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ABSTRACT

Oncology phase II clinical trials are often used to evaluate the initial effect of a new regimen to determine if there is warrant further study in a phase III clinical trial. Simon's two-stage design is a commonly used design in specifying sample sizes and critical values in phase II oncology clinical trials. It is common, however, for attained sample sizes in these trials to be different than planned. In this thesis, we examine the problems in hypothesis testing for two stage phase II clinical trial designs when attained sample sizes differ from the planned design. We describe methods for redesigning trials when attained sample sizes that differ from planned and introduce a new method for redesigning a two stage clinical trial when the first stage sample sizes deviates from planned. These methods would primarily be used for prespecifying redesigns for the cases when the Simon-like design does not have planned accrual. We find that the Likelihood approach has more desireable characteristics for deviations from the planned design, though if one wishes to remain with a Frequentist approach, Olson and Koyama's method,an adaptation of a method that Chang *et al.* proposed, may also be appropriate.

Chapter 1

Introduction

Oncology phase II clinical trials are often used to evaluate the initial effect of a new regimen to determine if further study is warranted in a phase III clinical trial [1, 2, 3]. Simon's two-stage design [2] is a commonly used design in phase II oncology clinical trials. Koyama and Chen [3] point out that it is common for actual sample sizes of these phase II trials to differ from the planned, pre-specified sample sizes. This happens due to unanticipated accruement speed or drop-out rates, and multi-center trials can be delayed in communication of enrollment and response information causing over enrollement. Currently, when attained sample sizes differ from planned, common practice is to treat the attained sample sizes as planned. Though, when acheived sample sizes differ from planned, testing the attained sample sizes as planned leads to invalid inference and hypothesis testing in these cases is not straightforward [1, 3]. Therefore, extensions of two-stage designs for hypothesis testing with unplanned sample size changes is essential.

Many Frequentist methods have been proposed to that handle unplanned sample sizes in the second stage while using the planned stage I sample size; however, our literature review found that only a few Frequentist methods handle unplanned sample sizes in stage I. Moreover, when focusing on deviations in sample sizes in the second stage, many proposed methods are adjusting inference procedures rather than proposing a redesign. Likelihood based designs, can be used to extend Simon's design, offer a nice solution to this problem because these designs offer flexibility in sample size without inflation of type I error rate. Because calculations of p-values are complicated when attained sample sizes are different from planned [3], we focus on methods that offer redesigns of a planned two-stage design that will be prespecified along with the planned design.

In this paper, we discuss the different methods for Simon's design when the attained stage II sample size is different from planned and when attained sample sizes in both stages are different from planned. We review Simon-like designs in chapter 2 and illustrate redesign methods in chapters 3 and 4. In chapter 5, we review a concrete example from a Likelihood-based clinical trial, and in chapter 6, we present results of a numerical and theoretical study comparing Frequentist properties of approaches in the setting where stage I sample size differs from planned are presented.

Chapter 2

Background

Simon's two stage designs for clinical trials are common designs for phase II oncology clinical trials [2]. In Simon's designs, the null hypothesis $\mathrm{H}_0 : p \leq p_0$ is tested against the alternative $\mathrm{H}_1 : p > p_1$, where p is the true response probability, p_0 is the highest probability of response that would indicate that the research regimen is uninteresting and p_1 is the lowest probability of response that would indicate that the research regimen warrants further investigation. Under these hypotheses, it is required that the type I error rate remain less than α and power remain above $1-\beta$. The general framework of Simon's design includes a sample size and critical value in each of the two stages. Let n_1 denote the first stage sample size, n_t the sample size at the end of the second stage, and let n_t be the sample size for the second stage; $n_2 = n_t - n_1$. Let r_1 be the first stage critical value, and r_t the critical value for the end of the second stage. Let X_1 be the number of successes observed in the first stage and X_2 be the number of additional success in the second stage so that $Z_1 \sim \text{Binomial}(n_1, p$ and $X_2 \sim \text{Binomial}(n_2, p)$. Also, let $X_t = X_1 + X_2$. In the first stage, n_1 subjects are enrolled. If r_1 or fewer subjects ($X_1 \leq r_1$) are successes, then the regimen is rejected and the trial is stopped for futility. If $r_1 + 1$ or more subjects are successful, then the trial continues to the second stage by enrolling n_2 additional subjects. If r_t or fewer out of the n_t subjects are successful ($X_t = X_1 + X_2 \leq r_t$), the treatment is considered to be futile, otherwise if $X_t \geq r_t + 1$ subjects succeed, the treatment is considered to be effective and will warrant further study.

Let b denote the binoial proability mass function, $\binom{n}{x} p^x (1-p)^{n-x}$ for $x = 1, 2, .., n$, and B denote the cumulative binomial distribution function $\sum_{i=0}^{x} \binom{n}{i} p^i (1-p)^{n-i}$. The probability of early termination with probability p in Simon's designs is given by $\text{PET} = B(r_1, p, n_1)$.

The expected sample size for probability p is then $\mathrm{EN} = n_1 + (1 - \mathrm{PET})n_2$, and the probability of rejecting a drug for probability p is then

$$PR(p) = B(r_1, p, n_1) + \sum_{x=r_1+1}^{min[n_1,r_t]} b(x, p, n_1)B(r_t - x, p, n_2)$$

. It is required that $PR(p) \geq 1 - \alpha$ and $PR(p) \leq \beta$. Given these constraints, it follows that unconditional power, $UCP(p)$, given probability p, is given by

$$\begin{aligned} 1 - PR(p) &= 1 - \left(B(r_1, p, n_1) + \sum_{x=r_1+1}^{min[n_1,r_t]} b(x, p, n_1)B(r_t - x, p, n_2) \right) \\ &= \sum_{r_1+1}^{n_1} \left\{ \sum_{x_2=r_t-x_1+1}^{n_2} b(x_2, p, n_2) \right\} b(x_1, p, n_1) \end{aligned}$$

and $UCP(p_1) \geq 1 - \beta$ and $UCP(p_0) \leq \alpha$.

Simon introduced Optimal and Minimax designs. An Optimal two-stage design is a Simon's design in which minimizes the expected sample size under the null hypothesis with response value p_0 (EN_0) while still satisfying the type I and type II error probability restrictions. The Minimax design will minimize the maximum sample size ($n_t = n_1 + n_2$). Jung *et al.* [4] introduced an extension of Simon's designs called Admissible designs that are considered a compromise between Optimal and Minimax designs because they have similar maximim sample size as the minimax design and a similar EN_0 to the optimal design. Admissible designs optimize a straight line on the (n, EN)-plane, $q \times n + (1 - q) \times \mathrm{EN}$, for some $q \in [0, 1]$ [4]. Admissible designs satisfy (α, β) constraints and obtain an expected sample size somewhere between Optimal and Minimax designs. Admissible designs may be attractive because they have agreeable properties of both the Minimax and Optimal design. Simon does not allow for early termination of the trial for efficacy [2], and we do not consider that design here. We focus this paper on extensions of Minimax, Optimal, and Admissible designs and call these Simon-like designs.

