})$ and $\hat{\theta}_j^* = \frac{1}{N_j^*} S_j^*$, respectively.

Assume that the potential outcomes are immediately observed. Without loss of generality, assume that positive values of θ indicate superiority of the new treatment. It is desired to test the null hypothesis $H_0 : \theta = \theta_0 = 0$ against the one-sided alternative $\theta > 0$ with type I error probability $\alpha = 0.025$. First consider a fixed sample design. In order to detect the alternative $\theta = \Delta$ with power β, the trial requires a fixed sample size on each treatment arm of

$$n = \frac{(z_{1-\alpha} + z_\beta)^2}{\Delta^2}$$

where $z_p = \Phi^{-1}(p)$. Alternatively, consider a GSD. We use the following general framework [19] for such candidate sequential designs. At the jth interim analysis, we compute some statistic $T_j = T(X_1, ..., X_{N_j})$ on the basis of the first N_j observations. Then, for specified stopping boundaries $a_j \leqslant d_j$, we stop with a decision of non-superiority of the new treatment if $T_j \leqslant a_j$, stop with a decision of superiority of the new treatment if $T_j \geqslant d_j$, or continue the study if $a_j < T_j < d_j$. We restrict attention to families of stopping rules described by the extended Wang and Tsiatis unified family [20], in which the P parameter reflects the early conservatism of the stopping boundaries.

In order to reduce the dimensionality of the space of candidate clinical trial designs, we only consider symmetric designs. Symmetric sequential sampling plans consist of continuation and stopping sets that treat the null and alternative hypotheses symmetrically with respect to early stopping. Such designs arise naturally when minimizing an objective function that places half its weight on the average sample size under the null and half its weight on the average sample size under the alternative for which the study has power equal to 1 minus the type I error. We consider the one-parameter family of symmetric one-sided designs described by Emerson and Fleming [21] and shown to be nearly as efficient as the larger class introduced by Jennison [22]. Symmetric designs attain power $1 - \alpha$ at the alternative hypothesis and therefore reject the two design hypotheses with the same level of confidence. With $\alpha = 0.025$, these designs thus have the desirable property that a 95% confidence interval for the estimated treatment effect computed at the end of the trial will discriminate between the null and the alternative hypotheses. In such a setting, we assume that the alternative hypothesis $\theta = \Delta$ is based on the therapeutic index and thus represents an effect size that would be considered clinically meaningful when weighed against such treatment characteristics as toxicity, side effects, and cost. We note that any design with 97.5% power at $\theta = \Delta$ will obtain 80% and 90% power at some intermediate treatment effects $\theta < \Delta$, and thus, these symmetric designs can be used to target one of these common desired levels of power at an important alternative hypothesis.

3. The completely pre-specified adaptive design

In the spirit of the 'sequentially planned decision procedures' proposed by Schmitz [12] and discussed further by Jennison and Turnbull [10], we can completely pre-specify adaptation sets at the design stage of the trial. With a pre-specified adaptive sampling plan, we can easily write out the distribution of the minimal sufficient statistic. In order to develop a better understanding of these designs in the most basic sequential setting, we restrict our attention to adaptive designs with a maximum of two analyses. Consider the following simple example.

Suppose that we will base inference on the estimate of treatment effect equal to the difference in sample means: $\hat{\theta}_j = \overline{X}_{A,j} - \overline{X}_{B,j}$. At the first analysis, with sample size n_1 accrued on each arm, we stop early for superiority if $\hat{\theta}_1 \geqslant d_1$ or non-superiority if $\hat{\theta}_1 \leqslant a_1$. Now suppose that we additionally want to add a single adaptation region inside the continuation set (a_1, d_1) at the first analysis. Conceptually, the idea is that we have observed results sufficiently far from our expectations and from both stopping boundaries such that additional data (a larger sample size) might be desired. Denote this adaptation region $C_1 = [A, D]$ where $a_1 \leqslant A \leqslant D \leqslant d_1$. Denote the rest of the continuation region $C_2 = (a_1, A) \cup (D, d_1)$. The sampling plan proceeds as follows:

- If $\hat{\theta}_1 \leqslant a_1$, stop with a decision of non-superiority (futility).
- If $\hat{\theta}_1 \geqslant d_1$, stop with a decision of superiority (efficacy).
- If $\hat{\theta}_1 \in C_1$, continue the study, proceeding to pre-specified, fixed sample size $n_2^{(1)}$, at which stop with a decision of superiority if $\hat{\theta}_2 \geqslant d_2^{(1)}$, where $\hat{\theta}_2 \equiv \hat{\theta}\left(n_2^{(1)}\right) = \frac{1}{n_2^{(1)}} \sum_{i=1}^{n_2^{(1)}} (X_{Ai} - X_{Bi})$.
- If $\hat{\theta}_1 \in C_2$, continue the study, proceeding to pre-specified, fixed sample size $n_2^{(2)}$, at which stop with a decision of superiority if $\hat{\theta}_2 \geqslant d_2^{(2)}$, where $\hat{\theta}_2 \equiv \hat{\theta}\left(n_2^{(2)}\right) = \frac{1}{n_2^{(2)}} \sum_{i=1}^{n_2^{(2)}} (X_{Ai} - X_{Bi})$.

Figure 1 illustrates the stopping and continuation boundaries for one such sequential sampling plan, in which the design is symmetric so that $d_2^{(1)} = d_2^{(2)} = d_2$ (on the sample mean scale). We can choose values of $n_2^{(1)}, n_2^{(2)}, d_2^{(1)}$, and $d_2^{(2)}$ so that the type I error rate is α, that is,

$$P_{\theta_0}\left(\hat{\theta}_1 \geqslant d_1\right) + P_{\theta_0}\left(\hat{\theta}_1 \in C_1, \hat{\theta}_2 \equiv \hat{\theta}\left(n_2^{(1)}\right) \geqslant d_2^{(1)}\right) + P_{\theta_0}\left(\hat{\theta}_1 \in C_2, \hat{\theta}_2 \equiv \hat{\theta}\left(n_2^{(2)}\right) \geqslant d_2^{(2)}\right) = \alpha. \quad (1)$$

We will discuss strategies for selecting these values and give optimal choices in simple settings later in the paper. The key point is that, with a completely pre-specified adaptive sampling plan like this one, we can specify exactly the distribution of the sufficient statistic and proceed with inference in a manner analogous to a standard GSD.

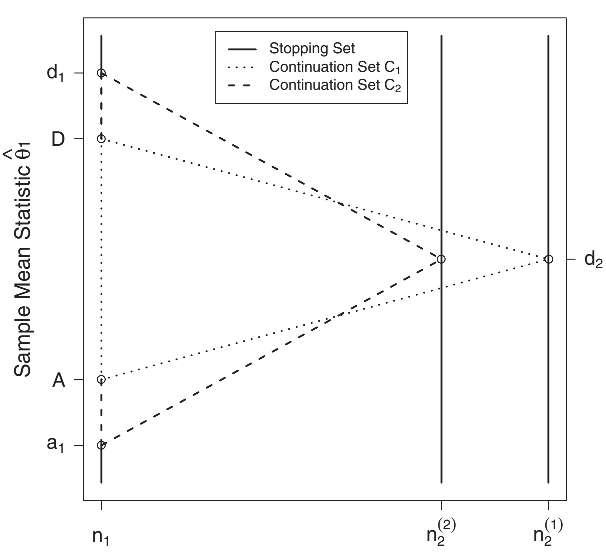


Figure 1. An illustration of possible continuation and stopping boundaries on the sample mean scale for a completely pre-specified adaptive design.

