Optimal Two-Stage Phase II Designs with Long-Term Endpoints

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Abstract

Phase II trials are often designed with an interim analysis so they can be stopped early if a drug is ineffective. One problem with interim analyses is incomplete follow-up for some patients. Standard designs such as Simon(1989) require suspension of accrual until patient follow-up is completed. Case and Morgan (2003) presented a two-stage design for a phase II oncology trial with a long-term endpoint that does not suspend accrual when the interim analysis is conducted. We review the Case and Morgan design and propose modifications to ensure protection of Type I error and improved robustness to non-optimal conditions likely to be encountered in practice. Software (R package) is described to create the optimal designs and easily simulate their properties to check asymptotic approximations and the robustness of the performance of the designs in operational conditions.

1 Introduction

Phase II oncology trials are undertaken to assess the activity of a new treatment with activity most frequently defined in terms of tumor response. With some of the new targeted therapies, it may not be appropriate to use tumor shrinkage to evaluate activity. Instead, the primary endpoint is time to death, time to progression, or some other endpoints that must be evaluated over a longer time period.

Phase II trials are often designed with an interim analysis so they can be stopped early if a drug is ineffective. However, when the primary endpoint requires a longer observation period, interim analyses are challenging because of incomplete follow-up for some patients at the time of the interim analysis. Standard designs such as Simon (1989) require suspension of accrual while patient follow-up is completed. Case and Morgan (2003) presented a two-stage design for a phase II oncology trial with a long-term endpoint that does not suspend accrual while the interim analysis is conducted. They proposed to use the Kaplan-Meier or Nelson-Aalen estimators of the event probability, using methods like those in Lin et al (1996). Estimation at the time of the interim analysis includes patients with partial follow-up without necessitating trial suspension, as also proposed by Jennison and Turnbull (2000). The design minimizes either the expected sample size, expected duration of accrual, or the expected total study length under the hypothesis that the drug is ineffective. The null hypothesis for the new design is an (assumed) known event-free rate within a specified time, which has been judged to represent ineffective treatment. This is similar to the hypothesis in the Simon design, but with much longer specified times for events to occur.

Schaid, Wieand, and Therneau (1990) proposed a similar design using the log rank statistic, which also incorporates patients with incomplete follow-up; the log rank statistic is not evaluated here, but could be inlcuded as a future software option.

Both Lin et al (1996) and Case and Morgan (2003) assume a constant accrual rate throughout the trial, which is not typical in practice. We further investigate the design properties by generalizing the accrual distribution to have different accrual rates in user-specified intervals. As noted in Case and Morgan (2003), when only partial follow-up data are available, the level of the testing procedure can depend on the assumed accrual distribution and the assumed time-to-event distribution under the null hypothesis. We evaluate an optimal design and corresponding analysis that ensure the Type I error rate is below the target level. The reduction in power or corresponding increase in sample size necessary to achieve the conservative type I error rates is also evaluated.

The theoretical derivations of the optimal designs specify a fixed time to end the first stage of accrual and to conduct the interim analysis, with corresponding projected sample size. Case and Morgan (2003) also evaluated a modified interim timing rule that ends the first stage when the projected number of patients has been accrued regardless of the planned interim time. They showed this rule has more robust statistical properties when the accrual rate is mis-specified. We also evaluate this interim timing rule and an additional rule based on the projected patient exposure at the optimal interim time. This rule not only accounts for the number of patients actually accrued, but also the length of time patients have been observed. All of the interim timing rules can be easily applied in practice.

An R package was created to generate the optimal designs and resulting analyses. The package includes code to perform simulations to validate the theoretical calculations, some of which depend on asymptotic approximations. The package also has several options for evaluating a proposed design under conditions that differ from those assumed when the design was created.

In Section 2, we summarize the method for estimating the survival function, based on the properties in Lin et al. (1996), and indicate the change needed for more general accrual distributions. In Section 3, we summarize the design of Case and Morgan (2003) with necessary modifications. The basic design and analysis is further modified to ensure preservation of Type I error in Section 4. Methods for adjusting the timing of the interim analysis so that study conditions match the design assumptions are presented in Section 5. Optimal designs for an example involving colon cancer are evaluated under non-optimal conditions that are likely to attain in practice in Section 6. A detailed optimization algorithm implemented in an R package is presented in Appendix A.

2 Statistical Analysis of the Survival Function

Following Lin et al (1996), assume n patients are accrued to a trial at study times $Y_1, \cdots, Y_n$ ($\min(Y_i)$=0). Let $T_1, \cdots, T_n$ denote the event times, which are measured from study entry for each patient. The targeted length of event-free time is denoted by x, which is also measured from study entry for each patient. It is assumed there is no unplanned loss to follow-up. The $(Y_i, T_i), i = 1, \cdots, n$ are assumed to be independent and identically distributed throughout. The survival function for T_i is denoted by S, the hazard function by h, and the cumulative hazard function by Λ.