Chapter 3

Deviation from Planned Sample Sizes In Second Stage

When over- or under-enrollment occurs, a straightforward solution is to perform an interim analysis on the planned number of first stage subjects, and adjust the testing procedure for a sample size in the second stage that is different than planned. This is possible under the assumption of non-informative dropouts; stage one is concluded when the number of non-missing subjects is equal to the planned stage one sample size, and if over enrollment occurs in the first stage, they will only be considered for the second stage analysis [3]. Literature exists describing point estimation of the response rate and p-values for hypothesis testing when stage two sample size is modified. A review of these methods can be found by Porcher et al. [1]. Because Koyama and Chen have shown that the p-value in multistage trials will depend on the design and is complicated in the setting of unplanned sample sizes [3], we only focus on methods that use critical values for hypothesis testing, or redesigns, and will not focus on p-value calculations. **(Basically calculating a p-value is complicated in unplanned settings, so we are just going to use critical values instead)** Koyama et al. propose a method for inference when stage II sample sizes deviate from the planned stage II sample size [3]. Let $n_1, n_t, r_1, r_t, \alpha$ and β be the original design parameters. The authors let the first stage remain as planned and propose a redesign of the second stage. The authors first define conditional power, $\mathrm{A}(x_1, n_2, p) = P_p[X_2 \geq r_t]$. Using conditional power evaluated at p_0, they calculate a new critical value, r_t^*, by finding the value of r_t^* such that $\mathrm{A}^*(x_1, n_2^*, p_0) \leq \mathrm{A}(x_1, n_2, p_0) \equiv P_{p_0}[X_2^* \geq r_t^* | X_1 = x_1] \leq P_{p_0}[X_2 \geq r_t | X_1 = x_1]$, where $X_2^* \sim \mathrm{Binomial}(n_2^*, p_0)$ and n_2^* is the attained stage II sample size. This new critical value will result in a controlled unconditional type I error rate because the new critical value gives a conditional type I error rate that is more conservative than the original conditional type I error rate. The authors comment that the new critical value, r_t^* may require a different number of total responses to reject H_0 for different values of X_1 because it is conditional on the result of the first stage.

Chapter 4

Deviation from Planned Sample Sizes in First Stage

Because accruement of subjects can often be unexpected in the first stage and some situations require early evaluation of the first stage, it's imperative that methods are available to handle situations with attained sample sizes that differ from the planned sample size. Green and Dahlberg [5] and Chen and Ng [6] propose methods for inference when first stage sample sizes differ than planned. Recall that p_0 is the highest probability of response that would indicate that the research regimen is uninteresting and p_1 is the lowest probability of response that would indicate that the research regimen warrants further investigation. Green and Dahlberg extended Southwest Oncology Group's inference method by suggesting to perform a hypothesis test on $H_0 : p = p_1$ versus $H_1 : p < p_1$ in the first stage at the 0.02 α-level and concluding futility if the p-value is ≤ 0.02. They then suggest testing $H_0 : p = p_0$ versus $H_1 : p < p_0$ in the second stage at the 0.05 level. Li et al. indicate that this approach controls type I error and acheives desired power, though this approach is founded on an overall α-level of 0.05, and it is unclear how this method would generalize to any α-level [7]. Chang et al. also point out that Green and Dahlberg's designs can possibly be quite different than the planned designed. Chen and Ng suggest an approach to unplanned sample sizes by considering a range of sample sizes in both the first and second stage. They search these ranges for the Minimax and Optimal designs that satisfy error constraints using the average probability of termination for all possible first stage sample sizes and average expected sample size for all possible stage I and stage II sample size combinations [6]. Some limitations of this approach are that attained sample sizes may fall outside of the ranges specified, it does not consider admissible designs, and the average characteristics are only calculated rather than a specific design. Thus, we consider new approaches to unplanned sample sizes in the first stage in both the Frequentist and Likelihood settings. In the interest of prespecifying designs, we focus on deviation from the planned sample size only in the first stage. It is impractical to prespecify limitless combinations of unplanned sample sizes in both the first and second stages.

4.1 *Chang et al.* Alternative Designs and Adaptation

Chang *et al.* [8] proposed an alternative design that is an extension of Simon-like two stage designs in order to handle unplanned sample sizes in both the first and second stages. This method calculates new critical values for attained sample sizes, and thus one is able to create and pre-specify a new design based on a preferred Simon or Admissible design in defense of the events of unplanned sample sizes. We use this method to pre-specify new designs; that is, we calculate new critical values for different combinations of possible deviations in sample sizes pre-attainment. Because it's desired to stay as closely to the original design as possible, we investigate this method using only attained first stage sample sizes while maintaining the original second stage sample size or original total sample size. Again, let n_1, n_t, r_1, r_t, p_0, p_1, α, and β be the original, planned design parameters. In the case that we let the total sample size be planned, let n_1^{**} be the attained sample size in the first stage and $n_2^{**} = n_t - n_1^{**}$. In the case that we let the second stage sample size remain as planned, let n_1^{**} again be the attained sample size in the first stage and $n_t^{**} = n_2 + n_1^{**}$.

Chang *et al.* proposes that type II error probability spent in stage I is given by $\beta_1 = \mathrm{P}(X_1 \leq r_1 | n_1, p = p_1)$ Based on the attained sample sizes, we choose to spend type II error in the first stage established by the type II error probability spending function

$$\beta(m) = \begin{cases} \beta_1 m/n_1 & \text{if } m \leq n_1 \\ \beta_1 + (\beta - \beta_1)(m - n_1)/n_2 & \text{if } m > n_1 \end{cases}$$

We then find a new stage one critical value, s_1, using this probability spending function such that $P(X_1 \leq s_1|n_1^{**}) \approx \beta(n_1^{**})$, where $\approx$ means "closest to." After s_1 is selected, we then search for an integer for the second stage critical value, s_t, that satisfies

$$\begin{aligned}&P(X_1 > s_1, X_t > s_t|n_1^{**}, m_2, p_0)\\ =&\sum_{s_1}^{n_1^{**}} P(X_2 > s_t - X_1|X_1 = x_1)P(X_1 > s_1)\\ \leq&\alpha\end{aligned}$$

where $m_2 = n_2$ or n_2^{**}. Chang *et al.*'s design can be used for any α-level and is flexible, close to the original design, and preserves, on average, the desired Frequentist type I error rate.