3.1. The sampling density of the minimal sufficient statistic

In the simple two-stage setting, first consider the joint density of the incremental partial sum statistics S_1^* and S_2^*. By appealing to the central limit theorem, we have approximate distributions $S_1^* \sim N(n_1\theta,\, n_1)$ and $S_2^* \mid S_1^* \sim N\left(n_2^*\theta,\, n_2^*\right)$, as $N_2^* = n_2^*$ is fixed conditional on $S_1^* = s_1^*$. Therefore,

$$f\left(s_1^*,\, s_2^*;\, \theta\right) = f\left(s_2^* \mid s_1^*;\, \theta\right)\; f\left(s_1^*;\, \theta\right) \tag{2}$$

$$= \frac{1}{\sqrt{n_2^*}}\, \phi\left(\frac{s_2^* - n_2^*\theta}{\sqrt{n_2^*}}\right)\; \frac{1}{\sqrt{n_1}}\, \phi\left(\frac{s_1^* - n_1\theta}{\sqrt{n_1}}\right) \tag{3}$$

$$= \frac{1}{2\pi\sqrt{n_1 n_2^*}}\, \exp\left(-\frac{\left(n_2^* s_1^{*2} + n_1 s_2^{*2}\right)}{2 n_1 n_2^*}\right)\, \exp\left(\left(s_1^* + s_2^*\right)\theta - \frac{\left(n_1 + n_2^*\right)}{2}\theta^2\right) \tag{4}$$

where $\phi(x) = e^{-x^2/2}/\sqrt{2\pi}$ is the standard normal density.

Because $S_2 = S_1^* + S_2^*$ and $N_2 = n_1 + N_2^*$, it is clear from the factorization criterion and a result of Lehmann and Scheffé that (N_2, S_2) is minimal sufficient for θ. Equivalently, $\left(N_2, \hat{\theta}_2\right)$ is minimal sufficient because $\hat{\theta}_2 = \frac{1}{N_2} S_2$.

Therefore, define the test statistic (N, S), where N is the sample size when the trial is stopped and $S \equiv S_j$ is the partial sum statistic computed on the cumulative data at the time of stopping. For the simple two-stage setting presented in the previous section, following Armitage, McPherson, and Rowe [23], the sampling density for observation $(N = n, S = s)$ is then defined as

$$p(n,\, s;\, \theta) = \begin{cases} f(n,\, s;\, \theta) & \text{if } s \text{ falls in a stopping set} \\ 0 & \text{otherwise} \end{cases} \tag{5}$$

where the (sub)density is recursively defined as

$$f(n_1,\, s;\, \theta) = \frac{1}{\sqrt{n_1}}\, \phi\left(\frac{s - n_1\theta}{\sqrt{n_1}}\right) \tag{6}$$

$$f\left(n_2^{(1)},\, s;\, \theta\right) = \int_{C_1} \frac{1}{\sqrt{n_2^{(1)} - n_1}}\, \phi\left(\frac{s - u - \left(n_2^{(1)} - n_1\right)\theta}{\sqrt{n_2^{(1)} - n_1}}\right) f(n_1, u;\, \theta)\, \mathrm{d}u \tag{7}$$

$$f\left(n_2^{(2)},\, s;\, \theta\right) = \int_{C_2} \frac{1}{\sqrt{n_2^{(2)} - n_1}}\, \phi\left(\frac{s - u - \left(n_2^{(2)} - n_1\right)\theta}{\sqrt{n_2^{(2)} - n_1}}\right) f(n_1, u;\, \theta)\, \mathrm{d}u \tag{8}$$

Because we can write out exactly the sampling density of the minimal sufficient statistic, we can numerically compute any of the standard operating characteristics used to evaluate GSDs. For example, if the adaptation and stopping boundaries are chosen on the scale of the maximum likelihood estimate (MLE), which is the sample mean statistic $\hat{\theta} = \frac{1}{N} S$, the power ($\beta$) and expected sample size (ASN) of this design at a particular alternative θ are easily calculated as

$$\beta_\theta = P_\theta\left(\hat{\theta}_1 \geqslant d_1\right) + P_\theta\left(\hat{\theta}_1 \in C_1, \hat{\theta}_2 \equiv \hat{\theta}\left(n_2^{(1)}\right) \geqslant d_2^{(1)}\right) + P_\theta\left(\hat{\theta}_1 \in C_2, \hat{\theta}_2 \equiv \hat{\theta}\left(n_2^{(2)}\right) \geqslant d_2^{(2)}\right) \tag{9}$$

$$\mathrm{ASN}_\theta = n_1\left[P_\theta\left(\hat{\theta}_1 \geqslant d_1\right) + P_\theta\left(\hat{\theta}_1 \leqslant a_1\right)\right] + n_2^{(1)} P_\theta\left(\hat{\theta}_1 \in C_1\right) + n_2^{(2)} P_\theta\left(\hat{\theta}_1 \in C_2\right). \tag{10}$$

Thus, we can carefully evaluate the important operating characteristics of the adaptive sampling plan using standard software for GSDs [24] and then can compare these characteristics with those of alternative GSDs at the planning stage of the clinical trial. The ability to compute the sampling density and standard operating characteristics across the range of the parameter space easily generalizes to pre-specified adaptive designs with more than two continuation (adaptation) regions and to designs with a maximum of more than two analyses.

When using the bivariate minimal sufficient statistic, however, we do note that whereas the Neyman–Pearson lemma provides the optimality of a likelihood ratio-based test for simple hypotheses, in sequential sampling there is no uniformly most powerful test or uniformly most accurate confidence bounds for composite hypotheses. Hence, there are competing orderings of the outcome space based on the minimal sufficient statistic that might be considered. To our knowledge, no in-depth comparisons of possible orderings of the outcome space have been reported in the statistical literature, and it is beyond the scope of this manuscript to present such here. Both the MLE [25] and likelihood ratio orderings [26] have been shown to be generally well-behaved in the group sequential setting and are easily extended to adaptive clinical trial designs.

3.2. Finding the optimal adaptive design

In our investigations, we search for designs that minimize the average sample size under the null and alternative hypotheses. We use the following routine to find the 'optimal' adaptive design in two general settings that will be described subsequently. In each setting, we first clearly enumerate the optimality criteria governing the choice of RCT design. These optimality criteria include a particular null hypothesis and associated type I error and a design alternative at which there is a desired level of statistical power, along with constraints limiting the number of analyses desired and/or the minimal sample size at which early stopping is permitted.

In the class of symmetric pre-specified adaptive designs with up to two analyses, we need to specify the following parameters. We need to choose the number m of continuation regions at the first analysis. For each of these regions, we must specify one of the boundaries (A or D in the previous example). The other boundary is fixed by symmetry, as these boundaries are symmetric about the midpoint between the null and alternative hypotheses on the sample mean scale. Finally, we must choose the maximal sample size $N_2 = n_2^{(\ell)}$ to which the study will proceed if the estimate of treatment effect falls in each respective continuation region C_ℓ, for $\ell = 1, 2, ..., m$. We note that the *a priori* specification of desired type I and type II errors restricts the range of these parameters and ensures that the specification of the first $\ell - 1$ possible values for N_2 determines the final possible maximal sample size. We also note that the stopping boundary d_2 at the final analysis is determined by symmetry and is equal to the midpoint between the design alternatives on the sample mean scale. Such inference using the minimal sufficient statistic thus corresponds to the MLE ordering of the sample space.

Given these free parameters, our optimization procedure proceeds as follows:

- Start with a design containing $\ell = 2$ continuation regions. Holding constant the desired type I error and power, choose C_1 and $n_2^{(1)}$ to minimize the average sample size at the design alternatives (the ASN is the same at the null and alternative hypotheses because of symmetry). We perform a numerical grid search to minimize ASN over these two free parameters.
- Proceed to $\ell = 3$ continuation regions by holding C_1 constant and finding an optimal split of C_2 into two continuation regions (to minimize the ASN).
- Proceed to $\ell = 4$ continuation regions by finding an optimal split of C_1 (holding the other regions constant).
- Proceed with this method of increasing the number of continuation regions until there is evidence of approximate convergence to a minimum achieved ASN.