At study time t we observe for each individual either an event time T_i,censoring at time x, or censoring at time $t - Y_i < x$, whichever comes first. That is, we observe the time $X_i(t) = \min(T_i, x, (t-Y_i)_+)$ and the event indicator $\Delta_i(t) = I\{T_i \leq \min(x, (t - Y_i)_+)\}$, with $(\bullet)_+$ denoting the positive part. Let $\hat{S}(x;t) = e^{-\hat{\Lambda}(x;t)}$ denote the estimate of the event-free rate through study time x evaluated at time t based on the Nelson-Aalen estimator of the cumulative hazard function:

$$\hat{\Lambda}(x;t) = \sum_{i=1}^{n} \frac{\Delta_i(t)}{R_i(t)} \text{ with } R_i(t) = \sum_{j=1}^{n} I\{X_j(t) \geq X_i(t)\} \ .$$

The process, $n^{\frac{1}{2}}\{\hat{\Lambda}(x;t) - \Lambda(x)\}$, is asymptotically Gaussian provided $\Pr(t - Y_i > x) > 0$. Assuming no loss to follow-up and independently distributed Y_i, the process has asymptotic variance

$$\begin{aligned} \sigma^2(x;t) &= \int_0^x \frac{h(u)}{\Pr(X_i(t) \geq u)} du \\ &= \int_0^x \frac{h(u)}{S(u)\Pr(Y_i \leq t - u)} du \ . \end{aligned} \tag{1}$$

The hazard and survival functions under the null and alternative hypotheses are denoted by h_0, S_0, and h_1, S_1, respectively, and the corresponding variances in (1) are denoted by $\sigma_0^2(x;t)$ and $\sigma_1^2(x;t)$. The variance in (1) contains a general expression for the accrual distribution, $\Pr(Y_i \leq t - u)$.

Case and Morgan evaluated designs assuming that the accrual distribution is uniform over time, with the rate of accrual specified as a design input.

The form of $\Pr(Y_i \leq t-u)$ is generalized here so that accrual is uniform in pre-specified time intervals, with possibly different accrual rates in each interval. The model is flexible enough to reflect the typically slow accrual during early site startup, and the potential slowing of recruitment at some sites in the later stages of the trial. The density of Y_i is constant within pre-specified intervals, with the expected numbers of patients starting the study in each interval equal to the projected numbers that can be accrued in the interval.

The pre-specified time intervals are determined by b boundaries denoted by $0 < B_1 < \ldots < B_b$. The numbers of patients that can be accrued in the intervals are denoted by $m_1, \ldots, m_b$. If the maximum number of patients that can be accrued, $\sum_{j=1}^{b} m_j > n$, then the final accrual period(s) will be shortened.

Setting $F_n(t) = \Pr(Y_i \leq t)$:

$$F_n(t) = \begin{cases} \frac{m_1}{n}\frac{t}{B_1}, & 0 < t \leq B_1 \\ \frac{m_1}{n} + \frac{m_2}{n}\frac{t-B_1}{B_2-B_1}, & B_1 < t \leq B_2 \\ \vdots & \vdots \\ \frac{\sum_1^{l-1} m_j}{n} + \frac{n-\sum_1^{l-1} m_j}{n}\frac{t-B_{l-1}}{MDA-B_{l-1}}, & B_{l-1} < t \leq MDA \\ 1, & t > MDA \end{cases}$$

with l is chosen so that $\sum_1^{l-1} m_j < n \leq \sum_1^{l} m_j$, and the MDA (maximum duration of accrual) is given by

$$MDA = B_{l-1} + (B_l - B_{l-1})\frac{n - \sum_1^{l-1} m_j}{m_l} \ . \tag{2}$$

When $l = 1$, $F_n(t) = min\{\frac{t}{MDA}, 1\}$, $MDA = B_1\frac{n}{m_1}$, the constant accrual case in Lin et al (1996) and Case and Morgan (2003).

Lin et al (1996) recommend assessing the hypothesis $H_0 : S(x) = S_0(x)$ versus the one-sided alternative $H_1 : S(x) > S_0(x)$ at study time t using the asymptotically standard normal test statistic computed from the log of the cumulative hazard function (i.e., the log of the event-free rate):

$$Z(x;t) = \frac{n^{\frac{1}{2}} \left\{ \ln\left(\Lambda_0(x)\right) - \ln\left(\hat{\Lambda}(x;t)\right) \right\} \hat{\Lambda}(x;t)}{\{\hat{\sigma}^2(x;t)\}^{\frac{1}{2}}} \ , \tag{3}$$

where

$$\hat{\sigma}^2(x;t) = \sum_{\{i: X_i(t) \leq x\}} \frac{\Delta_i(t)}{R_i^2(t)/n} \ . \tag{4}$$

Comments:

- Case and Morgan (2003) reversed the order of $\ln\left(\Lambda_0(x)\right)$ and $\ln\left(\hat{\Lambda}(x;t)\right)$ in the formula for Z. The goal is to reduce the number of events, which is indicated by a positive value of Z (a lower hazard in the treated group).

- The standard error is evaluated at the estimated parameter value, analogous to a Wald test. An alternative could be obtained with the standard error computed using the null value, analogous to the score test, a more robust and powerful test for small sample sizes (Agresti, 2002).