We modify Chang *et al.*'s method because we prefer to be conservative when straying from a desired Simon or Admissible design. We modify the design by selecting s_1 that is closest to the probability of early termination under the null, rather than using a type II error probability spending function. We select s_1 such that

$$P(X_1 \leq s_1|n_1^{**}, p_0) \approx P(X_1 \leq r_1|n_1, p_0)$$

We then select the stage two critical value, s_t, in the same fashion as Chang's design. Another option would be to be choose s_1 such that the probability of early termination with the redesign is conservative relative to the original design. In either case, the designs tend to be close when the attained sample size is close to the original, so we consider the case where the probability of early termination is closest to the original. We call this adaptation to Chang *et al.*'s design "Olson and Koyama's design"

4.2 Likelihood Design

Briefly, the Likelihood methods use the likelihood ratio as a measure of evidence [9]. Here, the likelihood ratio is

$$\begin{aligned} \mathrm{LR}_n &= \frac{\mathrm{L}_n(p_1)}{\mathrm{L}_n(p_0)} \\ &= \frac{p_1^{x_t}(1-p_1)^{n_t-x_t}}{p_0^{x_1}(1-p_0)^{n_t-x_t}} \\ &\in \{[0,1/k],[1/k,k],[k,\infty)\} \end{aligned}$$

and has three evidential zones: evidence for the null hypothesis, weak evidence, and evidence for the alternative hypothesis. If the $\mathrm{LR}_n \in [0,1/k]$, there is evidence for the null hypothesis, if $\mathrm{LR}_n \in [1/k,k]$, there is weak evidence for either hypothesis, and if $\mathrm{LR}_n \in [k,\infty]$, there is evidence for the alternative hypothesis. The probability of observing weak evidence is $\mathrm{PW}_i = P(k_a \leq LR_n \leq k_b|H_i), k_a \leq 1 \leq k_b$, where k_a and k_b are benchmarks for description of evidence, the probability of observing strong evidence is

$$\mathrm{PS}_i = \begin{cases} P(LR_n > k_b|H_i) & \text{if } i = 1 \\ P(LR_n < k_b|H_i) & \text{if } i = 0 \end{cases}$$

and the probability of obseving misleading evidence is

$$\mathrm{PM}_i = \begin{cases} P(LR_n > k_b|H_i) & \text{if } i = 0 \\ P(LR_n < k_b|H_i) & \text{if } i = 1 \end{cases}$$

One advantage to a likelihood sequential design is that the universal bound of misleading evidence under the null hypothesis is $P(LR_n > k_b|H_0) \leq \frac{1}{k_b}$ for any n ≥ 1 when $\frac{1}{k_a} = k_b = k > 1$.

Blume and Ayers [9] consider a phase II Likelihood two-stage design. The Likelihood two stage design will enroll n_1 observations into the first stage. If we observe a likelihood ratio that is $k_{a_1} < LR_{n_1} < k_{b_1}$, where k_{a_1} and k_{b_1} are benchmarks for description of evidence in the first stage, we continue to the second stage. If we observe $\mathrm{LR}_{n_1} \leq k_{a_1}$, the study will stop for futility and if we observe $\mathrm{LR}_{n_1} \geq k_{b_1}$, the study will stop for efficacy. Then, n_2 subjects are enrolled. If the $\mathrm{LR}_{n_t} = \mathrm{LR}_{n_1}\mathrm{LR}_{n_2}$ is $k_{a_t} < \mathrm{LR}_{n_t} < k_{b_t}$, where k_{a_t} and k_{b_t} are benchmarks at the end of stage II, then the study will conclude with weak evidence. The study will conclude with evidence for the alternative hypothesis if $\mathrm{LR}_{n_t} \geq k_{b_t}$ and evidence for the null hypothesis if $\mathrm{LR}_{n_t} \leq k_{a_t}$. Because these designs are not restricted by error rates, and rather use the likelihood ratio, this method offers favorable flexibility for unplanned sample sizes in the first stage. Likewise, one is able to add cohorts and the end of the second stage when there proves to be weak evidence without penalization.

One can adapt the Likelihood two stage design to emulate conventional, Simon-like designs such as Optimal, Minimax, or Admissible designs with binary evidential zones: reject the null or fail to reject the null. In order to do this, one can start with a Simon-like design and redesign with a likelihood ratio approach by setting

$$\begin{aligned}
k_{a_1} &= {\frac{p_1(1-p_0)}{p_0(1-p_1)}}^{r_1} {\frac{1-p_1}{1-p_0}}^{n_1} = {\frac{1-p_0}{1-p_1}}^{r_1-n_1} {\frac{p_1}{p_0}}^{r_1}, \\
k_{a_t} &= {\frac{p_1(1-p_0)}{p_0(1-p_1)}}^{r_t} {\frac{1-p_1}{1-p_0}}^{n_t} = {\frac{1-p_0}{1-p_1}}^{r_t-n_t} {\frac{p_1}{p_0}}^{r_t}, \\
k_{b_1} &= \infty, \\
k_{b_t} &= \infty,
\end{aligned}$$

where n_1, n_t, r_1, r_2 are Simon-like two-stage design parameters. Then, using k_{a_j} and k_{b_j}, we recalculate the critical values, s_1 and s_t, using

$$s_1 = \frac{log(k_{a_1}) - n_1^{**} log(\frac{1-p_1}{1-p_0})}{log(\frac{p_1(1-p_0)}{p_0(1-p_1)})}$$

$$s_t = \frac{log(k_{a_t}) - n_t log(\frac{1-p_1}{1-p_0})}{log(\frac{p_1(1-p_0)}{p_0(1-p_1)})}$$

If s_1 or $s_t < 0$, they are set equal to zero. It is possible for these critical values to be less than 0 when the study design has low sample sizes and deviation from the planned sample size is extreme.

add other likelihood properties here. i.e. how to calculate p(weak), p(strong), EN, and PET.

Blume and Ayers describe that the Likelihood designs preserve type I error rate and are bounded by $\frac{1}{k_{b_t}}$ and are equal to $O_{p_i}\left(n^{-1/2}\right)$. Under the likelihood design, error rates tend to be less of an issue because the the average of the error rates, $\frac{\alpha+\beta}{2}$, is minimized with the likelihood approach [9]. For the purpose of comparing methods, we do not consider the cases in which cohorts can be added after the second stage and let the total sample size remain as planned similar to the Frequentist approach. We also only consider Likelihood redesign methods to emulate Frequentist designs – to calculate new critical values – and do not consider pure Likelihood method two-stage design as formerly introduced.

