Drug Designing: Open Access
ISSN: 2169-0138

Lu et al., Drug Des 2014, 3:3
DOI: 10.4172/2169-0138.1000114

Research Article Open Access

On Two-Stage Adaptive Seamless Design with Count Data from Different Study Durations under Weibull Distribution

Qingshu Lu[1], Shein Chung Chow[2] and Siu Keung Tse[3]*

[1]Singapore Clinical Research Institute, Singapore
[2]Duke University School of Medicine, Durham, North Carolina, USA
[3]City University of Hong Kong, Republic of China

Abstract

In clinical development, a two-stage design combining two separate studies (e.g., a phase II dose finding study and a phase III confirmatory study) into a single trial is commonly considered. The purpose of a two-stage design is not only to reduce lead time between the two studies, but also to evaluate the treatment effect in a more efficient way. In practice, one of the difficulties in utilizing a two-stage design is that the study endpoints at different stages may be different. For example, a biomarker (or the same study endpoint with different duration) may be considered at the first stage, while a regular study endpoint is used at the second stage. As per the studies the case where both study endpoints are continuous variables with certain correlation structure. In this paper, our attention is on the case where the study endpoints are count data which are obtained at the two stages with different time intervals. Statistical procedure for combining data observed from the two different stages are proposed. Furthermore, results on hypotheses testing and sample size calculation are derived for the comparison of two treatments based on data observed from a two-stage design.

Keywords: Biomarker; Count data; Sample size determination; Two-stage design; Weibull distribution

Introduction

In recent years, the use of a two-stage adaptive seamless design that combines a phase IIb study and a phase III study into a single study has received much attention [1-4]. The purpose of a two-stage adaptive seamless design is not only to accelerate drug development but also to evaluate the treatment in a more efficient way. The major characteristics of a two-stage adaptive phase II/III design include (i) it is able to address study objectives of individual phase IIb and phase III studies and (ii) it utilizes data collected from both phase IIb and phase III studies for a combined final analysis. The efficiency of a two-stage design, however, has been challenged by some researchers [5]. Moreover, it is not clear how the final combined analysis should be performed if the study objectives and/or study endpoints are similar but different at different phases [6].

In practice, a two-stage design is often applied to combine a phase IIb dose finding study and a phase III efficacy confirmatory trial. Thus, the study objectives at different stages are different (i.e., dose selection versus efficacy confirmation). Moreover, to speed up the drug development, the study endpoints at different stages may be different. For example, a biomarker may be considered at the first stage and a regular study endpoint is used at the second stage provided that the biomarker is predictive of the regular study endpoint. In these cases, the validity of the standard test statistics for combining data collected from both phases is questionable. In particular, this will have an impact on the sample size allocation in order to achieve the desired power at a pre-specified level of significance at each stage.

In general, there may be four different scenarios for a two-stage adaptive seamless design. In particular, in the two stages, (i) the study objectives and the study endpoints are the same; (ii) the study objectives are the same but the study endpoints are different; (iii) the study objectives are different but the study endpoints are the same; (iv) the study objectives and the study endpoints are different. Certainly, these different cases are formulated for different purposes. For instance, case (iii) is often set up for dose finding in the first stage and efficacy confirmation in the second stage. Study with biomarker or clinical endpoint with different durations at the two stages while the objective is for dose selection in the first stage but efficacy confirmation in the second stage would lead to the scenario described in case (iv).

Under the similar setting, Chow et al. [6] proposed a test statistic utilizing data collected from both phases assuming that there is a well-established relationship between the two different study endpoints and derived formulas for sample size calculation/allocation based on the proposed test statistic. However, in many clinical studies, it may not be feasible to monitor the patients continuously. For example, the number of subjects "survived" or "onset of a disease" out of the n test subjects at the end of the study period is observed instead of recording the exact time. In other words, the exact time where the event occurred after a treatment is administered cannot be observed. Thus, the main theme of this paper is to develop testing procedures for the comparison of the effects of different treatments based on event data collected from two stages. In particular, we assume that the durations of the two stages are different. The second stage is with duration L whilst the duration of the first stage is cL with $0<c<1$. This setup would facilitate the gathering of some information in a relative short period of time and then settle on the plan for the future stages.