This optimization procedure conditions on all but one of the continuation regions and the corresponding selected maximal sample sizes that were chosen at the previous step. Therefore, it is not guaranteed that for $\ell > 2$ continuation regions, we have actually achieved the minimum ASN possible for this class of designs. However, sensitivity procedures iterating back and forth between adjacent regions do not provide further reduction in the ASN. In fact, most of the potential gain in efficiency is achieved with the first step, as will be discussed further in the subsequent examples. It is also important to note that minimizing the average sample size at other values of the treatment effect (e.g., moderate effect sizes) or minimizing the expected ASN with respect to some prior distribution on the parameter space would produce different 'optimal' adaptive designs.

4. Comparing adaptive and alternative designs

4.1. Setting #1

In this setting, we are interested in finding the most efficient clinical trial design given a constraint on the number of analyses that can be conducted. We acknowledge that statistical efficiency should never

Table I. Average and maximal sample sizes of adaptive designs in setting #1.

	Number of continuation regions								
	0[a]	1[b]	2	3	4	5	6	7	8
$\text{ASN}_{\theta=0,\Delta}$	1	0.6854	0.6831	0.6828	0.6825	0.6824	0.6824	0.6824	0.6824
% Difference	+45.9%	*Ref*	−0.34%	−0.38%	−0.42%	−0.43%	−0.43%	−0.44%	−0.44%
Maximal N	1	1.18	1.24	1.24	1.26	1.26	1.26	1.26	1.28

[a]Fixed sample design.
[b]Group sequential design (*Reference* design).

be the sole factor leading to a particular choice of clinical trial design because of the numerous ethical, economic, and scientific issues that must be considered first at the design stage. However, it is still important to describe the optimal rules for making interim adaptations to the sample size and to discuss the gains that can be attained by the use of an adaptive design in a setting where efficiency is the primary concern. Suppose the following optimality criteria govern the choice of RCT design:

- The number of analyses is constrained to a maximum of two, which in our experience is the typical proposed setting for an adaptive design.
- The desired type I error is $\alpha = 0.025$, and power is $\beta = 0.975$ at the design alternative $\theta = \Delta$. The initial candidate design is a fixed sample design with $n = \frac{(z_{1-\alpha}+z_\beta)^2}{\Delta^2}$ subjects required to meet these operating characteristics.
- The primary interest is in finding the most efficient design meeting these constraints. Efficiency is measured by the average sample size in the presence of a truly ineffective (under the null hypothesis) or effective (under the alternative hypothesis) treatment.

The first alternative design is a standard GSD. Given the preceding constraints, we consider all symmetric group sequential sampling plans in the unified family with a maximum of $J = 2$ analyses. We choose values for P (degree of early conservatism) and N_1 (spacing of the two analyses) in order to maintain the desired α and β while minimizing the ASN at the design alternatives. This yields a two-analysis GSD with $P = 0.542$ (close to a Pocock design, which corresponds to $P = 0.5$) and analyses at 50% and 118% of the original fixed sample size n. The stopping boundaries for futility and efficacy at the first analysis are 0.21Δ and 0.79Δ on the sample mean scale, respectively. These boundaries correspond to $(0.57, 2.21)$ on the Z-scale, (4.9%, 95.1%) on the conditional power scale assuming the interim MLE $\hat{\theta}_1$ is the true treatment effect, and (81.8%, 99.0%) on the conditional power scale assuming the design alternative Δ is the true treatment effect. This choice of GSD achieves an average sample size of 68.54% of the fixed sample size n at the design alternatives.

Next we consider optimal adaptive designs. We hold constant the timing and stopping boundaries of the first analysis of the optimal GSD and search for optimal adaptive designs over the different possible divisions of the continuation region at $n_1 = 0.5n$ (using the optimization routine described previously). Table I displays the average and maximal sample sizes of optimal adaptive designs with an increasing number of continuation regions (displayed in units of the original fixed sample size n), as well as the corresponding percent reduction in ASN as compared with the optimal GSD.

All of the designs displayed in Table I have power $\beta = 0.975$ at the design alternative $\theta = \Delta$. The adaptive design with one continuation region is the reference GSD. The efficiency gain achieved by the optimal adaptive design is minimal (less than 0.5% per treatment arm) and is largely produced by the first split of the GSD's single continuation set into two regions. The ASN is decreased by 0.34%, from $0.6854n$ to $0.6831n$, at this first split. Allowing more than four continuation regions leads to negligible decreases in the ASN, and approximate convergence to a minimum ASN is achieved by a design with eight different regions. It is interesting that increasing the number of continuation regions of the optimal adaptive design only marginally increases the maximal N, to as large as $1.28n$ with eight continuation regions. This result suggests that adaptive designs that include the possibility of very large increases in the sample size, to as much as twice or more the original n, are not efficient designs in terms of the ASN. Figure 2 displays the optimal rule for N_2 as a function of the interim test statistic, computed on four commonly used scales, for a symmetric adaptive design with eight continuation regions.

The gains in efficiency at the design alternatives ($\theta = 0$ and $\theta = \Delta$) are offset by losses in efficiency at intermediate values of the treatment effect. Figure 3 displays de-trended power and ASN curves,

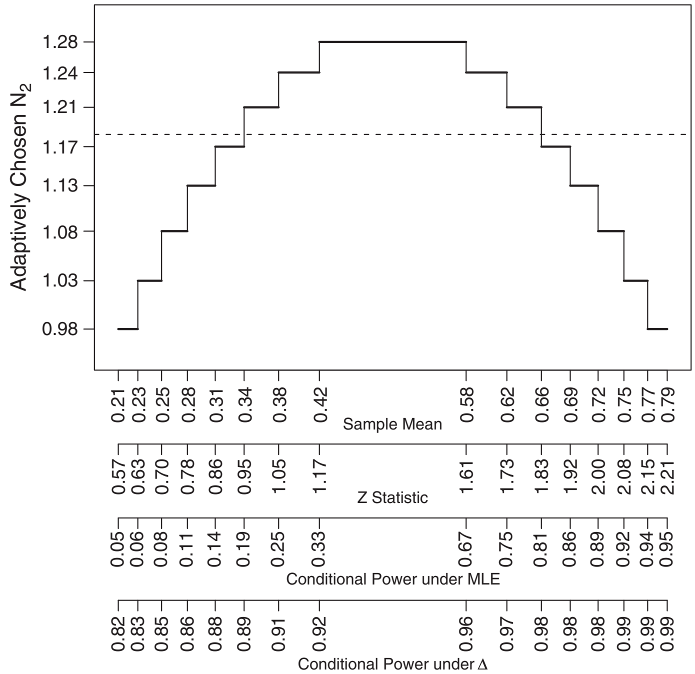
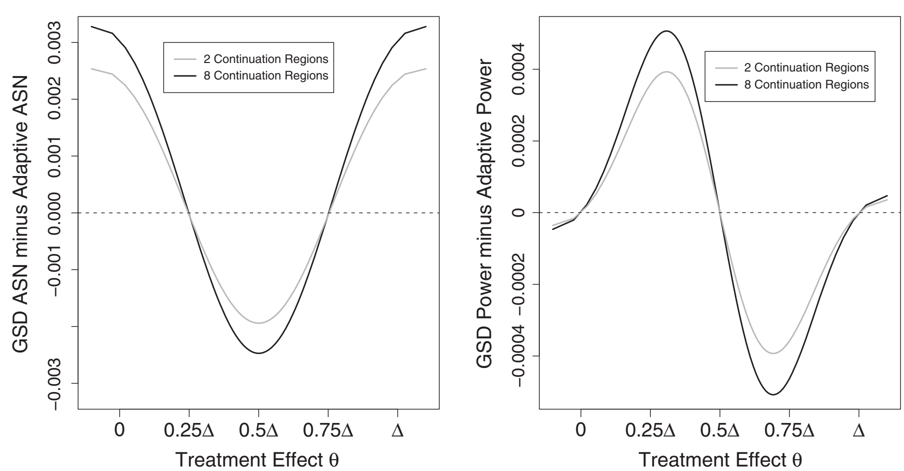


Figure 2. The optimal choice of N_2, in units of the fixed sample size n, as a function of the test statistic computed at the first analysis for a symmetric adaptive design with eight continuation regions. The interim test statistic is displayed on the following scales: the crude estimate of treatment effect (or sample mean) scale (in units of the design alternative Δ), the normalized Z statistic scale, the conditional power scale under the interim estimate of treatment effect ($\theta = \hat{\theta}_1$), and the conditional power scale under the alternative ($\theta = \Delta$). The dotted line represents n_2 under the optimal group sequential design. The adaptive design stops early for efficacy or futility (at $n_1 = 0.5n$) if the sample mean at the first analysis is greater than 0.79Δ or less than 0.21Δ, respectively. MLE, maximum likelihood estimate.