Chapter 5

Example

In order to compare these new Frequentist and Likelihood methods for deviation of sample size in the first stage, we first introduce a concrete example. An actual phase II cancer clinical trial was designed using a Likelihood two-stage design. In order to stick to convention, the trial would only stop early for futility. The planned design parameters are $n_1 = 17$, $n_t = 41$, $r_1 = 7$, $r_t = 21$, $p_0 = 0.4$, and $p_1 = 0.6$. This study design has an expected sample size of 25.6 and a probability of early termination under the null hypothesis of 64%. This is considered an Admissible design and meets the nominal type I error rate, $\alpha = 0.05$, and type II error rate, $\beta = 0.2$. The authors provide alternative interim stopping rules for sample sizes that deviate from the planned design using the Likelihood approach. These new designs have a probability of early termination under the null that exceed 50% and preserve type I and type II error rates. Using the original likelihood design, but varying n_1, one can use Chang *et al.*'s method and Olson and Koyama's method, which uses probability of early termination criteria, to obtain similar results. We keep total sample size equal to the planned total sample size in this case. We compare attained methods characteristics, in particular, type I error, power, probability of early termination under the null hypothesis, and expected sample size under the null hypothesis. We refer to the Likelihood redesign, Chang and Olson and Koyama redesigns as "attained methods."

This example illustrates the comprability of the three adapted design methods. Generally, the stopping rules between the Chang designs and the Likelihood design are the same when n_1^{**} ranges from 16 to 23. When $n_1 = 16$, the Olson and Koyama's design gives a more conservative critical value; this is expected by design and because of the discreteness of the binomial distribution.

Table 5.1: Stopping rules for deviations from first stage planned sample size concrete example

Design	r_1	n_1	PET$_0$	EN$_0$	Likelihood ratio favoring H_0 that corresponds to Simon's futility stopping rule
Likelihood	7	17	64%	25.6	1/3.375
Chang	7	17	64%	25.6	
Olson and Koyama	7	17	64%	25.6	
Likelihood	8	19	67%	26.3	1/3.375
Chang	8	19	67%	26.3	
Olson and Koyama	8	19	67%	26.3	
Likelihood	9	21	69%	27.2	1/3.375
Chang	9	21	69%	27.2	
Olson and Koyama	9	21	69%	27.2	
Likelihood	10	23	71%	28.2	1/3.375
Chang	10	23	71%	28.2	
Olson and Koyama	10	23	71%	28.2	
Likelihood	6	16	53%	27.8	1/5.062
Chang	6	16	53%	27.8	
Olson and Koyama	7	16	72%	23.1	
Likelihood	7	18	56%	28	1/5.062
Chang	7	18	56%	28	
Olson and Koyama	7	18	56%	28	
Likelihood	8	20	60%	28.5	1/5.062
Chang	8	20	60%	28.5	
Olson and Koyama	8	20	60%	28.5	

Chapter 6

Results

We suggest keeping the original total planned sample size or the original planned second stage sample size the same when utilizing Chang's and Olson and Koyama's methods. We choose to keep total sample size the same in our investigation because it results in a more similar design in terms of error rates than maintaining the original second stage sample size. Likelihood methods can result in suffering type I error, which may be a concern in this constrained setting. We also see a parabolic decrease in power in Chang's method, which isn't a fruitful result (Figure 6.1 and 6.2). We also suggest setting $n_t^{**} = n_t$ because this inhibits the ability to stray extremely far from the planned design. If one employs Chang's method, is radical in the first stage, and the resulting probability of continuing is less than 0.05, it will be impossible to make a type I error. This will then reduce the two-stage design to a one-stage design.

We present results that are limited to our primary problem of interest in Tables 6.1 through 6.6. In each design table, the planned design is specified and the first stage sample size varies from planned, while maintaining the original total sample size. We compare attained methods characteristics, in particular, type I error, power, probability of early termination under the null hypothesis, and expected sample size under the null hypothesis. We refer to the Likelihood redesign, Chang and adaptation to Chang redesigns as "attained methods."

Table 6.1 displays a planned Admissible design with varying first stage sample size ± 10. We notice that under low p_0 and p_1, s_1 will vary between each method. Though, power and type I error are likely to be similar between and within each attained method, and expected sample size is also consistent. The Likelihood and Chang method are at risk of low

Figure 6.1: Monte Carlo Simulation of Average Power of 20 Simon-like Designs when Stage I Sample Size Deviates from Planned for Attained Designs ($n_t^{**} = n_1^{**} + n_2$). Number of Simulations = 500.

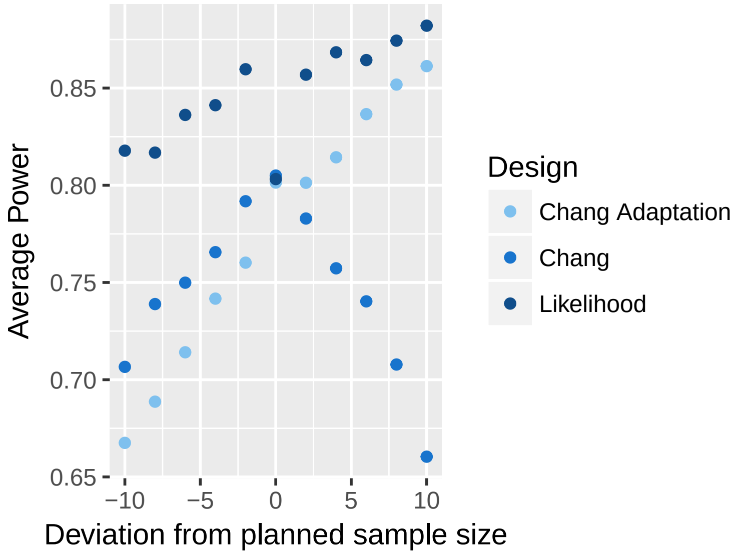
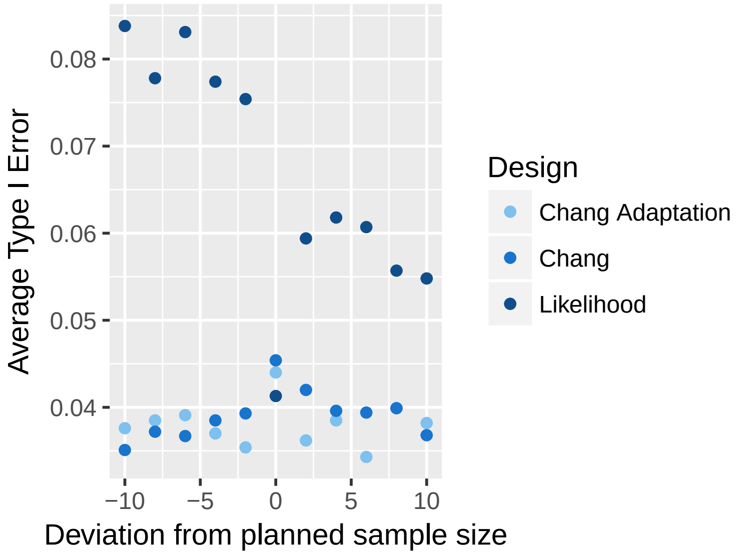


Figure 6.2: Monte Carlo Simulation of Average Power of 20 Simon-like Designs when Stage I Sample Size Deviates from Planned for Attained Designs ($n_t^{**} = n_1^{**} + n_2$) Number of Simulations = 500.



probability of early termination, especially when the sample size is lower than planned. Table 6.2 shows an Optimal design when p_0 is 0.5. Between attained designs, particularly when there is overaccrual, s_1 is inconsistent. We particularly see a large difference when $n_1^{**} = n_1 + 10$ between the Likelihood and Olson and Koyama designs and the Chang design. The Likelihood design is anticonservative in type I error and conservative in type II error here, displaying a $\alpha^{**} > \alpha$ and $1 - \beta^{**} > 1 - \beta$. The Chang designs both have a conservative type I error for all sample size deviations, though Chang and Likelihood designs maintain higher power than Olson and Koyama's. Probability of early termination is closest to the original under Olson and Koyama's, and thus have a much lower expected sample size under the null hypothesis, with as much as a difference of approximately 23.