In this paper, we propose an improved test statistic under a Weibull distribution based on the location parameter of median. In the next section, the proposed method for combining data observed from

***Corresponding author:** Siu Keung Tse, City University of Hong Kong, Republic of China, Tel: +852 34428578; E-mail: mssktse@cityu.edu.hk

Received May 01, 2014; **Accepted** July 11, 2014; **Published** July 16, 2014

Citation: Lu Q, Chow SC, Tse SK (2014) On Two-Stage Adaptive Seamless Design with Count Data from Different Study Durations under Weibull Distribution. Drug Des 3: 114. doi:10.4172/2169-0138.1000114

two different stages is described. Results for the hypotheses testing of equality, superiority, non-inferiority and equivalence of two treatments are presented in the Section: Hypothesis Testing. Section: Sample Size Calculation gives results for the sample size calculation for achieving a desired power corresponding to each of the hypotheses considered in the section Hypothesis Testing. Section: Numerical Study gives the results of a numerical study. A brief concluding remark is given in the last section.

Description of the Problem

Consider a two-stage adaptive seamless design for comparing two treatments, namely, a test treatment versus a control agent. Suppose that the study duration of the 1st stage is cL and the study duration of the 2nd stage is L with $c<1$. Assume that the response is determined by the lifetime t, and the corresponding lifetime distribution function for the test treatment and the control agent are $G1(t,\boldsymbol{\theta 1})$ and $G2(t,\boldsymbol{\theta 2})$, respectively. Suppose that a respondent is defined as an individual with survival time larger than the study duration. Let r_1 and s_1 be the numbers of respondents out of n_1 and m_1 *randomly* selected individuals in the first and second stages for the test treatment respectively. Similarly, r_2 and s_2 are the numbers of respondents out of n_2 and m_2 individuals in the first and second stages for the control treatment respectively.

Based on the observed data, the likelihood functions for the test and control treatments can be obtained as follows

$$L_i(\boldsymbol{\theta}_i) = G_i^{r_i}(cL,\boldsymbol{\theta}_i)[1-G_i(cL,\boldsymbol{\theta}_i)]^{n_i-r_i} G_i^{s_i}(L,\boldsymbol{\theta}_i)[1-G_i(cL,\boldsymbol{\theta}_i)]^{m_i-s_i} \quad (2.1)$$

for $i=1, 2$; where $i=1$ represents the test treatment and $i=2$ represents the control treatment. Assume that the lifetimes under the test and control treatments are both Weibull distributed. Denote by G(t;λ,β) the cumulative distribution function of a Weibull distribution with $\lambda,\beta>0$ then, $G(t;\lambda,\beta)=1-e^{-(t/\lambda)^{\beta}}$. In particular, for $i=1, 2$, $G_i(t;\boldsymbol{\theta}_i)=G(t;\lambda_i,\beta_i)$ and the likelihood functions become

$$L_i(\lambda_i,\beta_i) = \left(1-e^{-(cL/\lambda_i)^{\beta_i}}\right)^{r_i} e^{-(n_i-r_i)(cL/\lambda_i)^{\beta_i}} \left(1-e^{-(L/\lambda_i)^{\beta_i}}\right)^{s_i} e^{-(m_i-s_i)(L/\lambda_i)^{\beta_i}} \quad (2.2)$$

The maximum likelihood estimators (MLE) of λ_i and β_i can be found by solving the following equations $(n_i-r_i)/n_i = e^{-(cL/\lambda_i)^{\beta_i}}$ and $(m_i-s_i)/m_i = e^{-(L/\lambda_i)^{\beta_i}}$, which are obtained by setting the first order partial derivatives with respect to the parameters to zero. In particular, the MLEs of and are given as β_i and λ_i, are given as

$$E(\hat{\lambda}_i) = \quad (2.3)$$

and

$$\hat{\lambda}_i = L[\log(m_i/(m_i-s_i))]^{-\hat{\beta}_i^{-1}} \quad (2.4)$$

Note that the MLEs of λ_i and β_i exists only when $0 < r_i/n_i < s_i/m_i < 1$.