(a) Differences in Expected Sample Size (b) Differences in Power

Figure 3. Comparison of the GSD with two representative optimal adaptive designs with respect to power and ASN across a range of plausible treatment effects. Differences between the group sequential and adaptive operating characteristics are shown on the y-axes. ASN differences are in units of the fixed sample size n. The dotted line indicates equality. GSD, group sequential design; ASN, expected sample size.

comparing two representative optimal adaptive designs with the original GSD. We can see that the adaptive designs suffer efficiency losses for values of θ between 0.25Δ and 0.75Δ, with worst-case behavior relative to the GSD at $\theta = 0.5\Delta$. Worst-case efficiency losses are nearly the same magnitude as efficiency gains at the design alternatives. Although the addition of continuation regions modestly increases efficiency gains at the design alternatives, it also increases efficiency losses at intermediate values of the treatment effect. Our optimality criteria and optimization procedure force the group sequential and adaptive designs to have equal power at the design alternatives, but Figure 3 demonstrates that there are some slight differences in the power of these designs at other possible values of the treatment effect. However, differences in power are less than 0.001 and thus are negligible.

It is also important to note that adding an additional analysis to the GSD leads to a much larger efficiency gain than allowing adaptive modifications to the final sample size. For example, if we hold constant the stopping boundaries at the first analysis and choose two additional analysis times from among the eight adaptive values for N_2 shown in Figure 2, we can decrease the ASN at the design alternatives to as low as $0.643n$. Thus, a three-analysis GSD is able to reduce the average sample size of the optimal two-analysis GSD by 6.2% as compared with the less than 0.5% reduction achieved by the optimal two-analysis adaptive design. This is an important result in considering the tradeoffs between the cost of carrying out additional analyses and the costs of enrolling additional patients and increasing study duration.

4.2. Setting #2

In this second setting, we are interested in the possible gains in efficiency that can be attained by using an early analysis to help determine the optimal sample size for the analysis at which inference will be carried out. Consider a scenario in which the following optimality criteria govern the choice of RCT design:

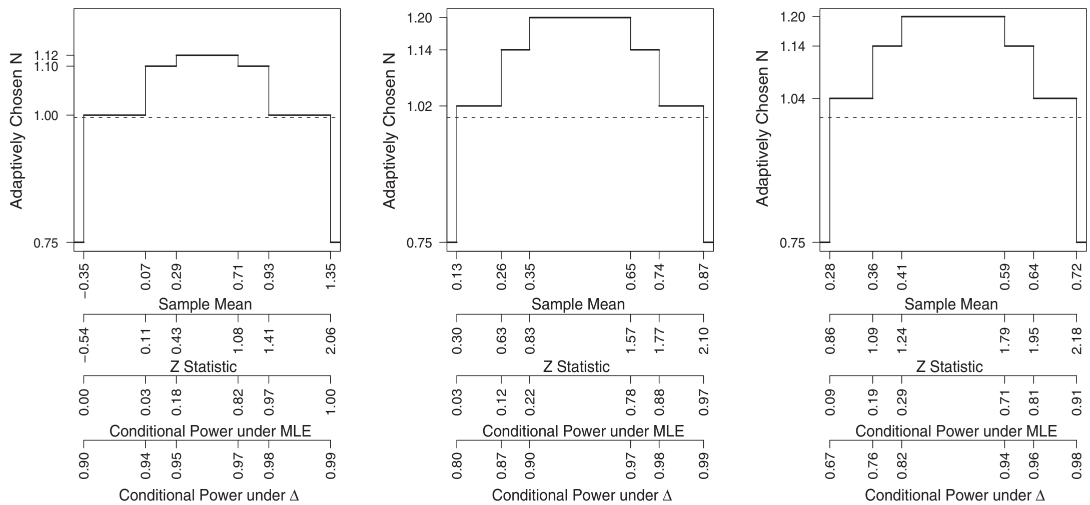
- There will be only one analysis at which an efficacy decision can be made. An earlier 'adaptation' analysis is permitted to help determine the optimal sample size for the final analysis.
- The desired type I error is $\alpha = 0.025$, and power is $\beta = 0.975$ at the design alternative $\theta = \Delta$. The initial candidate design is a fixed sample design with $n = \frac{(z_{1-\alpha}+z_\beta)^2}{\Delta^2}$ subjects required to meet these operating characteristics.
- A minimum sample size for early stopping of $n_{\min} < n$ is required so that an adequate safety profile for the new treatment can be developed. We assume that the minimal sample size for early stopping is $n_{\min} = 0.75n$. Similar patterns to those described subsequently were observed when $n_{\min}$ was set at different proportions of the fixed sample size.
- The primary interest is in finding the most efficient design satisfying these constraints, where efficiency is measured by the ASN at the design alternatives.

Given the preceding constraints, we consider a range of adaptive designs. The 'adaptation' analysis, at which the estimate of treatment effect will be used to determine the sample size for the final analysis, may occur at a range of time points n_{adap} prior to the accrual of $n_{\min}$ subjects. Let $n_{\text{adap}} = R * n_{\min}$, and consider $R \in \{0.1, 0.2, ..., 0.9, 1.0\}$. The adaptive design with $R = 1.0$ is the only one of the 10 candidate adaptive designs that allows stopping for futility and efficacy both at the analysis used to determine the final sample size and at the final analysis. Each adaptive design described in Table II includes four continuation regions, as adding additional regions had negligible effects on the ASN. We display the average and maximal sample sizes, in units of the fixed sample size n, for these optimal adaptive designs. Table II also provides the probabilities that the sample size will exceed n, $1.1n$, and $1.2n$ for each of the candidate designs.

These results demonstrate several interesting characteristics of adaptive designs in this setting. First, it is clear that adapting the sample size on the basis of minimal statistical information is not a good idea. Adaptations at 10% and 20% of $n_{\min}$, for example, provide very small efficiency gains (1% and

Table II. Characteristics of the sample size distribution of adaptive designs in setting #2.

	R (Proportion of $n_{\min}$ at which adaptation occurs)									
	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
$\text{ASN}_{\theta=0,\Delta}$	0.99	0.97	0.94	0.91	0.88	0.86	0.84	0.82	0.80	0.78
Maximal N	1.07	1.12	1.16	1.18	1.20	1.21	1.21	1.20	1.18	1.17
$P_{\theta=0,\Delta}(N > 1.0)$	0.61	0.68	0.55	0.45	0.36	0.29	0.23	0.18	0.14	0.09
$P_{\theta=0,\Delta}(N > 1.1)$	0	0.38	0.36	0.28	0.23	0.18	0.14	0.11	0.09	0.06
$P_{\theta=0,\Delta}(N > 1.2)$	0	0	0	0	0	0.11	0.09	0.07	0	0



(a) R = 0.2 (b) R = 0.5 (c) R = 0.8

Figure 4. Optimal adaptive rules for the choice of N when the adaptation occurs at different stages of the trial. Adaptive designs select the final sample size N on the basis of the test statistic computed after accrual of $n_{\text{adap}} = R * n_{\min}$ subjects. The interim test statistic is displayed on the following scales: the crude estimate of treatment effect (or sample mean) scale (in units of the design alternative Δ), the normalized Z statistic scale, the conditional power scale under the interim estimate of treatment effect ($\theta = \hat{\theta}_1$), and the conditional power scale under the alternative ($\theta = \Delta$). Adaptively chosen values of N are displayed in units of the fixed sample size n. All designs proceed to accrual of a total of $n_{\min} = 0.75n$ subjects if the estimate at n_{adap} falls outside the outermost boundaries. MLE, maximum likelihood estimate.