The $\hat{\sigma}^2(x;t)$ estimates the asymptotic variance of $\hat{\Lambda}(x;t)$ under both the null and alternative hypotheses, $k = 0, 1$. The asymptotic standard error of $\sqrt{n}(\ln(\Lambda(x)) - \ln(\hat{\Lambda}(x;t)))$ is $\sigma_k(x;t)/\Lambda(x)$, which is estimated by $\hat{\sigma}/\hat{\Lambda}$. The transformation is applied to improve the asymptotic normal approximation. Let $I_k(x;t) \equiv 1/\sigma_k^2(x;t)$ denote the information available for estimating $\Lambda(x)$ at study time t, with $k = 0, 1$ for the null and alternative distributions.

The joint distribution of $Z(x;t)$ and $Z(x;t^*)$ at two study times t, t^* is asymptotically bivariate normal with correlation given by

$$\rho_k(t,t^*) = \sqrt{I_k(x,t)/I_k(x,t^*)}\ , \tag{5}$$

where $t \leq t^*$ and $k = 0,1$ (Lin et al, 1996). Note that $\rho_k(t,t^*)$ is also the square root of the ratio of information for estimating $\ln(\Lambda(x;t))$ and $\ln(\Lambda(x;t^*))$, because the derivative terms $\Lambda(x)^{-1}$ in the asymptotic variances cancel.

It is assumed that there is no loss to follow-up, which may not be true, depending on how event-free times are defined. We can further define a censoring variable V_i for patient i and assume the random triplets (Y_i, T_i, V_i) are independent and identically distributed. The analyses in the section can be generalized, for example, $\Delta_i(t) = I\{T_i \leq \min(x, V_i, (t - Y_i)_+)\}$. For the purpose of creating designs, however, we do not account for unplanned loss to follow-up.

3 The Sequential Design of Case and Morgan (2003)

Consider a phase II design with a single interim analysis conducted at a pre-specified time. At the interim analysis, the trial may be stopped for futility (low response or event-free rate), but it will not be stopped for a positive efficacy outcome. Accrual is not suspended at the time of the interim analysis. Following the notation and derivations in Case and Morgan (2003) with some minor modifications:

MDA : Maximum duration of accrual, which is the time to accrue all patients if the study does not stop at the interim analysis.

$MTSL$: Maximum total study length=$MDA + x$.

t_1 : Time at the interim analysis.

t_2 : Time from the interim analysis to the end of accrual assuming the study does not stop at the interim analysis. If the interim analysis occurs after the end of accrual, t_2 is 0.

n : The maximum sample size if both stages of the trial are completed.

n_1 : Number of patients accrued at the time of the interim analysis (t_1). The n_1 can equal n if the interim analysis occurs after all patients have been accrued but before the maximum total study length ($MTSL$).

n_2 : Number of patients accrued between the interim analysis (t_1) and the end of accrual. If the interim analysis occurs after the end of accrual, $n_2 = 0$.

P_s : Probability of stopping at t_1 under H_0.

EDA : Expected duration of accrual = $\min(t_1, MDA)+(1-P_s)t_2$, calculated under H_0. When $t_1 > MDA$, $EDA = MDA$.

ESS : Expected sample size = $n_1 + (1 - P_s)n_2$, which is calculated under H_0.

$ETSL$: Expected total study length = $t_1 + (1 - P_s)(MTSL - t_1)$, which is calculated under H_0.

I_{1k}, $k = 0, 1$: Information at t_1 under the null and alternative hypotheses.

$I_{max,k}$, $k = 0, 1$: Information at $MTSL$ under the null and alternative hypotheses.

Note that MDA and $MTSL$ are pre-specified fixed quantities. The other quantities are derived from them, the accrual distribution, and the survival functions specified in Section 2. The two-stage design proceeds as follows.

Stage 1: Accrue n_1 patients between time 0 and time t_1. Each patient is followed until they have an event or successfully reach time x, or until study time t_1, whichever is first. Calculate the Z-statistic in (3), and denote it by $Z_1(x;t_1)$. If $Z_1(x;t_1) < C_1$, stop the study for futility; otherwise, continue to the next stage. The optimal time for the interim analysis, t_1, the total number of patients, n, and test boundary, C_1, will be derived as part of the design. The probability of stopping under the null hypothesis is approximated by $P_s = \Phi(C_1)$, where Φ is the standard normal cummulative distribution function. The n_1 is a random variable determined by t_1 and the accrual distribution.

Stage 2: Accrue n_2 additional patients between times t_1 and MDA. Follow all patients (both stages) until they have an event or successfully reach time x, then calculate a second Z statistic, denoted by $Z_2(x;MTSL)$, and reject H_0 if $Z_2(x;MTSL) > C_2$. The test boundary, C_2 will also be derived as part of the optimal design.

The non-parametric estimator $\hat{\Lambda}(x;t)$ is defined for any value of $t > x$, so an interim analysis (i.e., t_1) could be done anytime after time x and before time $MTSL$. If t_1 is close to x, the interim analysis will be based on a small effective sample size. The maximum amount of information for estimating $\Lambda(x)$ is $I_{max,k} = I_k(x, MTSL)$, which is achieved at any $t \geq MTSL$. The joint distribution of Z_1 and Z_2 is bivariate normal with correlation $\rho_0 = \sqrt{I_{10}/I_{max,0}}$ under H_0, and $\rho_1 = \sqrt{I_{11}/I_{max,1}}$ under H_1. The information at any time $I(x;t) = 1/\sigma^2(x;t)$ can be obtained by numerically evaluating equation (1).