The expectations of $\hat{\lambda}_i$ and $\hat{\beta}_i$ are obtained based on normal approximation of $(n_i-r_i)/n_i$ and $(m_i-s_i)/m_i$ for sufficiently large n_i and m_i. In particular,

$$E(\hat{\lambda}_i) = \lambda_i + B_{\lambda_i} + o(m_i^{-1}) + o(n_i^{-1}) \quad (2.5)$$

and

$$E(\hat{\beta}_i) = \beta_i + B_{\beta_i} + o(m_i^{-1}) + o(n_i^{-1}), \quad (2.6)$$

where

$$B_{\lambda_i} = \frac{(e^{x_{i2}^{\beta_i}}-1)\lambda_i \log x_{i1}}{2m_i x_{i2}^{2\beta_i}\beta_i^2 \log^2 c}\left(\log x_{i1} - 2 + \beta_i(1-x_{i2}^{\beta_i})\log c\right) + \frac{(e^{x_{i1}^{\beta_i}}-1)\lambda_i \log x_{i2}}{2n_i x_{i1}^{2\beta_i}\beta_i^2 \log^2 c}\left(\log x_{i2} - 2 - \beta_i(1-x_{i1}^{\beta_i})\log c\right),$$

and

$$B_{\beta_i} = \frac{1}{2x_{i1}^{2\beta_i}\log c}\left[\frac{c^{2\beta_i}(1-x_{i2}^{\beta_i})(e^{x_{i2}^{\beta_i}}-1)}{m_i} - \frac{(1-x_{i1}^{\beta_i})(e^{x_{i1}^{\beta_i}}-1)}{n_i}\right],$$

with $x_{i1}=cL/\lambda_i$ and $x_{i2}=L/\lambda_i$, $i=1, 2$. Note that for sufficiently large m_i and n_i, both $(\hat{\lambda}_i - E(\lambda_i))/\sigma_{\lambda_i} \xrightarrow{d} N(0,1)$ and $(\hat{\beta}_i - E(\beta_i))/\sigma_{\beta_i} \xrightarrow{d} N(0,1)$, where $\sigma_{\lambda_i} = \frac{\lambda_i}{\beta_i x_{i1}^{\beta_i}|\log c|}\sqrt{\frac{(e^{x_{i2}^{\beta_i}}-1)c^{2\beta_i}\log^2 x_{i1}}{m_i} + \frac{(e^{x_{i1}^{\beta_i}}-1)\log^2 x_{i2}}{n_i}}$ and $\sigma_{\beta_i} = \frac{1}{x_{i1}^{\beta_i}|\log c|}\sqrt{\frac{c^{2\beta_i}(e^{x_{i2}^{\beta_i}}-1)}{m_i} + \frac{(e^{x_{i1}^{\beta_i}}-1)}{n_i}}$.