3% reductions in the ASN) while more substantially increasing the maximal N. Reductions in the ASN achieved by the adaptive designs grow larger as the quantity of accrued statistical information at the adaptation increases. We attain the largest efficiency gain when the adaptation occurs at an analysis that also allows early stopping ($R = 1.0$). In addition, in this setting, the designs that adapt the sample size at one-half to two-thirds of $n_{\min}$ provide worse behavior than designs with later-stage adaptations, with respect to both the maximal N and the probabilities of exceeding important sample size thresholds. These results suggest that the frequently proposed adaptive sampling plans that allow modifications to the sample size at or around one-half of the minimal stopping sample size may not represent efficient choices for an RCT design.

Our results do in fact show that adding an interim analysis to modify the sample size leads to meaningful efficiency gains relative to a fixed sample test, reducing the ASN at the design alternatives by as much as approximately 20%. However, just as in the first setting, it is clear that the largest efficiency gain is attained by adding an analysis at which stopping for futility and efficacy can occur. These results suggest that, if an RCT sampling plan is to include the possibility of interim modifications to the sample size, such an adaptation should occur at an analysis that also permits early stopping. Finally, we note that these optimal adaptive designs lead to maximal increases in the sample size of only about 20%, much less than the 50% or twofold increases often proposed in the literature.

Figure 4 displays the optimally chosen adaptation boundaries on commonly used scales, along with the corresponding choices of N, for three representative values of R. Taking into account the different ranges of values plotted on the x-axes of these three plots, we can see that the boundaries outside of which the optimal adaptive designs proceed only to accrue $n_{\min}$ subjects grow tighter as the timing of adaptation gets later (as R and thus n_{adap} increase). It is interesting to examine the chosen boundaries on the conditional power scale assuming that the interim MLE is the true treatment effect. When $R = 0.5$, for example, so that the adaptation occurs at half the minimum sample size, the adaptive design proceeds to the smallest possible sample size $n_{\min}$ only if the conditional power is as low as 3% or as high as 97%. This choice deviates greatly from adaptive designs that have been proposed in the literature, which have set this lower threshold for proceeding to only the minimal sample size to as high as 36% [6].

The optimal adaptive designs attain smaller efficiency gains over the original fixed sample design at treatment effects falling in between the design alternatives. Figure 5 displays de-trended power and ASN

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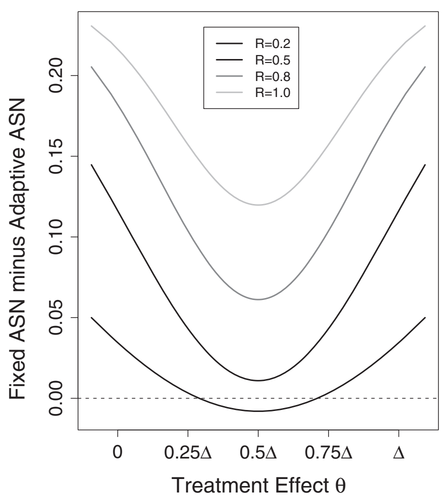
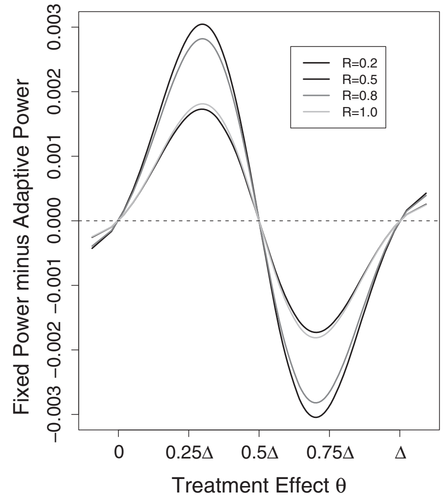


(a) Differences in Expected Sample Size



(b) Differences in Power

Figure 5. Comparison of the fixed sample design with four representative optimal adaptive designs with respect to power and ASN across a range of plausible treatment effects. Differences between the fixed sample and adaptive operating characteristics are shown on the y-axes. ASN differences are in units of the fixed sample size n. The dotted line indicates equality. ASN, expected sample size.

curves, comparing four representative optimal adaptive designs with the original fixed sample design. We can see that, as long as the adaptation analysis occurs after the accrual of at least $0.5n_{\text{min}}$ subjects, the adaptive design is uniformly superior to the fixed sample design with respect to the ASN. However, it is clear that the adaptive design with $R = 1.0$ is most efficient, again suggesting that a larger efficiency gain can be attained by adding an analysis at which early stopping is permitted than by adding an analysis solely used to adapt the sample size. Differences in power are small with no clear benefit for either the fixed sample or adaptive design.

4.3. Sufficiency and generalizability

By considering pre-specified sampling plans with inference based on the minimal sufficient statistic in the previous sections, we are evaluating adaptive designs in their best possible light. When the adaptive sampling plan has not been pre-specified, however, alternative methods must be used to preserve the validity of inference. Commonly used methods that allow unplanned adaptations to the sample size violate the sufficiency principle and subsequently come with costs in efficiency when compared with GSDs [9–11]. It is thus of interest to explore the possible impact of such approaches on our results from the previous sections.

One common proposed adaptive method for maintaining the overall type I error is to preserve the 'conditional error' of the original design, that is, to use the interim estimate of treatment effect at the adaptation analysis to change the critical efficacy boundary at the final analysis in order to preserve the conditional type I error under some original reference design [3]. This approach is equivalent to a variety of other adaptive methods (such as the Cui, Hung, and Wang (CHW) combination statistic [5]) in the simple two-stage setting [11]. The hallmark of these methods is the pre-specification of weights that would be used in combining the data obtained prior to and after any adaptive change in the sampling plan. The degree to which these methods might lead to less precise inference might logically depend on the way that the weighting scheme departs from what might be judged the best weighting given the sampling scheme. The factors that might affect that precision include the efficiency of the conditional error function that corresponds to the weighting scheme, the efficiency of the sample size adaptation rule, and the timing of the adaptation analysis. In this section, we present some examples to demonstrate that these factors may combine to lead to substantial decreases in precision relative to inference based on the minimal sufficient statistic, whereas in some other settings, the impact of the re-weighting of observations may be negligible.

In setting 1, we derived an optimal pre-specified adaptive design with two continuation regions, basing inference on the minimal sufficient statistic that achieved an ASN of $0.6831n$, a 0.34% reduction relative to the ASN ($0.6854n$) of the efficient reference GSD. Consider the following alternative adaptive design. At the first analysis, we use a 'conditional error' approach by discretizing: we divide each of the two continuation regions into several smaller subregions and then, for each subregion, modify the final critical efficacy boundary in order to preserve the conditional type I error at the subregion's midpoint under the original GSD. This method violates the sufficiency principle as the final critical boundary is a function of the first-stage estimate of treatment effect. Thus, it is possible for the same value of the minimal sufficient statistic, which is the final sample size and the estimate of treatment effect based on the cumulative data at the time of stopping, to lead to opposite decisions at the end of the trial. Using the optimization routine described earlier and holding α and β constant, we derived the 'optimal' adaptive design with two continuation regions, two corresponding pre-specified final sample sizes, and critical boundaries at the final analysis computed using this conditional error approach. Such a design attained an ASN of $0.6842n$ and thus is slightly more efficient than the GSD and slightly less efficient than the adaptive design that uses the sufficient statistic.