There are two constraints (Type I and II errors) and four design parameters: n, t_1, C_1, C_2. We assume the accrual distribution throughout the trial is fixed and known. Following Case and Morgan (2003), we obtain solutions that minimize either the EDA, ESS or the $ETSL$ under H_0, subject to the constraint that the Type I error is approximately α, and the power is approximately $1-\beta$. Minimizing the EDA and minimizing the ESS are the same in Case and Morgan (2003) as the accrual rate is assumed to be constant throughout. In the more flexible design setting, however, they may be different, so minimizing the ESS is more practical. The change required to permit more general forms of the accrual distribution is that more complex integrals must be evaluated in the asymptotic variance formula for the estimator in (1).

From Lin et al (1996), the Type I error is asymptotically approximated by $B(C_1, C_2, \rho_0)$, and the power is approximated by $B(C_1 - \rho_1 u, C_2 - u, \rho_1)$, where $B(C_1, C_2, \rho)$ denotes the bivariate normal probability that $Z_1 > C_1$ and $Z_2 > C_2$, given a correlation between Z_1 and Z_2 of ρ, and u is described below. The C_1, C_2 are chosen so that $B(C_1, C_2, \rho_0) = \alpha$ and $B(C_1 - \rho_1 u, C_2 - u, \rho_1) = 1-\beta$. The u in the power approximation is the mean of Z_2 under the alternative hypothesis. The asymptotic approximations for the Type I error and power are derived from equations (1) and (3), and the means of the asymptotic distributions of Z_1 and Z_2 under H_1 are:

$$\mathrm{E}(Z_1 \mid H_1) = \frac{n^{1/2}\left\{\ln\left(\Lambda_0(x)\right) - \ln\left(\Lambda_1(x)\right)\right\}\Lambda_1(x)}{\sigma_{11}}\ , \tag{6}$$

$$u \equiv \mathrm{E}(Z_2 \mid H_1) = \frac{n^{1/2}\left\{\ln\left(\Lambda_0(x)\right) - \ln\left(\Lambda_1(x)\right)\right\}\Lambda_1(x)}{\sigma_{21}}\ , \tag{7}$$

where

$$\sigma_{11}^2 \equiv \sigma_1^2(x; t_1) = \int_0^x \frac{h_1(u)du}{S_1(u)\,\Pr(Y_i \le t_1 - u)}\ , \tag{8}$$

$$\begin{aligned} \sigma_{21}^2 = \sigma_1^2(x; MTSL) &= \int_0^x \frac{h_1(u)du}{S_1(u)\,\Pr(Y_i \le MTSL - u)} \\ &= \int_0^x \frac{h_1(u)}{S_1(u)}du \end{aligned} \tag{9}$$

Combining equations (5) and (6), $\mathrm{E}(Z_1 \mid H_1)$ becomes $\rho_1 u$. The asymptotic variances of Z_1 and Z_2 equal one by construction under both H_0 and H_1, with correlation given by ρ_0, ρ_1 under H_0, H_1.

Details of an *R* algorithm implementing the optimization calculations in this section and a modified design in the next section are given in Appendix A.

4 A modified analysis and design to preserve Type I error

The two-stage design and resulting analyses are based on evaluation of a non-parametric estimator of event rates at a single pre-specified time. The correlations between test statistics at the interim and second stages, Z_1 and Z_2, which are required for computation of the test boundaries, C_1 and C_2, depend on the entire survival curve up to the specified evaluation time x under both H_0 and H_1. These distributions must be specified as a design input; an R package *OptimPhase2* currently implements Weibull distributions with user-specified parameters. The dependence of C_1 and C_2 on the specified distributions is weak, but it does result in dependence of the Type I error and power on the choice of the parametric distributions (see Case and Morgan (2003) for simulation results). This dependence can be easily overlooked because the test statistic is based on non-parametric estimation evaluated at a single event time (x).

The dependence of the Type I error rate on the accrual and survival distributions arises because a small percentage of potential Type I errors during the second stage of testing are avoided when the trial is terminated at the end of the first stage. The percentage of potential Type I errors avoided is typically small because the trial is terminated after the first stage only when the response (or event-free) rate is low. Data sequences that yield low first-stage estimates, followed by high second-stage estimates are rare, with the frequency determined by the correlation between the estimators at the first and second stages. The method described in Section 3 uses the correlation derived from the accrual and survival distributions to recover the alpha from the potential Type I errors avoided at the first stage.

The dependence of the Type I error rate on the assumed distributions can be eliminated by including the Type I errors avoided in the first stage in the calculation of the error rate. A more conservative alternative method becomes: choose C_1, C_2 so that $\Phi(C_2) = \alpha$ and $B(C_1 - \rho_1 u, C_2 - u, \rho_1) = 1 - \beta$. This procedure is consistent with regulatory guidance to protect Type I error even with interim analyses where the stated intention is to stop only for futility (FDA, Section 4.3.2, 2006).

Also note that the test based on the normal approximation at the end of the second stage can be replaced by an exact binomial test (assuming no loss to follow-up), with the role of the normal approximation reduced to futility testing at the first stage, and the selection of sample size and timing of the first-stage analysis.