Using the invariance property of maximum likelihood estimation, the MLE $\hat{\sigma}_{\lambda_i}$ of σ_{λ_i} can be obtained by substituting λ_i and β_i with their corresponding MLEs, $\hat{\lambda}_i$ and $\hat{\beta}_i$, respectively. Similarly, $\hat{\sigma}_{\beta_i}$, $\hat{B}_{\lambda_i}$ and $\hat{B}_{\beta_i}$ are defined accordingly. Using normal approximation, $\left(\hat{\lambda}_i - \hat{B}_{\lambda_i} - z_{\alpha/2}\hat{\sigma}_{\lambda_i},\ \hat{\lambda}_i - \hat{B}_{\lambda_i} + z_{\alpha/2}\hat{\sigma}_{\lambda_i}\right)$ and $\left(\hat{\beta}_i - \hat{B}_{\beta_i} - z_{\alpha/2}\hat{\sigma}_{\beta_i},\ \beta_i - B_{\beta_i} + z_{\alpha/2}\sigma_{\beta_i}\right)$ are approximate 100(1-α)% confidence intervals of λ_i and β_i where $\hat{B}_{\lambda_i}$ and $\hat{B}_{\beta_i}$ may be omitted when n_i and m_i are large enough.

Hypothesis Testing

In pharmaceutical applications, it is usually of interest to estimate the median lifetime. Thus, the comparison of the control and test treatments is usually based on the medians of the corresponding lifetime distributions. In particular, let M be the median of a Weibull distribution, which is given as $\lambda(\log 2)^{1/\beta}$. The following sections discuss the results for the testing of equality, superiority, non-inferiority and equivalence between the medians of the control and test treatments.

Test for equality

For the testing of equality, the hypotheses are formulated as

$$H_0: M_1 = M_2 \quad vs \quad H_1: M_1 \neq M_2, \quad (3.1)$$

where M_i, $i=1, 2$ is the median of the lifetime distribution of the test and control treatment respectively. Denote the MLE of M_i by $\hat{M}_i$. Applying Taylor series expansion, it can be showed that $E(\hat{M}_i) = M_i + n_i^{-1}B_{1M_i} + m_i^{-1}B_{2M_i} + o(n_i^{-1}) + o(m_i^{-1})$, for $i=1, 2$, where

$$B_{1M_i} = \frac{M_i(e^{x_{i1}^{\beta_i}}-1)}{2\beta_i^2 x_{i1}^{2\beta_i}\log^2 c}\left[\log x_{i2}\left(\log(\lambda_i cLM_i^{-2})-2\right) + \log(\lambda_i^{-1}M_i)\left(2+\log(\lambda_i^{-1}M_i)\right) + \beta_i(1-x_{i1}^{\beta_i})\log c\log(L^{-1}M_i)\right]$$

and

$$B_{2M_i} = \frac{M_i(e^{x_{i2}^{\beta_i}}-1)}{2\beta_i^2 x_{i2}^{2\beta_i}\log^2 c}\left[\log x_{i1}\left(\log(\lambda_i cLM_i^{-2})-2\right) + \log(\lambda_i^{-1}M_i)\left(2+\log(\lambda_i^{-1}M_i)\right) + \beta_i(1-x_{i2}^{\beta_i})\log c\log(cLM_i^{-1})\right].$$

Based on the asymptotic normality of $(\hat{\lambda}_i, \beta_i)$, $\hat{M}_i$ can be approximated by a normal distribution for sufficiently large n_i and m_i. In particular,

$$\upsilon_i^{-1/2}\left(\hat{M}_i - E(M_i)\right) \xrightarrow{d} N(0,1), \quad (3.2)$$

where $\upsilon_i = \frac{M_i^2}{\beta_i^2 x_{i1}^{2\beta_i}\log^2 c}\left[m_i^{-1}c^{2\beta_i}(e^{x_{i2}^{\beta_i}}-1)\log^2(cLM_i^{-1}) + n_i^{-1}(e^{x_{i1}^{\beta_i}}-1)\log^2(LM_i^{-1})\right]$.

Note that $\hat{M}_1$ and $\hat{M}_2$ are independent. Thus, $(\upsilon_1+\upsilon_2)^{-1/2}(\hat{M}_1 - M_2 + E(M_2) - E(M_1)) \xrightarrow{d} N(0,1)$.