However, we provide another example to demonstrate that the loss in efficiency incurred by violating the sufficiency principle may be substantial, depending on the choice of conditional error function. We start with a symmetric O'Brien Fleming GSD with two equally spaced analyses (at $0.51n$ and $1.01n$, where n is the sample size of a fixed sample design with the same power), a type I error of $\alpha = 0.025$ at $\theta = 0$, and power equal to 0.975 at $\theta = \Delta$. The critical final efficacy boundary is $a_2 = d_2 = 0.5\Delta$ on the sample mean scale. Next, we optimally add one adaptation region at the first analysis, requiring the accrual of at least 10% more subjects for a second analysis (this results in $C_1 = (0.20\Delta, 0.80\Delta)$, $n_2^{(1)} = 1.16n$, $n_2^{(2)} = 0.56n$). We compare two candidate adaptive designs. The first design, *Adap1*, is the optimal adaptive design with two continuation regions at the first analysis and the preservation of the original final efficacy boundary $a_2 = d_2 = 0.5\Delta$. The second design, *Adap2*, consists of the same two continuation regions at the first analysis and the same optimal choices of N_2 corresponding to those regions but uses the conditional error approach to change the boundary at the final analysis (it now ranges from 0.29Δ to 0.91Δ on the sample mean scale). Both of our candidate designs have the same type I error and ASN. However, the second design Adap2 suffers a substantial loss in power as a result of its failure to base inference on the minimal sufficient statistic. On the basis of the results of 1,000,000 simulations, under the design alternative $\theta = \Delta$, designs Adap1 and Adap2 have powers 0.975 and 0.921, respectively. Under the intermediate alternative $\theta = \Delta/2$, Adap1 attains power equal to 0.501, as compared with 0.490 for Adap2. If we instead require the accrual of at least 20% more subjects at the second analysis, designs Adap1 and Adap2 attain powers 0.975 and 0.944, respectively, under $\theta = \Delta$. In common fixed sample or group sequential settings, an increase of 35–38% in the maximal sample size (and ASN) is required to increase power from 0.921 to 0.975, whereas an increase in sample sizes of 22–24% is required to raise power from 0.944 to 0.975. This simple example thus demonstrates that the loss in efficiency resulting from the violation of the sufficiency principle can be meaningful.

We have also examined potential efficiency loss as the timing of the adaptation analysis is varied. As shown in the previous section, early adaptive modification of the final sample size is associated with less efficient sampling plans compared with adaptation occurring later. However, it is the later adaptation that we might imagine has the greater potential to lead to inefficiency of the weighted combination statistics because a large increase in the sample size would only carry the inferential weight of a relatively small proportion of the originally planned design. To illustrate this point, we considered adaptive modification of a planned sample size occurring at $0.25n$, $0.5n$, $0.75n$, and $0.9n$. At the adaptation analysis, the final sample size was increased from n to $2n$ inside a single continuation region. This adaptation increased unconditional power for a clinically important alternative from 50% to approximately 80% or, equivalently, from 80% to approximately 97.5% when using the MLE or likelihood ratio ordering with the minimal sufficient statistic. In those settings, the relative efficiency of inference based on the minimal sufficient statistic (either the MLE or likelihood ratio ordering) compared with the CHW combination statistic is approximately 1.03, 1.07, 1.17, and 1.31, respectively. As we considered more restricted adaptation in terms of the magnitude of interim results that would lead to a doubling of the sample size, an adaptation rule that increased the power from 50% to 78% when using the minimal sufficient statistic yielded statistical power of 69% with the CHW statistic for a relative efficiency loss of 24%. An adaptation that increased the power from 50% to 68% using the minimal sufficient statistic yielded power of 66% power with the CHW statistic (a relative efficiency loss of 6%).

Although these findings on sufficiency are important considerations in interpreting and generalizing our results on efficiency, we want to emphasize that the sufficiency principle is not the focus of the current paper. Here, we remove this source of inefficiency and evaluate the class of adaptive designs in which the sampling plan is completely pre-specified and inference is based on the minimal sufficient statistic. Importantly, this means that differences in important operating characteristics between competing adaptive (and group sequential) designs in Sections 4.1 and 4.2 can be attributed solely to the contrasting boundaries and sample size rules rather than the method of inference. That being said, methods such as the CHW combination statistic approach that provide the flexibility to make adjustments to pre-specified decision rules while maintaining the experiment-wise type I error rate may be desirable in certain settings. We have not in this section exhaustively explored the limits of settings in which the use of an adaptive combination statistic does or does not substantially affect the precision of inference. In a setting where the more flexible adaptive designs are warranted, the results of this section suggest that it is highly important that a clinical trialist fully evaluate all aspects of all candidate adaptive designs, as it is difficult to anticipate the behavior of a particular combination of conditional error function, sample size modification rule, and adaptation analysis timing.

5. Other issues with adaptive designs

The evaluation of the suitability of a particular adaptive design for some specific RCT setting should not be limited to type I error control and efficiency considerations. It is also critical that any confirmatory phase III clinical trial design is able to produce results that are interpretable and that investigators are able to provide reliable inference on the treatment effect of interest. Regulatory agencies must balance estimates of efficacy against safety concerns in deciding whether to approve a new drug and also need reliable estimates and intervals for the development of new drug labeling. In addition, clinicians may use estimates of treatment effect to compare one treatment option with alternative interventions for a particular patient and indication. Confirmatory trial designs should allow the computation of unbiased and sufficiently precise estimates of treatment effect and the construction of well-behaved confidence intervals with the correct frequentist coverage probabilities for both efficacy and safety endpoints.

Full frequentist inference is possible in the context of a completely pre-specified design with adaptations to the maximal sample size. The ability to compute the sampling density of the sufficient statistic allows the extension of methods for estimation and inference developed for the analysis of group sequential trials. Orderings of the outcome space previously described for GSDs [25–29] can be generalized to the adaptive setting in order to compute median-unbiased estimates of the treatment effect, p-values, and confidence intervals. Jennison and Turnbull enumerated the desirable properties of estimates, p-values, and confidence intervals [18], and extensive research has been conducted using such criteria to compare different statistics and orderings in the group sequential setting [18, 25–31]. Such research is also needed in the adaptive setting. The extension of previously described orderings of the outcome space to adaptive designs may exhibit different and less desirable behavior than is observed with group sequential tests with respect to properties such as generation of convex confidence intervals, agreement of p-values and intervals with test decisions, and width of confidence intervals. This may be particularly true in the case of non-symmetric adaptive designs. There is some literature on this topic [7, 32], but more research is needed to rigorously evaluate the behavior of inferential methods under different orderings of the outcome space and when using a range of different adaptive designs.

We note, however, that the ability to provide inference is even more difficult if adaptations to the sample size are based on unplanned rules or if modifications are made to scientific aspects of the study design. For example, adaptive designs with unplanned changes to the study population (e.g., ‘adaptive enrichment’), the primary endpoint, or the treatment strategy on the basis of interim estimates of treatment effect alter the scientific hypotheses being tested in the different stages of the trial and compromise the investigators’ ability to provide reliable inference on a particular treatment indication at the study’s end. Some authors have described general theory for such inference [33], and others have proposed specific approaches [32]. None have yet evaluated these methods to the degree previously reported for group sequential inference, so it is not yet clear what the settings are in which the use of methods accommodating unplanned adaptation might lead to substantial efficiency loss or might be nearly fully efficient when compared with methods available for the minimal sufficient statistic.

There are also a number of logistical issues inherent in adaptive designs. Pre-specifying exact rules for interim modifications to aspects of the study design leads to a more complicated protocol and thus may extend the design stage of the trial. Such an increase in the duration of the design stage could outweigh small efficiency gains made during the conduct of the trial. In addition, the pre-specification of rules for adapting the maximal sample size could cause interim analyses to essentially reveal the current estimate of treatment effect to study investigators who should remain blinded until the trial's conclusion. If the choice of maximal sample size is a continuous function of the interim estimate, such as in the case of designs based on increasing the conditional power to a fixed target, investigators would be able to use the new final sample size target to infer the current estimate of treatment effect. It is well known that in certain settings, unblinding of investigators or patients to treatment results can introduce multiple sources of bias and can compromise the validity of a confirmatory trial. This issue becomes less of a concern in the case of an adaptive design containing only a few adaptation regions and corresponding possible choices for the maximal sample size. With such a design, investigators would only be able to identify a region containing the interim estimate and may be less likely to change trial conduct. In our research, we have found that there is little advantage to using a design with more than a few possible adaptively chosen final sample sizes.