5 Adjusting the timing of the interim analysis to match observed study conditions

The optimal time to perform the interim analysis, t_1, is dependent on correct specification of the patient accrual and survival distribution. Case and Morgan (2003) evaluated a modified rule for the time of the interim analysis based on matching the number of patients actually accrued in the study to the expected number of patients to be accrued at the time of the interim analysis under the original design assumptions. This timing rule for the interim analysis performed better in their simulations, so it will be evaluated in Section 6.3.

Further refinement of the timing rule is also possible by matching the observed patient exposure time to the expected exposure time under the optimal design conditions. This refinement accounts for the time patients have been in the study, which is potentially important if many patients are accrued shortly before the interim analysis, and thus contribute little information to the estimated event rate at time x.

The total expected patient exposure truncated by x under the optimal design assumptions is

$$n\mathrm{E}\left(\min\left(x, [t_1 - Y_i]_+\right)\right) = n * \Pr(Y_i \leq t_1)\mathrm{E}\left(\min\left(x, [t_1 - Y_i]_+\right) \mid Y_i \leq t_1\right) .$$

The $\Pr(Y_i \leq t_1)$ is evaluated directly from the accrual distribution. The distribution of Y_i given $Y_i \leq t_1$ is required to compute the conditional expectation. Find k so $B_{k-1} < \min(MDA, t_1) \leq B_k$ and truncate this interval at $\min(MDA, t_1)$ so B_k is re-assigned the value $\min(MDA, t_1)$. The expected accrual, m_k, is also re-defined to $m_k(\min(MDA, t_1) - B_{k-1})/(B_k - B_{k-1})$. The proportion and density in each interval of the conditional accrual distribution become $P_j = m_j / \sum_{l=1}^{k} m_l$ and $D_j = P_j/(B_j - B_{j-1})$, $j = 1, \cdots, k$.

The truncated conditional expected exposure time is then found by summing over the intervals with constant density, which have one of three possible configurations:

1. The $t_1 - x \geq B_j$, which contributes $x \Pr(Y_i \in (B_{j-1}, B_j)) = xD_j(B_j - B_{j-1})$.

2. The $B_j > t_1 - x \geq B_{j-1}$, which contributes

$$\begin{aligned} & x \Pr(Y_i \in (B_{j-1}, t_1 - x)) + D_j \int_{t_1 - x}^{B_j} (t_1 - y) dy = \\ & xD_j(t_1 - x - B_{j-1}) + D_j t_1 (B_j - t_1 + x) + D_j (B_j^2 - (t_1 - x)^2)/2 \ . \end{aligned}$$

3. The $t_1 - x < B_{j-1}$, which contributes

$$D_j \int_{B_{j-1}}^{B_j} (t_1 - y) dy = D_j t_1 (B_j - B_{j-1}) - D_j (B_j^2 - B_{j-1}^2)/2 \ .$$

The number of patients accrued and their truncated exposure are not known at future times, but they can be reliably projected based on currently accrued patients, and projections of future accrual for short durations of time (e.g., 2 months), thus permitting practical operational planning for the interim analysis. Because exact targeting for accrual and exposure times will not be achieved in real practice, simulation studies will be included in Section 6.3 to evaluate the impact of small differences between planned and actual timing of the interim analysis.

Patient exposure is evaluated because we anticipate it will be a better predictor of expected information than the number of accrued patients. Exploratory simulations were also performed with timing rules based on the observed information. Matching on the observed information did not improve performance, however, because it depends on the estimated time-to-event distribution, which is not stably estimated during early accrual. The observed information was not always a monotone function of time, and would be difficult to project with sufficient lead time for operational purposes. Because it did not improve theoretical performance of the designs and analyses, and it would be hard to implement and explain, the interim timing rule based on the observed information was not pursued.

6 Example

6.1 Background

Potential designs based on a recent study involving refractory metastatic adenocarcinoma of the colon are evaluated to demonstrate the methods that have been implemented to create an optimal design. We also evaluate the optimal designs under non-optimal conditions. All of the methods are implemented by functions in the R package *OptimPhase2*. The primary objective of the study was to evaluate overall survival at 6 months from enrollment. The null survival rate at 6 months was 0.45 based on the findings of Jonker

(2007), Rao, et al (2004), and Van Cutsem, et al (2007). An alternative rate of 0.60 or greater was selected as a success rate warranting further development. We assume an exponential survival curve for both hypotheses during the design stage, but the resulting designs are also evaluated by simulations assuming an accelerating hazard function. It is assumed that 3 patients can be accrued per month for up to 3.5 years if needed for a maximum of 126 patients.

6.2 Optimal designs

Designs were created with targeted one-sided Type I errors of 0.05 or 0.10, and power of 0.80. The sample sizes for simple non-sequential designs based on the normal approximation are 80 with $\alpha = 0.05$, and 58 with $\alpha = 0.10$. The corresponding duration of accrual (DA) and study length (SL) for the fixed designs are 26.67, 32.67, and 19.33, 25.33 (months).