Let $\hat{\upsilon}_i$ be the MLE of υ_i, which is obtained by estimating λ_i and β_i with the corresponding MLE, for $i=1, 2$. Similarly, $\hat{B}_{jM_i}$ is the MLE of B_{jM_i}, $i=1, 2$, $j=1, 2$. Then, according to the Slutsky's

Theorem, (3.2) also holds if υ_i is replaced by $\hat{\upsilon}_i$. Consequently, $(\hat{\upsilon}_1+\upsilon_2)^{-1/2}(\hat{M}_1-M_2-n_1^{-1}B_{1M_1}-m_1^{-1}B_{2M_1}+n_2^{-1}B_{1M_2}+m_2^{-1}B_{2M_2})$ asymptotically follows the standard normal distribution under the null hypothesis H_0 defined in (3.1). Thus, the null hypothesis H_0 is rejected at an approximate α level of significance if

$$(\hat{\upsilon}_1+\hat{\upsilon}_2)^{-1/2}\,|\,\hat{M}_1-\hat{M}_2-n_1^{-1}\hat{B}_{1M_1}-m_1^{-1}\hat{B}_{2M_1}+n_2^{-1}\hat{B}_{1M_2}+m_2^{-1}\hat{B}_{2M_2}\,|>z_{\alpha/2}, \quad (3.3)$$

where z_α is the $100\times(1-\alpha)^{\text{th}}$-percentile of the standard normal distribution.

Test for superiority

The following hypotheses are considered to identify superiority of the test treatment over the control,

$$H_0: M_1-M_2\le\delta \qquad vs \qquad H_1: M_1-M_2>\delta, \quad (3.4)$$

where $\delta>0$ is a difference of clinical importance. Obviously, the null hypothesis should be rejected for large value of $(\hat{\upsilon}_1+\upsilon_2)^{-1/2}(\hat{M}_1-M_2-\delta)$. Under the null hypothesis defined in (3.4), $(\hat{\upsilon}_1+\upsilon_2)^{-1/2}(\hat{M}_1-M_2-\delta)$ approximately follows a normal distribution for large n_i and m_i. Thus, the null hypothesis in (3.4) is rejected at an approximate α level of significance if

$$(\hat{\upsilon}_1+\upsilon_2)^{-1/2}(\hat{M}_1-M_2-\delta)>z_\alpha. \quad (3.5)$$

Test for non-inferiority

To show that the test treatment is not worse than the control, the hypotheses $H_0: M_2-M_1\ge\delta$ vs $H_1: M_2-M_1<\delta$ are considered, which are equivalent to

$$H_0: M_1-M_2\le-\delta \qquad vs \qquad H_1: M_1-M_2>-\delta, \quad (3.6)$$

where δ>0 is the difference of clinical importance. The hypotheses in (3.6) are of similar form as those for the testing of superiority in (3.4). Thus, the null hypothesis is rejected at an approximate α level of significance if

$$(\hat{\upsilon}_1+\upsilon_2)^{-1/2}(\hat{M}_1-M_2+\delta)>z_\alpha. \quad (3.7)$$

Test for equivalence

In clinical trial, it is commonly unknown whether the performance of test treatment is better than the (active) control, especially when prior knowledge of the test treatment is not available. In this case, it is more appropriate to consider the following hypotheses for therapeutic equivalence:

$$H_0: |M_1-M_2|\ge\delta \qquad vs \qquad H_1: |M_1-M_2|<\delta. \quad (3.8)$$

The above hypotheses can be tested by constructing the confidence interval of M_1 - M_2. Based on Schuirmann (1987) two one-sided tests procedure, it can be verified that the null hypothesis defined in (3.8) is rejected at a significance level α if and only if the 100(1-2α)% confidence interval

$$\left(\hat{M}_1-\hat{M}_2-n_1^{-1}\hat{B}_{1M_1}-m_1^{-1}\hat{B}_{2M_1}+n_2^{-1}\hat{B}_{1M_2}+m_2^{-1}\hat{B}_{2M_2}\right)\pm z_\alpha\sqrt{\hat{\upsilon}_1+\hat{\upsilon}_2}$$