There are a number of other important scientific issues in clinical trial design that may become more challenging to adequately address in the adaptive setting. These include the use of non-binding boundaries, the incorporation of data on a secondary efficacy endpoint into decision-making and inference, and the possibility of accumulating additional data after stopping (overrunning). Many of the methods that have been proposed to address these concerns in the group sequential setting, although perhaps not perfect solutions, could also be implemented when carrying out pre-specified adaptive sampling plans such as those described in our manuscript. For example, with respect to binding boundaries, one could easily design an adaptive trial with separate significance and non-binding futility boundaries, such as those expressed in Equations (1) and (2) of Liu and Anderson's 2008 paper on adaptive trials [7]. This would simply require a modification of our Equation (1) for the type I error because of the use of non-binding rather than binding futility bounds. Methods proposed by Whitehead [34] and Hall and Liu [35] to handle data accrued after stopping under a GSD could be generalized to the adaptive setting. We also note that the findings in this paper relate to settings in which outcomes are immediately observed. A more detailed evaluation of adaptation rules is necessary in the presence of longitudinal outcomes when it is important to consider both the number of subjects accrued and the trial duration. Emerson *et al*. found some benefits of pre-specified adaptive designs over GSDs in certain time-to-event survival settings [24].

Although all of these ethical, logistical, and scientific issues are critically important to consider in designing any RCT, they are not the focus of this current manuscript. Here, we have set out to describe the effects of different types of adaptation rules on standard measures of efficiency.

6. Conclusions and discussion

The goal of this paper was to critically evaluate a range of simple and easily implemented pre-specified adaptive sampling plans in order to contribute to the understanding of adaptive designs with interim modifications to the maximal sample size. To that end, we focused on the efficiency of adaptation, although we acknowledge that a great many other considerations go into the selection of a sequential monitoring plan, including the need to be able to address long-term safety and secondary endpoints.

In the context of two general clinical trial settings, where different optimality criteria govern the choice of RCT design, we compared a variety of fixed sample, group sequential, and adaptive designs with respect to standard operating characteristics. We found simple and easily implemented symmetric adaptive designs with completely pre-specified stopping and continuation boundaries and inference based on the minimal sufficient statistic that were 'optimal' in the sense that they minimized the ASN at the design alternatives. Our comparisons of alternative designs provide a commentary on the efficiency gains that can be attained with the use of adaptive designs in simple and realistic settings. They also offer insight into what are efficient rules for adapting the sample size at an interim stage of the trial in those settings where the greater flexibility of an adaptive design might be desired.

Our results from the first setting are consistent with those discussed in several previous works [10, 14–16] in demonstrating that optimal completely pre-specified adaptive designs with inference based on the minimal sufficient statistic can only lead to very small efficiency gains over optimal GSDs with the same number of analyses. We attained these efficiency gains when the number of analyses was held constant—this differs from prior research by Tsiatis and Mehta in which GSDs were permitted more interim analyses than competing adaptive designs [9]. Our study builds on previous research by quantifying precisely the efficiency gains that can be attained with the use of simple and easily implemented adaptive sampling plans in realistic RCT design settings. Constraining the RCT design to a maximum of two analyses, we found adaptive designs that attained an ASN at the design alternatives of nearly 0.5%

lower than an efficient GSD. However, these gains were offset by losses in efficiency at intermediate values of the treatment effect. In addition, adding a third analysis to the GSD decreased the ASN by more than 6%, suggesting that the addition of stopping analyses provides more substantial efficiency gains than adding analyses used to adapt the sample size.

In addition to quantifying efficiency gains, the results of our study provide important insight into what are good and bad types of adaptation rules. In particular, we found that dividing the original group sequential continuation boundary into more than a few adaptation regions leads to negligible efficiency gains. In fact, we achieved most of the efficiency gain obtained through adaptation by adding the first adaptation region (allowing two different potential maximal sample sizes). We have found this to be true for asymmetric adaptive procedures as well. Briefly, we investigated the use of an adaptive rule on the basis of the procedure of Gao, Ware, and Mehta [36], which is designed to achieve a specified conditional power, conditional on the estimated effect size, by modifying both the critical value and the maximal sample size. Whereas the procedure proposed by Gao, Ware, and Mehta uses a continuous function of the interim estimate to determine the maximal sample size, we modified this approach by discretizing: dividing the set of possible interim effect sizes into disjoint regions of values inside of which the same future boundary and sample size will be used. We computed the future boundary and sample size for each region by carrying out these computations at the region's midpoint using the formulae of Gao, Ware, and Mehta, an approach that preserves the type I error while boosting the conditional power to 90%. For this procedure, the goal of adaptation was to increase power (rather than decrease ASN). We found a negligible difference between the use of only a few adaptation regions and the use of what essentially is a continuous function to determine the final sample size and boundary: a design with 101 adaptation regions achieved a maximal power increase of less than 0.04% over a design with five adaptation regions. These findings suggest that the frequently proposed use of a continuous function of the interim estimate to determine the maximal sample size (e.g., to raise the conditional power to a desired level) may be unnecessary. This is especially noteworthy considering the logistical issues that accompany such continuous rules. On the other hand, it is straightforward to implement and compute the operating characteristics of simple adaptive designs that contain only a few adaptation regions using standard group sequential software.

Our results also provide interesting commentary on the merit of other characteristics of adaptation rules. The findings from our second RCT design setting demonstrate that adding an interim analysis to modify the sample size leads to meaningful efficiency gains relative to a fixed sample test, reducing the ASN at the design alternatives by as much as approximately 20%. However, just as in the first setting, our results demonstrate that a greater efficiency gain can be attained by adding an analysis at which stopping for futility and efficacy can occur. These findings suggest that, if an RCT sampling plan is to include the possibility of interim modifications to the sample size, such an adaptation should occur at an analysis that also permits early stopping.

Our results also suggest that adaptive designs frequently proposed in the literature do not include optimal timing for the adaptation analyses or optimal rules for modifying the sample size. It is common for such designs to include interim modifications after the accrual of one-half the original fixed sample size, which may be inefficiently early. We also note that the optimal adaptive sampling plans found for the RCT design settings considered in this paper only lead to maximal increases in the sample size of about 20% to 30%, much less than the 50% or twofold increases often proposed in the literature. Designs with the possibility of such large increases in the maximal sample likely do not result in sufficient efficiency gains to offset the huge potential investment required of the sponsor. It is also common for proposed adaptive designs to use suboptimal thresholds and rules on the conditional power scale for modifying the sample size.

We believe that inefficient adaptive designs are frequently proposed in the literature because investigators choose adaptation rules based on intuitive and seemingly desirable changes in poorly understood scales such as conditional power. They do so without a careful evaluation of the effects on important unconditional operating characteristics and without rigorous comparisons with alternative adaptive designs and GSDs. Many believe that the true value of sample size adaptation to a sponsor is its ability to avoid a large up-front commitment in sample size by allowing a staged investment of resources, especially in settings where a range of treatment effects may be considered both plausible and clinically meaningful [6]. We do not present this perspective on adaptive designs in this paper because we disagree with the contention that typically proposed adaptive designs avoid large up-front commitments in the confirmatory setting. We have addressed this issue in detail in a previous commentary [8]. As has been discussed in a manuscript on the frequentist evaluation of group sequential trials [37] that readily applies to the adaptive setting, investigators should choose a design using an iterative search based on important operating characteristics while ensuring that the scientific and ethical constraints of the particular trial setting are satisfied. Because a stopping or adaptation rule on one scale (such as conditional power under a presumed treatment effect or Bayesian predictive power under some prior) induces a stopping rule on all other scales, the choice of boundary scale is relatively unimportant as long as the important scientific operating characteristics of the trial are carefully investigated. Our results provide optimally chosen boundaries on several scales for different design settings and thus should help investigators better understand what are good and bad choices of adaptive sampling plans. At a minimum, we hope that these results cause investigators to more rigorously evaluate candidate group sequential and adaptive designs.