Two-stage designs were created that recover the α from early stopping, and more conservative designs that do not recover the α were also created (see Section 4). The designs minimize the expected sample size (ESS), but the other criteria (EDA and $ETSL$) are also monitored. The assessment of each optimality criteria is displayed in Figure 1 as a function of potential maximum sample size n for the design with alpha level of 0.05 and no recovery of α. The criteria and the maximum sample sizes are expressed as ratios relative to the values of the single-stage fixed design with the same Type I error and power. The ESS and EDA criteria coincide because the accrual rate is assumed constant. The $ETSL$ is minimized by a trial with a larger maximum sample size, but the $ETSL$ curve is nearly flat over a range of designs that includes its optimal sample size and the optimal size for the ESS criteria. The design is thus robust to the choice of optimality criteria. In some settings, a compromise design yielding good but non-optimal results for all of the criteria can be selected using a plot like Figure 1. The R-package can produce two-stage designs for a pre-specified value of the maximum sample size n to support the choice of compromise designs.

The properties of the two-stage design are sumamrized in Table 1. The two-stage designs reduce the expected number of patients by approximately 20 and the expected study length by 10 months when $\alpha = 0.05$, and by 8 patients and 5 months when $\alpha = 0.10$. The more conservative combination of design and decision criteria that does not recover α from the interim analysis requires $2-3$ more expected patients to maintain the same power compared to designs with α recovery. The magnitude of the potential saving is dependent on the accrual rate as little saving is possible if most of the patients are accrued by the time a sufficient number of patients have reached the time of the endpoint evaluation. The more information required for the final decision criteria (i.e., lower α, higher β), the more patients that must be accrued, and thus potential reductions from two-stage designs are larger.

Simulated data were created under conditions matching the design assumptions (e.g., accrual rate, shape of survival curves). The results are summarized in Table 2. Each simulation setting was replicated $10,000$ times. The simulation standard errors for estimated proportions (e.g. α levels) are ≤ 0.003. The timing of the interim analysis was based on the rules that match the sample size and the patient exposure under the design assumptions. Because the results from the two rules were very close under the design

Table 1: Optimal Design Characteristics

	$\alpha = 0.05$ R=Y	$\alpha = 0.05$ R=N	$\alpha = 0.10$ R=Y	$\alpha = 0.10$ R=N
max N	93	94	65	64
interim Time	13.53	14.05	11.18	11.75
interim N	41	43	34	36
ESS	58.87	61.50	48.16	50.29
EDA	19.62	20.50	16.06	16.76
ETSL	21.71	22.74	18.84	19.90
MTSL	37	37.33	27.67	27.33
interim P	0.506	0.495	0.464	0.442
final P	0.533	0.538	0.527	0.533

Note: R=Y,N for recovery of α equal yes/no.

assumptions, the small differences were averaged for reporting in Table 2.

All of the design and decision criteria produced conservative control of the Type I error when the target $\alpha = 0.05$; the exact and normal approximation yielded the same rejection rates, but both differed from the target levels. The testing procedure based on the normal approximation with recovery of α, however, had Type I error that appreciably exceeded the targeted 0.10 level. This is due to the normal approximation errors with interim and final sample sizes of 34 and 65. Approximation errors of this magnitude are common in designs of this size. Because the method with α recovery does not sufficiently control the Type I error in some settings, it is not evaluated in the next section.

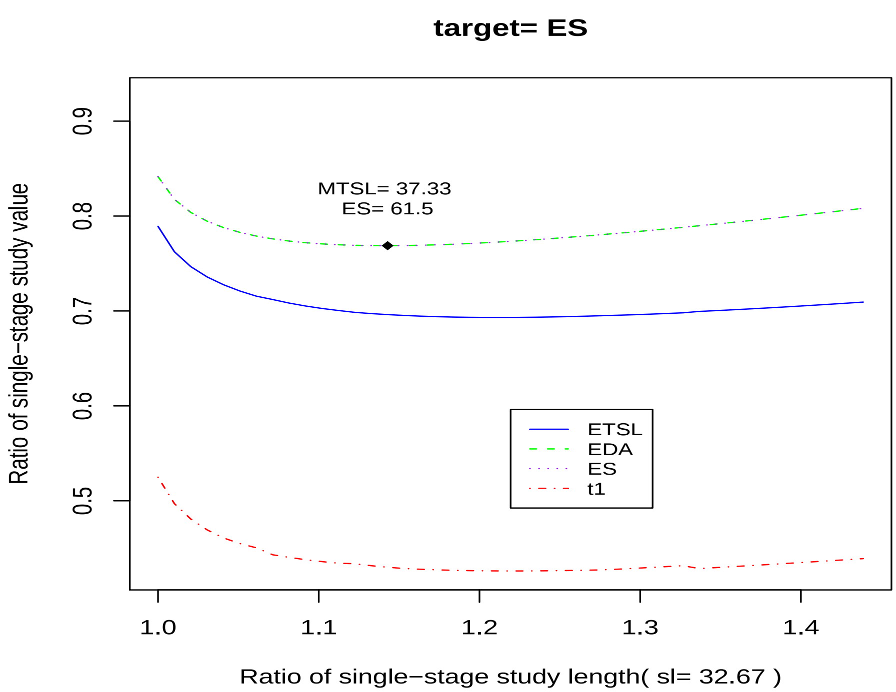
All of the designs had power exceeding the targeted 80% level by $1 - 6$ percent. The higher achieved power levels are also due to normal approximation errors. A tendency to produce higher than targeted power levels was also noted when the same methods were applied to single-stage fixed designs with null event-free rates of 40 percent or higher. For lower null event-free rates, the normal approximation tends to produce lower powers than the targeted levels. Corresponding to the higher power, the expected number of patients was $1 - 2$ larger than projected for the design under the null hypothesis, and the expected study length is longer by approximately 0.5 months. The higher powers and larger expected sample sizes occur in part because the frequency of futility stopping at the interim analysis is slightly lower than projected for the design. Case and Morgan (2003) suggested a sample size adjustment based on the ratio of the sample sizes for the fixed single-stage design from an exact test versus the normal approximation test. These adjustments reduce the sample sizes to better approximate the power under ideal conditions in the current example. Because power tends to be reduced somewhat in more realistic operational conditions, as evaluated in the next section, the conservative tendency of the designs in the ideal conditions may be desirable in practice.