falls within $(-\delta,\delta)$. In other words, the test treatment is concluded to be equivalent to the control if

$$(\hat{\upsilon}_1+\upsilon_2)^{-1/2}(\hat{M}_1-M_2-n_1^{-1}B_{1M_1}-m_1^{-1}B_{2M_1}+n_2^{-1}B_{1M_2}+m_2^{-1}B_{2M_2}-\delta)<-z_\alpha \quad (3.9)$$

and

$$(\hat{\upsilon}_1+\upsilon_2)^{-1/2}(\hat{M}_1-M_2-n_1^{-1}B_{1M_1}-m_1^{-1}B_{2M_1}+n_2^{-1}B_{1M_2}+m_2^{-1}B_{2M_2}+\delta)>z_\alpha. \quad (3.10)$$

Sample Size Calculation

In this section, the problem of determining the sample size used in each phase is considered. In practice, the total sample size N for the two phases is often determined such that the corresponding statistical test would achieve a given level of power (1−β). Consequently, a related question is how to allocate the samples sizes in the two phases given the total sample size is N. Thus, the corresponding results of sample size determination for each of the four tests discussed in Section: Hypothesis Testing are presented in the following.

To facilitate the understanding of the idea, the problem is restricted to the case of one treatment in order to get some insight for the generalization to the two treatment case. Suppose that the following hypotheses are considered

$$H_0: M_1=M_0 \qquad vs \qquad H_1: M_1\ne M_0, \quad (4.1)$$

where M_0 is a pre-specified value. Based on the asymptotic normality of MLE $\hat{M}_1$ of M_1, the null hypothesis H_0 defined in (4.1) is rejected at an approximate α level of significance if $\hat{\upsilon}_1^{-1/2}\,|\,\hat{M}_1-M_0-n_1^{-1}B_{1M_1}-m_1^{-1}B_{2M_1}\,|>z_{\alpha/2}$. Since $\hat{\upsilon}_1^{-1/2}(\hat{M}_1-M_1-n_1^{-1}B_{1M_1}-m_1^{-1}B_{2M_1})$ can be approximated by the standard normal distribution, the power of the above test under the alternative hypothesis H_1 can be approximated by $\Phi(\upsilon_1^{-1/2}\,|\,M_1-M_0\,|-z_{\alpha/2})$, where Φ is the cumulative function of the standard normal distribution. Hence, in order to achieve a power level of 1−β, the required sample size satisfies $\upsilon_1^{-1/2}\,|\,M_1-M_0\,|-z_{\alpha/2}=z_\beta$. Let $m_1=\rho\,n_1$. Then the required sample size N for the two stages is given by $N=(1+\rho)n_1$ with

$$n_1=\frac{(z_{\alpha/2}+z_\beta)^2\tilde{\upsilon}_1}{(M_1-M_0)^2}, \quad (4.2)$$

and

$$\tilde{\upsilon}_1=\frac{M_1^2}{\beta_1^2x_{11}^{2\beta_1}\log^2c}\left[\rho^{-1}c^{2\beta_1}(e^{x_{12}^{\beta_1}}-1)\log^2(cLM_1^{-1})+(e^{x_{11}^{\beta_1}}-1)\log^2(LM_1^{-1})\right]. \quad (4.3)$$

Note that with all the other parameters fixed, the required sample size N is a convex function of ρ and the optimal value of ρ is given as

$$\rho^*=\frac{(e^{x_{12}^{\beta_1}}-1)^{\frac{1}{2}}c^{\beta_1}}{(e^{x_{11}^{\beta_1}}-1)^{\frac{1}{2}}}\left|1+\frac{\log c}{\log(LM_1^{-1})}\right|. \quad (4.4)$$