As with any evaluation of alternative group sequential and adaptive designs, it is very challenging to carry out a fair and reasonable comparison. There are many parameters that can vary, such as the number and timing of analyses, the family of stopping boundaries, and the operating characteristics used to determine efficiency as well as possible scientific constraints on the conservatism of early boundaries or the minimal sample size for early stopping. In this paper, we address only a small fraction of this large space of designs. We focus our investigation on symmetric designs in two simple settings and define 'efficiency' and find 'optimal' designs based on the ASN at the design alternatives. However, we believe that these simple comparisons should provide insight into the broader class of adaptive designs and GSDs, just as the investigations of the properties of various boundary shape relationships in GSDs show great similarity of results in both single boundary and two boundary designs and when applied to one-sided or two-sided hypothesis testing. Many recent papers have failed to come up with fair comparisons of adaptive and alternative designs and thus lead to results that are challenging or impossible to interpret. We present comparisons of competing sampling plans by first clearly describing realistic optimality criteria governing the choice of RCT design and then finding candidate fixed sample, group sequential, and adaptive designs meeting these constraints. We do not claim that results will generalize exactly to all RCT design settings but do believe that our findings on the efficiency of different sample size modification rules will generalize qualitatively to the broader class of adaptive designs.

In summary, we have evaluated adaptive designs with pre-specified rules for modifying the maximal sample size on the basis of interim estimates of treatment effect and inference based on the minimal sufficient statistic. Completely pre-specified adaptive designs allow the computation of the sampling density of the sufficient statistic and thus should allow investigators to carry out full frequentist inference at the end of the clinical trial. Our results suggest that simple and easily implemented pre-specified adaptive sampling plans achieve only small efficiency gains over alternative GSDs with the same number of analyses in realistic settings. We would argue that these very small efficiency gains are often not worth the additional logistical challenges that come with adaptive designs and that standard GSDs best address the complex ethical, scientific, and efficiency issues inherent in most, if not all, RCT settings. However, adaptive designs continue to be proposed in actual clinical research, and thus, it is important to critically evaluate such sampling plans so that investigators have the tools to choose an efficient design that satisfies the scientific constraints of a specific RCT setting. To this end, our findings provide optimal adaptation rules in simple design settings and thus provide some insight into what are efficient choices of adaptive sampling plans and where it may be best to dedicate future research efforts. In particular, our results suggest that in searching for adaptive sampling plans, it is likely adequate to restrict attention to simple designs with only a few adaptation regions.

References

1. Bauer P, Kohne K. Evaluation of experiments with adaptive interim analyses. *Biometrics* 1994; **50**(4):1029–1041.
2. Proschan MA, Hunsberger SA. Designed extension of studies based on conditional power. *Biometrics* 1995; **51**(4):1315–1324.
3. Müller HH, Schäfer H. Adaptive group sequential designs for clinical trials: combining the advantages of adaptive and of classical group sequential approaches. *International Biometric Society* 2001; **57**(3):886–891.
4. Fisher LD. Self-designing clinical trials. *Statistics in Medicine* 1998; **17**:1551–1562.
5. Cui L, Hung HMJ, Wang SJ. Modification of sample size in group sequential clinical trials. *Biometrics* 1999; **55**:853–857.
6. Mehta C, Pocock S. Adaptive increase in sample size when interim results are promising: a practical guide with examples. *Statistics in Medicine* 2011; **30**(28):3267–3284.
7. Liu Q, Anderson KM. On adaptive extensions of group sequential trials for clinical investigations. *Journal of the American Statistical Association* 2008; **103**(484):1621–1630.
8. Emerson SS, Levin GP, Emerson SC. Comments on 'adaptive increase in sample size when interim results are promising: a practical guide with examples'. *Statistics in Medicine* 2011; **30**(28):3285–3301.

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9. Tsiatis AA, Mehta C. On the inefficiency of the adaptive design for monitoring clinical trials. *Biometrika* 2003; **90**(2):367–378.
10. Jennison C, Turnbull BW. Adaptive and nonadaptive group sequential tests. *Biometrika* 2006; **93**(1):1–21.
11. Jennison C, Turnbull BW. Mid-course sample size modification in clinical trials based on the observed treatment effect. *Statistics in Medicine* 2003; **22**:971–993.
12. Schmitz N. *Optimal Sequentially Planned Decision Procedures*. Springer-Verlag: New York, 1991.
13. Food and Drug Administration. Guidance for industry: adaptive design clinical trials for drugs and biologics, 2010.
14. Jennison C, Turnbull BW. Efficient group sequential designs when there are several effect sizes under consideration. *Statistics in Medicine* 2006; **25**:917–932.
15. Benerjee A, Tsiatis AA. Adaptive two-stage designs in phase II clinical trials. *Statistics in Medicine* 2006; **25**:3382–3395.
16. Lokhnygina Y, Tsiatis AA. Optimal two-stage group-sequential designs. *Journal of Statistical Planning and Inference* 2008; **138**:489–499.
17. S+SeqTrial. Insightful corporation, 2002. Seattle, Washington.
18. Jennison C, Turnbull BW. *Group Sequential Methods with Applications to Clinical Trials*. Chapman and Hall/CRC: Boca Raton, 2000.
19. Kittelson JM, Emerson SS. A unifying family of group sequential test designs. *Biometrics* 1999; **55**:874–882.
20. Wang SK, Tsiatis AA. Approximately optimal one-parameter boundaries for group sequential trials. *Biometrics* 1987; **43**:193–199.
21. Emerson SS, Fleming TR. Symmetric group sequential test designs. *Biometrics* 1989; **45**(3):905–923.
22. Jennison C. Efficient group sequential tests with unpredictable group sizes. *Biometrika* 1987; **74**:155–165.
23. Armitage P, McPherson CK, Rowe BC. Repeated significance tests on accumulating data. *Journal of the Royal Statistical Society: Series A* 1969; **132**:235–244.
24. Emerson SC, Rudser KD, Emerson SS. Exploring the benefits of adaptive sequential designs in time-to-event endpoint settings. *Statistics in Medicine* 2011; **30**(11):1199–1217.
25. Emerson SS, Fleming TR. Parameter estimation following group sequential hypothesis testing. *Biometrika* 1990; **77**(4):875–892.
26. Chang MN, O'Brien PC. Confidence intervals following group sequential tests. *Controlled Clinical Trials* 1986; **7**:18–26.
27. Tsiatis AA, Rosner GL, Mehta CR. Exact confidence intervals following a group sequential test. *Biometrics* 1984; **40**(3):797–803.
28. Rosner GL, Tsiatis AA. Exact confidence intervals following a group sequential test: a comparison of methods. *Biometrika* 1988; **75**:723–729.
29. Chang MN. Confidence intervals for a normal mean following a group sequential test. *Biometrics* 1989; **45**:247–254.
30. Chang MN, Gould AL, Snapinn SM. P-values for group sequential testing. *Biometrika* 1995; **82**(3):650–654.
31. Gillen DL, Emerson SS. A note on p-values under group sequential testing and nonproportional hazards. *Biometrics* 2005; **61**(2):546–551.
32. Brannath W, Mehta CR, Posch M. Exact confidence bounds following adaptive group sequential tests. *Biometrics* 2009; **65**:539–546.
33. Liu Q, Proschan MA, Pledger GW. A unified theory of two-stage adaptive designs. *Journal of the American Statistical Association* 2002; **97**(460):1034–1041.
34. Whitehead J. Overrunning and underrunning in sequential clinical trials. *Controlled Clinical Trials* 1992; **13**:106–121.
35. Hall WJ, Liu A. Sequential tests and estimators after overrunning based on maximum-likelihood ordering. *Biometrika* 2002; **89**(3):699–707.
36. Gao P, Ware J, Mehta C. Sample size re-estimation for adaptive sequential design in clinical trials. *Journal of Biopharmaceutical Statistics* 2008; **18**(6):1184–1196.
37. Emerson SS, Kittelson JM, Gillen DL. Frequentist evaluation of group sequential clinical trial designs. *Statistics in Medicine* 2007; **26**:5047–5080.