Table 2: Simulation results under the optimal design conditions

	Target $\alpha = 0.05$			Target $\alpha = 0.10$		
	Exact R=N	Normal R=N	Normal R=Y	Exact R=N	Normal R=N	Normal R=Y
α	0.040	0.040	0.045	0.070	0.106	0.131
Power	0.842	0.842	0.842	0.816	0.865	0.859
ESS	63.36	63.36	60.05	51.37	51.37	49.35
EDA	20.83	20.83	19.73	16.83	16.83	16.14
ETSL	23.46	23.46	22.16	20.31	20.31	19.31

Note: R=Y,N for recovery of α equal yes/no.

Figure 1: The optimality criteria displayed for a range of maximum sample sizes. The criteria and the maximum sample sizes are expressed as ratios relative to the corresponding value in a single-stage fixed design ($\alpha = 0.05$ is not recovered).



6.3 Evaluating optimal designs under non-optimal conditions

Simulations were conducted under several plausible operating conditions that differ from those assumed when creating the design. Both of the interim timing methods were evaluated for each simulation setting. The designs for both levels of α were evaluated, and reported separately due to differences in performance.

Two sets of survival curves were simulated: 1) the null and alternative exponential curves assumed in the designs, and 2) Weibull distributions with shape parameter of 3, which yield very few early events and rapidly accelerating hazard close to the endpoint time of 6 months. All of the survival curves match the hypothesized values at 6 months.

The time of the interim analysis was varied from the optimal time to represent operational constraints. The proportions of the optimal target (sample size or patient exposure) were 1.0, 0.95, and 1.05.

Three accrual patterns were simulated: target rate (3 per month), slow starting (1 per month for 4 months followed by 3 per month), and fast accruing (5 per month).

The simulation results are summarized in Table 3. The Type I errors based on the exact tests remained conservative and the normal approximation performed adequately, but there were small elevations of the Type I errors for some settings using the normal approximation. The power varied somewhat across the simulation settings, but severe loss in power did not occur. Matching on patient exposure reduced the small loss of power in some non-optimal settings compared to matching on the targeted sample size for the timing of the interim analysis. These improvements in power were accomplished by increasing the sample sizes at the interim analyses in some settings that resulted in small increases in the ESS.

Analysis of variance (ANOVA) was applied to the power and ESS results across the factors in the simulation to determine the predominant sources of variation. For power, the dominant factors were the accrual rate, shape of the survival curve, the accuracy of the timing of the interim analysis, the method used to time the interim analysis, and the interaction between the interim method and the accrual rate. The factors were the same for both α levels. The lowest power levels occurred with the fastest accrual, accelerating hazard rate, and smaller than planned interim sample sample size. ANOVA applied to the ESS results yielded the same factors except that the hazard function determining event rates was not predictive.

Table 3: Simulation results under non-optimal conditions

	Target $\alpha = 0.05$		Target $\alpha = 0.10$	
	E1	N1	E1	N1
α (exact)	0.040	0.039	0.069	0.068
	0.039, 0.042	0.036, 0.042	0.066, 0.071	0.063, 0.071
α (normal)	0.040	0.039	0.105	0.103
	0.039, 0.042	0.036, 0.042	0.100, 0.109	0.094, 0.108
Power (exact)	0.840	0.828	0.812	0.802
	0.807, 0.859	0.769, 0.857	0.784, 0.824	0.762, 0.822
Power (normal)	0.840	0.828	0.860	0.849
	0.807, 0.859	0.769, 0.857	0.830, 0.873	0.805, 0.873
ESS	65.80	64.82	52.93	52.31
	63.12, 69.72	63.18, 66.76	50.97, 55.79	51.44, 53.44

Note: E1=matching optimal exposure, N1=matching optimal n_1.
The upper number in each cell is the mean across simulation conditions.
The lower numbers are the minimum, maximum.

7 Discussion

The Case and Morgan generalization of the Simon two-stage design was reviewed and additional modifications were proposed and evaluated to ensure protection of the Type I error and more robust performance under likely operational conditions. In settings with slow accrual, long-term endpoint (e.g. 1-year survival) and a low probability of efficacy, the two-stage designs can reduce the number of patients exposed to ineffective drugs and reduce time to decisions while maintaining control of type I error and type II error.