Table 6.3 displays results from a planned Minimax design when p_0 is larger than 0.5. Here, the Likelihood design has desireable properties with type I error and power consistently closed to the planned design for all deviations in sample size. Though, when the sample size is severely underaccrued, the probability of early termination nearly halves. The expected sample size is consistent between designs. The Chang designs stray from the planned nominal type I and type II errors when there is overaccrual. The PET_0 for the original Chang design varies significantly between deviations.

Table 6.4 through 6.6 display results for planned designs when $\alpha = \beta = 0.1$. Table 6.4 displays attained design characteristics for deviations in sample size when the planned first stage sample size is low. In all three attained designs, we see that as the attained sample size is lower than planned, there is a significant drop in power and a moderate to severe drop in type I error. The probability of early termination almost occurs with probability 1 when the attained sample size is $n_1^{**} = 1$. In practice, though, accrual lower than planned here is not practical. When there is overaccrual, attained design characteristics are not concerning.

Table 6.5 illustrates the similarity between attained designs when p_0 = 0.3. All designs and their deviations are relatively consistent in type I error, power, and PET_0. Though, the Olson and Koyama's design is most consistent in the probability of early termination with the planned design, but we see a conservative deviation in type I error for large overaccrual. Table 6.6 displays similar results as Table 5.3.

Table 6.1: Attained design characteristics from deviation of Admissible II stage design ($p_0 = 0.1$, $p_1 = 0.25$, $\alpha = 0.05$, $\beta = 0.20$)

Planned Design						Attained Sample Size			Redesign																	
									Chang Design						Olson and Koyama Design						Likelihood Design					
p_0	p_1	n_1	n	r_1	r_t	PET$_0$	EN$_0$	n_1^{**}	s_1	s_t	α^{**}	$1-\beta^{**}$	PET$_0^{**}$	EN$_0^{**}$	s_1	s_t	α^{**}	$1-\beta^{**}$	PET$_0^{**}$	EN$_0^{**}$	s_1	s_t	α^{**}	$1-\beta^{**}$	PET$_0^{**}$	EN$_0^{**}$
0.1	0.25	15	41	1	7	0.549	26.725	5	0	7	0.034	0.671	0.590	19.742	0	7	0.034	0.671	0.590	19.742	0	7	0.034	0.671	0.590	19.742
0.1	0.25	15	41	1	7	0.549	26.725	7	0	7	0.040	0.754	0.478	24.738	0	7	0.040	0.754	0.478	24.738	0	7	0.040	0.754	0.478	24.738
0.1	0.25	15	41	1	7	0.549	26.725	9	0	7	0.043	0.797	0.387	28.603	0	7	0.043	0.797	0.387	28.603	0	7	0.043	0.797	0.387	28.603
0.1	0.25	15	41	1	7	0.549	26.725	11	0	7	0.045	0.819	0.314	31.586	1	7	0.035	0.718	0.697	20.079	0	7	0.045	0.819	0.314	31.586
0.1	0.25	15	41	1	7	0.549	26.725	13	0	7	0.046	0.830	0.254	33.883	1	7	0.040	0.771	0.621	23.602	0	7	0.046	0.830	0.254	33.883
0.1	0.25	15	41	1	7	0.549	26.725	15	1	7	0.043	0.803	0.549	26.725	1	7	0.043	0.803	0.549	26.725	1	7	0.043	0.803	0.549	26.725
0.1	0.25	15	41	1	7	0.549	26.725	17	1	7	0.045	0.821	0.482	29.437	1	7	0.045	0.821	0.482	29.437	1	7	0.045	0.821	0.482	29.437
0.1	0.25	15	41	1	7	0.549	26.725	19	2	7	0.041	0.792	0.705	25.480	1	7	0.046	0.831	0.420	31.754	1	7	0.046	0.831	0.420	31.754
0.1	0.25	15	41	1	7	0.549	26.725	21	2	7	0.044	0.814	0.648	28.032	2	7	0.044	0.814	0.648	28.032	1	7	0.047	0.836	0.365	33.705
0.1	0.25	15	41	1	7	0.549	26.725	23	3	7	0.040	0.785	0.807	26.469	2	7	0.046	0.827	0.592	30.345	2	7	0.046	0.827	0.592	30.345
0.1	0.25	15	41	1	7	0.549	26.725	25	3	7	0.043	0.810	0.764	28.783	2	7	0.047	0.834	0.537	32.406	2	7	0.047	0.834	0.537	32.406

Table 6.2: Attained design characteristics from deviation of Simon's Optimal II stage design ($p_0 = 0.5$, $p_1 = 0.65$, $\alpha = 0.05$, $\beta = 0.2$)

Planned Design						Attained Sample Size			Redesign																	
									Chang Design						Olson and Koyama Design						Likelihood Design					
p_0	p_1	n_1	n	r_1	r_t	PET$_0$	EN$_0$	n_1^{**}	s_1	s_t	α^{**}	$1-\beta^{**}$	PET$_0^{**}$	EN$_0^{**}$	s_1	s_t	α^{**}	$1-\beta^{**}$	PET$_0^{**}$	EN$_0^{**}$	s_1	s_t	α^{**}	$1-\beta^{**}$	PET$_0^{**}$	EN$_0^{**}$
0.5	0.65	28	83	15	48	0.714	43.719	18	8	49	0.036	0.815	0.407	56.528	10	48	0.037	0.685	0.760	33.622	9	48	0.048	0.796	0.593	44.472
0.5	0.65	28	83	15	48	0.714	43.719	20	10	48	0.050	0.811	0.588	45.950	11	48	0.039	0.716	0.748	35.859	10	48	0.050	0.811	0.588	45.950
0.5	0.65	28	83	15	48	0.714	43.719	22	11	49	0.034	0.788	0.584	47.370	12	48	0.042	0.743	0.738	37.966	11	48	0.051	0.824	0.584	47.370
0.5	0.65	28	83	15	48	0.714	43.719	24	12	49	0.034	0.798	0.581	48.745	13	48	0.044	0.765	0.729	39.967	12	48	0.052	0.835	0.581	48.745
0.5	0.65	28	83	15	48	0.714	43.719	26	14	48	0.045	0.785	0.721	41.880	14	48	0.045	0.785	0.721	41.880	13	48	0.053	0.845	0.577	50.083
0.5	0.65	28	83	15	48	0.714	43.719	28	15	48	0.047	0.802	0.714	43.719	15	48	0.047	0.802	0.714	43.719	15	48	0.047	0.802	0.714	43.719
0.5	0.65	28	83	15	48	0.714	43.719	30	16	48	0.049	0.816	0.708	45.494	16	48	0.049	0.816	0.708	45.494	16	48	0.049	0.816	0.708	45.494
0.5	0.65	28	83	15	48	0.714	43.719	32	17	49	0.033	0.793	0.702	47.214	17	49	0.033	0.793	0.702	47.214	17	48	0.050	0.828	0.702	47.214
0.5	0.65	28	83	15	48	0.714	43.719	34	19	48	0.043	0.782	0.804	43.592	18	49	0.034	0.803	0.696	48.886	18	48	0.051	0.839	0.696	48.886
0.5	0.65	28	83	15	48	0.714	43.719	36	20	48	0.045	0.798	0.797	45.518	19	49	0.035	0.811	0.691	50.516	19	48	0.053	0.848	0.691	50.516
0.5	0.65	28	83	15	48	0.714	43.719	38	21	48	0.047	0.813	0.791	47.398	20	49	0.035	0.818	0.686	52.110	20	48	0.054	0.856	0.686	52.110