Following the similar idea, the sample size to achieve a pre-specified power of 1−β for the tests discussed in Section: Hypothesis Testing with significance level α can be determined. For testing equality of two treatments based on the comparison of the medians, the required sample size for testing hypotheses (3.1) satisfies the following equation,

$$-z_{\alpha/2}+\frac{|M_1-M_2|}{\sqrt{\upsilon_1+\upsilon_2}}=z_\beta.$$

Let $m_1=\rho n_1$, $m_2=\xi n_2$ and $n_2=\gamma n_1$. υ_i can be expressed as $\upsilon_i=\tilde{\upsilon}_i/n_1$, $i=1,2$; where $\tilde{\upsilon}_1$ is given in (4.3) and

$$\tilde{\upsilon}_2=\frac{M_2^2}{\gamma\beta_2^2x_{21}^{2\beta_2}\log^2c}\left[\xi^{-1}c^{2\beta_2}(e^{x_{22}^{\beta_2}}-1)\log^2(cLM_2^{-1})+(e^{x_{21}^{\beta_2}}-1)\log^2(LM_2^{-1})\right].$$

The total sample size N_T for the two treatment groups is given by $n_1[1+\rho+(1+\xi)\gamma]$ with

$$n_1 = \frac{(z_{\alpha/2} + z_\beta)^2(\upsilon_1 + \upsilon_2)}{(M_1 - M_2)^2}. \quad (4.5)$$

Similarly, for the testing superiority, non-inferiority and equivalence, the corresponding n_1 is given as $\frac{(z_\alpha + z_\beta)^2(\upsilon_1 + \upsilon_2)}{(M_1 - M_2 - \delta)^2}$, $\frac{(z_\alpha + z_\beta)^2(\upsilon_1 + \upsilon_2)}{(M_1 - M_2 + \delta)^2}$ and $\frac{(z_\alpha + z_{\beta/2})^2(\upsilon_1 + \upsilon_2)}{(|M_1 - M_2| - \delta)^2}$, respectively.

Numerical Study

Note that the results derived in the above sections are based on asymptotic approximation. Thus, in this section, numerical studies are considered to assess the finite sample performance of these results. In practical applications, one has to know the values of L and c in order to determine the required sample size N. Therefore, one of the objectives of this numerical study aims to provide some insights to determine the "best" L such that the corresponding sample size is minimized. Furthermore, this numerical study also aims to provide some evidence whether the sample size derived based on approximation, as given in Section: Sample Size Calculation, can actually achieve the nominal power level.

It should be noted that the optimal ρ, as given in (4.4), may be very extreme which leads to the sample sizes in the two phases being too unbalanced. To avoid this problem, truncated ρ^* is considered which is defined as

$$\rho_{tr} = \begin{cases} \rho_1 & \text{if } \rho^* < \rho_1 \\ \rho^* & \text{if } \rho_1 \le \rho^* \le \rho_2 \\ \rho_2 & \text{if } \rho^* > \rho_2 \end{cases} \quad \text{for constant } \rho_1 < \rho_2. \quad (5.1)$$

Since N is a convex function of ρ and attains its minimum at ρ^*, it is easy to verify that N attains its minimum at ρ_{tr} under the condition $\rho_1 \le \rho \le \rho_2$. For demonstration purpose, we choose ρ_1 =0.2 and ρ_2 = 5 in this numerical study.

Given α, β, α_1, β_1 and M_0, the required sample size N is a function of ρ, c and L. With ρ_{tr} substituted into (4.3), optimal values of c and L can be determined by numerical method. However, since N is a discrete function of c and L, there is a set of optimal values of c and L. In other words, each optimal L is accompanied by a set of optimal c. Thus the best choice of the study duration L is proposed to be the one such that the minimum sample size, say N^*, is achieved and this choice of L, denote by L^*, is most robust in c, where N^* is defined as $\min\{N(\rho, c, L) | \rho_1 \le \rho \le \rho_2,\ c > 0,\ L > 0\}$. In our numerical study, the grid search method was used to find L^*. Furthermore, set α=0.05, β=0.20 and the difference between M_1 and M_0 was chosen to be 0.2. Some results are presented in Table 1. It can be seen that L^* is roughly equal to the 53rd-pcercentile of the Weibull distribution. In addition, L^* is increasing in β_1 and λ_1 while N^* is decreasing in β_1 but increasing in λ_1.