The designs here focused on assessment of the event-free rate at a single time point. Tests based on such endpoints may be more appropriate than widely used non-parametric rank-based tests (e.g., log-rank test) for some regimens and cancer modalities such as immuno-oncology, in which it takes time for immune activation and building of an immune response, so comparisons to a results from a regimen yielding faster response might be misleading. In settings where comparison of time-to-event curves is more appropriate, the methods described here can be modified to use other test statistics. The methods could also be generalized to allow comparison to a concurrently randomized control group (see for example, Schaid, Wieand, and Therneau, 1990).

Software (R package *OptimPhase2*) is available to create optimal designs and explore alternative compromised designs under different settings. Code to easily generate simulations to check the asymptotic approximations and performance under non-optimal conditions is also supplied. A test function is also available to compute the test statistics during the trial conduct.

In addition to the R package, there are other available software sources to generate the original Case and Morgan's design. For example, the national cancer center in Singapore developed an Early Phase Clinical Trial (EPCT) software to create some commonly used phase I and phase II cancer clinical trial designs, including Case and Morgan's. An update version of the EPCT software has been incorporated into a book (Machin et al, 2008).

A Optimization Algorithm

An algorithm is specified to minimize either EDA, ESS or $ETSL$ is described in Steps 1-11. The user inputs are:

a. The Type I error and power, α, β.

b. The time to event distributions S_0 and S_1. The method is implemented with Weibull distributions for S_0 and S_1, so the user inputs two parameters per distribution.

c. The target time to evaluate the survival function, x.

d. The projected accrual during different time periods. The user specifies a set of intervals given by times $0(\equiv B_0), B_1, \cdots, B_b$ in which the accrual rates are approximately constant. The B_b is the longest feasible time to accrue the trial. The value of b can be one, corresponding to uniformly distributed accrual throughout the study. This is the accrual model specified by Case and Morgan. Associated with each time interval, (B_{j-1}, B_j), the user inputs the number of patients, m_j, that could be accrued within the interval.

If the Type I error and power constraints cannot be achieved with the specified accrual, the optimization algorithm will stop and report the problem.

The 11 steps of the optimization method are:

1. Fix values for n and ρ_1. Combined with the Type I error and power constraints, these determine all of the remaining parameters as described by steps 2-10.

2. Compute the MDA from equation (2) and form the study entry-time distribution to match the projected accrual rates input by the user.

3. Calculate σ_{21} (H_1) from equation (9), and similarly for σ_{20} (H_0) by replacing h_1 and S_1 by h_0 and S_0 in equation (9).

4. Obtain σ_{11} from $\rho_1 = \sigma_{21}/\sigma_{11}$, which implies $\sigma_{11} = \rho_1\sigma_{21}$.

5. Obtain t_1 by solving equation (8) for the value of σ_{11} computed in the previous step. An unique root exists because σ_{11} is monotone in t_1.

6. Calculate $t_2 = max(MDA - t_1, 0)$.

7. Calculate σ_{10} from equation (8) by replacing h_1 and S_1 by h_0 and S_0.

8. Calculate $\rho_0 = \sigma_{20}/\sigma_{10}$.

9. Calculate u from equation (7).

10. Obtain C_1 and C_2. When recovery of α is specified (Section 3), solve:

$$\begin{cases} B(C_1, C_2, \rho_0) - \alpha = 0 & (A) \\ B(C_1 - \rho_1 u, C_2 - u, \rho_1) - (1 - \beta) = 0 & (B) \end{cases}$$

The two-variable equations are solved using R function *optim*(). The idea is to minimize $(A)^2 + (B)^2$ to 0 (if possible, otherwise no solution), and the minimizers $\hat{C}_1$ and $\hat{C}_2$ are the desired roots. The default setting is to minimize $(A)^2 + (B)^2$ to within $1e^{-6}$. When recovery of α is not specified (Section 4), solve:

$$\begin{cases} \Phi(C_2) - \alpha = 0 & (A) \\ B(C_1 - \rho_1 u, C_2 - u, \rho_1) - (1 - \beta) = 0 & (B) \end{cases}$$

C_2 can be computed using the inverse normal CDF supplied in R. The remaining equation is monotone in C_1, and is solved for C_1 using the *uniroot* function.

11. The optimal design to minimize the EDA, ESS or $ETSL$ is found by evaluating all possible n. The optimal ρ_1 for each n is found using a combination golden-section search and parabolic interpolation minimization as described by Brent (1973). It is implemented by the function *optimize*() in R *stats* package. The range of ρ_1 is between 0 and 1. The search for optimal n can begin with the fixed sample size of the single-stage design. The two-stage design requires a larger maximum sample size than a single stage design with the same α and β. and thus, the fixed sample size is a lower bound. The fixed sample size n_0 for a 1-sided test with a normal approximation is

$$n_0 = \left[\frac{\sigma_{21}(Z_\alpha + Z_\beta)}{\{\ln(\Lambda_0(x)) - \ln(\Lambda_1(x))\}\, \Lambda_1(x)} \right]^2 .$$

The upper limit for n is input by the user, which is $\sum_1^b m_j$.

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