Table 6.3: Attained design characteristics from deviation of Simon's Minimax II stage design ($p_0 = 0.75$, $p_1 = 0.9$, $\alpha = 0.05$, $\beta = 0.2$)

Planned Design						Attained Sample Size			Redesign																	
									Chang Design						Olson and Koyama Design						Likelihood Design					
p_0	p_1	n_1	n	r_1	r_t	PET$_0$	EN$_0$	n_1^{**}	s_1	s_t	α^{**}	$1-\beta^{**}$	PET$_0^{**}$	EN$_0^{**}$	s_1	s_t	α^{**}	$1-\beta^{**}$	PET$_0^{**}$	EN$_0^{**}$	s_1	s_t	α^{**}	$1-\beta^{**}$	PET$_0^{**}$	EN$_0^{**}$
0.75	0.9	22	39	17	33	0.677	27.499	12	8	34	0.019	0.648	0.351	29.517	9	33	0.045	0.763	0.609	22.548	8	33	0.050	0.805	0.351	29.517
0.75	0.9	22	39	17	33	0.677	27.499	14	10	33	0.050	0.800	0.479	27.033	11	33	0.042	0.738	0.719	21.028	10	33	0.050	0.800	0.479	27.033
0.75	0.9	22	39	17	33	0.677	27.499	16	12	33	0.048	0.792	0.595	25.315	12	33	0.048	0.792	0.595	25.315	11	33	0.051	0.809	0.370	30.494
0.75	0.9	22	39	17	33	0.677	27.499	18	13	34	0.019	0.650	0.481	28.892	14	33	0.047	0.782	0.694	24.419	13	33	0.051	0.807	0.481	28.892
0.75	0.9	22	39	17	33	0.677	27.499	20	15	34	0.019	0.650	0.585	27.882	15	34	0.019	0.650	0.585	27.882	15	33	0.050	0.805	0.585	27.882
0.75	0.9	22	39	17	33	0.677	27.499	22	17	33	0.050	0.802	0.677	27.499	17	33	0.050	0.802	0.677	27.499	17	33	0.050	0.802	0.677	27.499
0.75	0.9	22	39	17	33	0.677	27.499	24	19	33	0.049	0.798	0.753	27.700	19	33	0.049	0.798	0.753	27.700	18	33	0.051	0.810	0.578	30.332
0.75	0.9	22	39	17	33	0.677	27.499	26	21	33	0.048	0.791	0.816	28.397	20	34	0.019	0.650	0.663	30.383	20	33	0.051	0.810	0.663	30.383
0.75	0.9	22	39	17	33	0.677	27.499	28	23	33	0.046	0.782	0.865	29.489	22	34	0.019	0.650	0.736	30.902	22	33	0.051	0.810	0.736	30.902
0.75	0.9	22	39	17	33	0.677	27.499	30	25	33	0.043	0.770	0.902	30.881	23	34	0.019	0.650	0.652	33.132	23	33	0.051	0.810	0.652	33.132
0.75	0.9	22	39	17	33	0.677	27.499	32	26	34	0.019	0.650	0.847	33.071	25	34	0.019	0.650	0.722	33.945	25	33	0.051	0.810	0.722	33.945

Table 6.4: Attained design characteristics from deviation of Simon's Optimal II stage design ($p_0 = 0.05$, $p_1 = 0.25$, $\alpha = 0.1$, $\beta = 0.1$)

Planned Design						Attained Sample Size			Redesign																	
									Chang Design						Olson and Koyama Design						Likelihood Design					
p_0	p_1	n_1	n	r_1	r_t	PET$_0$	EN$_0$	n_1^{**}	s_1	s_t	α^{**}	$1-\beta^{**}$	PET$_0^{**}$	EN$_0^{**}$	s_1	s_t	α^{**}	$1-\beta^{**}$	PET$_0^{**}$	EN$_0^{**}$	s_1	s_t	α^{**}	$1-\beta^{**}$	PET$_0^{**}$	EN$_0^{**}$
0.05	0.2	9	24	0	2	0.630	14.546	1	0	0	0.050	0.200	0.950	2.150	0	0	0.050	0.200	0.950	2.150	0	2	0.016	0.192	0.950	2.150
0.05	0.2	9	24	0	2	0.630	14.546	3	0	1	0.097	0.484	0.857	5.995	0	1	0.097	0.484	0.857	5.995	0	2	0.043	0.465	0.857	5.995
0.05	0.2	9	24	0	2	0.630	14.546	5	0	2	0.064	0.635	0.774	9.298	0	2	0.064	0.635	0.774	9.298	0	2	0.064	0.635	0.774	9.298
0.05	0.2	9	24	0	2	0.630	14.546	7	0	2	0.081	0.741	0.698	12.128	0	2	0.081	0.741	0.698	12.128	0	2	0.081	0.741	0.698	12.128
0.05	0.2	9	24	0	2	0.630	14.546	9	0	2	0.093	0.805	0.630	14.546	0	2	0.093	0.805	0.630	14.546	0	2	0.093	0.805	0.630	14.546
0.05	0.2	9	24	0	2	0.630	14.546	11	0	3	0.028	0.714	0.569	16.606	0	3	0.028	0.714	0.569	16.606	0	2	0.102	0.843	0.569	16.606
0.05	0.2	9	24	0	2	0.630	14.546	13	0	3	0.029	0.727	0.513	18.353	0	3	0.029	0.727	0.513	18.353	0	2	0.108	0.864	0.513	18.353
0.05	0.2	9	24	0	2	0.630	14.546	15	1	2	0.086	0.802	0.829	16.539	0	3	0.029	0.733	0.463	19.830	0	2	0.112	0.876	0.463	19.830
0.05	0.2	9	24	0	2	0.630	14.546	17	1	2	0.098	0.842	0.792	18.454	1	2	0.098	0.842	0.792	18.454	0	2	0.114	0.882	0.418	21.073

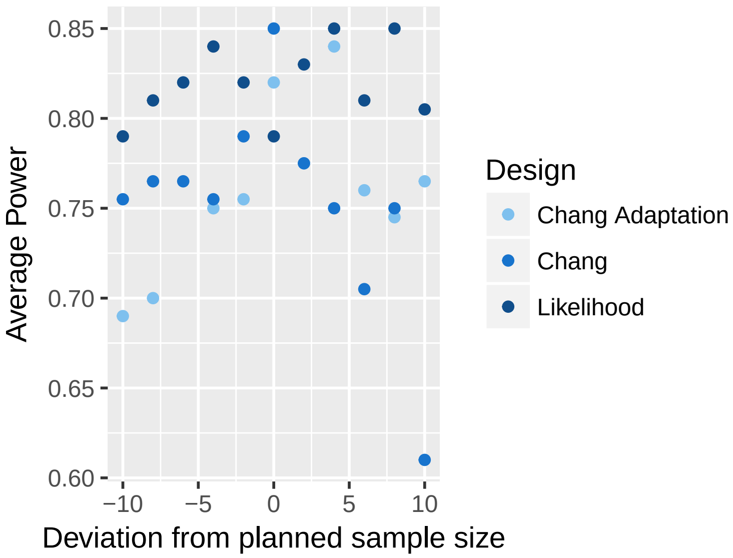
Table 6.5: Attained design characteristics from deviation of Admissible II stage design ($p_0 = 0.3$, $p_1 = 0.45$, $\alpha = 0.1$, $\beta = 0.1$)

		Planned Design					Attained Sample Size										Redesign									
									Chang Design						Olson and Koyama Design						Likelihood Design					
p_0	p_1	n_1	n	r_1	r_t	PET_0	EN_0	n_1^{**}	s_1	s_t	α^{**}	$1-\beta^{**}$	PET_0^{**}	EN_0^{**}	s_1	s_t	α^{**}	$1-\beta^{**}$	PET_0^{**}	EN_0^{**}	s_1	s_t	α^{**}	$1-\beta^{**}$	PET_0^{**}	EN_0^{**}
0.3	0.45	37	72	11	26	0.566	52.181	27	7	26	0.099	0.902	0.411	53.492	8	26	0.090	0.871	0.577	46.020	7	26	0.099	0.902	0.411	53.492
0.3	0.45	37	72	11	26	0.566	52.181	29	8	26	0.097	0.897	0.479	51.416	9	26	0.087	0.862	0.636	44.652	8	26	0.097	0.897	0.479	51.416
0.3	0.45	37	72	11	26	0.566	52.181	31	8	27	0.065	0.870	0.386	56.155	9	26	0.095	0.892	0.542	49.794	8	26	0.101	0.910	0.386	56.155
0.3	0.45	37	72	11	26	0.566	52.181	33	9	26	0.100	0.907	0.450	54.460	10	26	0.093	0.886	0.599	48.626	9	26	0.100	0.907	0.450	54.460
0.3	0.45	37	72	11	26	0.566	52.181	35	10	26	0.099	0.904	0.510	53.132	10	26	0.099	0.904	0.510	53.132	10	26	0.099	0.904	0.510	53.132
0.3	0.45	37	72	11	26	0.566	52.181	37	11	26	0.097	0.901	0.566	52.181	11	26	0.097	0.901	0.566	52.181	11	26	0.097	0.901	0.566	52.181
0.3	0.45	37	72	11	26	0.566	52.181	39	12	26	0.095	0.897	0.618	51.601	12	26	0.095	0.897	0.618	51.601	11	26	0.101	0.912	0.482	56.108
0.3	0.45	37	72	11	26	0.566	52.181	41	13	26	0.094	0.893	0.665	51.372	12	27	0.065	0.871	0.536	55.378	12	26	0.100	0.910	0.536	55.378
0.3	0.45	37	72	11	26	0.566	52.181	43	14	26	0.091	0.889	0.708	51.466	13	26	0.099	0.908	0.587	54.967	13	26	0.099	0.908	0.587	54.967
0.3	0.45	37	72	11	26	0.566	52.181	45	14	26	0.098	0.906	0.635	54.864	13	27	0.066	0.875	0.509	58.264	13	26	0.103	0.915	0.509	58.264
0.3	0.45	37	72	11	26	0.566	52.181	47	15	26	0.097	0.904	0.678	55.050	14	27	0.066	0.874	0.559	58.028	14	26	0.102	0.914	0.559	58.028

Table 6.6: Attained design characteristics from deviation of Simon's Minimax II stage design ($p_0 = 0.75$, $p_1 = 0.9$, $\alpha = 0.1$, $\beta = 0.1$)

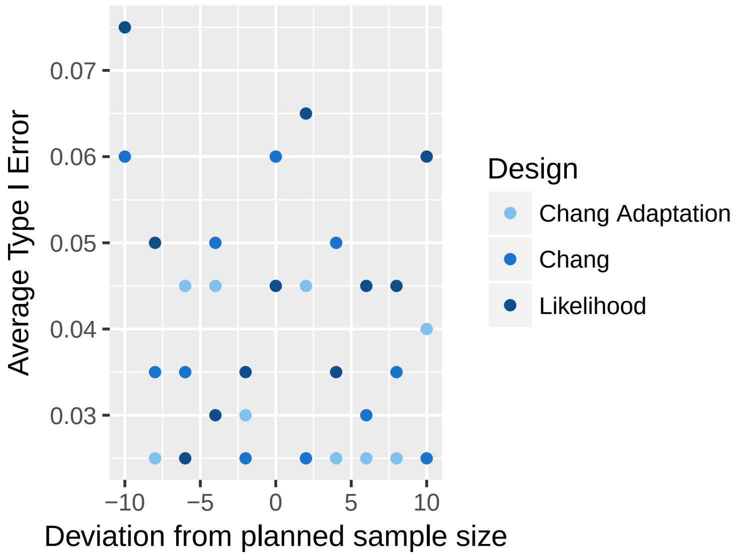
		Planned Design					Attained Sample Size										Redesign									
									Chang Design						Olson and Koyama Design						Likelihood Design					
p_0	p_1	n_1	n	r_1	r_t	PET_0	EN_0	n_1^{**}	s_1	s_t	α^{**}	$1-\beta^{**}$	PET_0^{**}	EN_0^{**}	s_1	s_t	α^{**}	$1-\beta^{**}$	PET_0^{**}	EN_0^{**}	s_1	s_t	α^{**}	$1-\beta^{**}$	PET_0^{**}	EN_0^{**}
0.75	0.9	27	40	20	33	0.529	33.121	17	11	33	0.096	0.900	0.235	34.602	12	33	0.094	0.895	0.426	30.199	11	33	0.096	0.900	0.235	34.602
0.75	0.9	27	40	20	33	0.529	33.121	19	13	33	0.096	0.900	0.332	33.023	14	33	0.092	0.890	0.535	28.774	13	33	0.096	0.900	0.332	33.023
0.75	0.9	27	40	20	33	0.529	33.121	21	15	33	0.095	0.899	0.433	31.765	15	33	0.095	0.899	0.433	31.765	14	33	0.096	0.900	0.256	35.129
0.75	0.9	27	40	20	33	0.529	33.121	23	16	33	0.096	0.900	0.346	34.113	17	33	0.095	0.898	0.532	30.964	16	33	0.096	0.900	0.346	34.113
0.75	0.9	27	40	20	33	0.529	33.121	25	18	33	0.096	0.900	0.439	33.416	18	33	0.096	0.900	0.439	33.416	18	33	0.096	0.900	0.439	33.416
0.75	0.9	27	40	20	33	0.529	33.121	27	20	33	0.096	0.900	0.529	33.121	20	33	0.096	0.900	0.529	33.121	20	33	0.096	0.900	0.529	33.121
0.75	0.9	27	40	20	33	0.529	33.121	29	22	33	0.096	0.900	0.613	33.255	22	33	0.096	0.900	0.613	33.255	21	33	0.096	0.900	0.443	35.124
0.75	0.9	27	40	20	33	0.529	33.121	31	24	33	0.096	0.900	0.688	33.805	23	33	0.096	0.900	0.527	35.255	23	33	0.096	0.900	0.527	35.255
0.75	0.9	27	40	20	33	0.529	33.121	33	26	33	0.096	0.900	0.753	34.727	25	33	0.096	0.900	0.606	35.757	25	33	0.096	0.900	0.606	35.757
0.75	0.9	27	40	20	33	0.529	33.121	35	28	33	0.096	0.900	0.808	35.960	26	33	0.096	0.900	0.526	37.372	26	33	0.096	0.900	0.526	37.372
0.75	0.9	27	40	20	33	0.529	33.121	37	30	33	0.096	0.900	0.853	37.441	28	33	0.096	0.900	0.600	38.199	28	33	0.096	0.900	0.600	38.199

Figure 6.3: Monte Carlo Simulation of Average Power of 20 Simon-like Designs when Stage I Sample Size Deviates from Planned for Attained Designs ($n_t^{**} = n_t$) Number of Simulations = 500.



Figures 6.3 and 6.4 display Monte Carlo simulation results for type I error and power, respectively. The results are an average of 20 Simon-like designs with $\alpha = 0.05, \beta = 0.2$ and stage I sample size deviations with $n_t^{**} = n_t$ for each attained design method. Therefore, each point will be an average of attained type I error or power under different sample size deviations. We see that, on average, the Likelihood two-stage design has power above the nominal power and below the nominal alpha level for all sample size deviations ± 10. Both Chang's and Olson and Koyama's methods are conservative in type I error for all sample size deviations, but are more likely to suffer in power.

Figure 6.4: Monte Carlo Simulation of Average Type I Error Rates of 20 Simon-like Designs when Stage I Sample Size Deviates from Planned for Attained Designs ($n_t^{**} = n_t$) Number of Simulations = 500.



Chapter 7

Discussion and Conclusion

Deviations from the planned second stage sample size has been better studied than deviations from the planned first stage sample size. Many methods have been proposed on decision rules, and Koyama et al. had introduced a redesign when the first stage sample size is as planned. Because the calculation of a p-value in this case is more straightforward than when stage I differs, there may be less literature proposing redesigns. Here, we focused our investigation and results on deviations from the planned first stage sample size. One argument against redesigning these trials in the first place could be that researchers always have the option to simply wait until stage I sample size is met. In practice, though, some ethical matters may arise that would give the researcher incentive to evaluate the first stage prematurely. For instance, if a new regimen appears to be more beneficial than historical treatments, but statistical requirements prevent new subjects from being enrolled until all currently enrolled subjects record responses, a researcher may consider this unethical. In this case, $n_1^{**} < n_1$ where n_1^{**} would be subjects who have recorded responses. Having a decision rule for a case such as this would alleviate some discomfort from both the researcher and statistician, though abuse of new decision rules would be discouraged.

A numerical study suggested that it may be desireable to redesign trials using the planned total sample size because it better controls type I error for all attained methods and power is closer to the nominal power, on average. Assuming that redesigns use the planned total sample size in the redesign, results from different Simon-like designs were presented. Chang and the Olson and Koyama methods primarily differ when there are extreme sample size shifts. This is most likely due to the nature of their methods and their primary goals of maintaining type II error spending or probability of early termination. Recommending the use of these designs in practice will depend on the desire of statistical approach of the researcher. If the researcher prefers to use a Frequentist approach in hypothesis testing, it may be recommended that the Olson and Koyama's approach is used because it results in higher average power across deviations. Because it may be of concern that researchers take advantage of the ability to deviate from the planned design, Olson and Koyama's method also penalizes deviation by resulting in a higher probability of early termination when there is underaccrual than Chang's method.

We do not consider redesigns when both the first and second stage accrual are not as planned because if one is interested in prespecifying stopping criteria for sample size deviations, the number of combinations needed to be specified in order to prespecify the exact combination that will occur is unreasonable. Though, these attained designs are able to accomodate if this is desired. One advantage to the Likelihood design is that it is able to add cohorts of subjects at the end of the second stage if weak evidence is obtained without threatening Frequentist properties such as type I error. Another advantage to the Likelihood approach is that inference is more straightforward because one is not concerned with error rates or p-values. Though we don't consider calculating p-values when stage I differs from planned, it would be complicated if one wished to do so, whereas Likelihood methods would not require this. Likelihood designs are also more generalizable. The Likelihood two-stage approach could be generalized easily to three stages, whereas the Chang designs would not be able to generalize. In this paper, though, we are very much constraining the Likelihood design and not taking full advantage of its natural characteristics. One could simply use a pure Likelihood design and avoid Frequentist issues altogether.

A main concern that we have with redesigning trials for unplanned sample sizes is that researchers could take advantage of the these new stopping criteria and stray from the planned design too often. It is for this reason that one may consider adapting Chang's design using a very conservative rule in the first stage and have the probability of early termination under the null always be higher than planned. When deviations are extreme, especially where there is underacrrual, evaluating the trial early would be highly penalized by potentially having a very high probability of early termination. Overall, intentional early or late evaluation of the first stage without sound reason is highly discouraged and will not result in optimal statistical properties.

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