In addition to the determination of the optimal duration L^*, an important issue is to explore the effect of c and deviation of L from its optimal value on the required sample size. To get some insight, a numerical study was conducted with $M_1 - M_0$ =0.2 and some selected values of L and c. The corresponding results are presented in Table 2. It can be noted that when $L < L^*$, the sample sizes are very sensitive to the choice of c; whilst N is relatively more robust to the choice of c when $L > L^*$. Thus, the results suggest that a study duration slightly larger than L^* should be used when an accurate estimate of L^* is not available.

Note that for the four types of comparison, i.e., testing equality, superiority, non-inferiority and equivalence, between the two treatments, the total sample size is dependent on the ratios of sample sizes in the two stages and the two treatments, i.e., ρ, ξ and γ. An interesting question is how to determine the optimal values of these ratios such that the required total sample size N_T is minimized. It can be proved that for given c and L, there exist optimal values of ρ, ξ and γ such that the total sample size N_T is minimized. This result is true for the four types of comparison. In particular, the optimal values of ρ, ξ and γ are given as

$$\rho^* = \frac{\left(e^{x_{12}^{\beta_1}} - 1\right)^{0.5} c^{\beta_1}}{\left(e^{x_{11}^{\beta_1}} - 1\right)^{0.5}} \left| 1 + \frac{\log c}{\log(LM_1^{-1})} \right|, \quad (5.2)$$

$$\xi^* = \frac{\left(e^{x_{22}^{\beta_2}} - 1\right)^{0.5} c^{\beta_2}}{\left(e^{x_{21}^{\beta_2}} - 1\right)^{0.5}} \left| 1 + \frac{\log c}{\log(LM_2^{-1})} \right|, \quad (5.3)$$

and $$\gamma^* = \frac{M_2 (e^{x_{21}^{\beta_2}} - 1)^{0.5} \beta_1 x_{11}^{\beta_1}}{M_1 (e^{x_{11}^{\beta_1}} - 1)^{0.5} \beta_2 x_{21}^{\beta_2}} \left| \frac{\log(LM_2^{-1})}{\log(LM_1^{-1})} \right|. \quad (5.4)$$

Following the similar idea of avoiding extreme values, let ρ_{tr}, ξ_{tr} and γ_{tr} be the truncated ρ^*, ξ^* and γ^*, respectively, which are defined similarly as ρ_{tr} in (5.1). Then, a grid search method is applied to determine the best duration L^* with which the total sample size N_T is minimized and N_T is most robust to c. In this study, ρ_{tr}, ξ_{tr} and γ_{tr} are used with the truncated limits chosen as $\rho_1 = \xi_1 = \gamma_1 = 0.2$ and $\rho_2 = \xi_2 = \gamma_2 = 5$. It should be noted that, unlike ρ_{tr} in the one treatment case, ρ_{tr}, ξ_{tr} and γ_{tr} may not necessary be the optimal combinations to give the minimum N_T. Determination of the required sample size for testing equality of two treatments is considered with α=0.05 and β=0.20. The corresponding optimal durations L^* for various combinations of Weibull model parameter values are given in Table 3. Furthermore, a numerical study was conducted to assess the effects of c and the deviation of L from its optimal value L^* on the sample size. The results are presented in Table 4. As shown in Table 4, N_T is more robust to c when $L > L^*$.

Furthermore, a simulation study was conducted to assess the

β_1	1				1.5				2				2.5			
λ_1	1.2	1.4	1.6	1.8	1.2	1.4	1.6	1.8	1.2	1.4	1.6	1.8	1.2	1.4	1.6	1.8
N^*	283	385	503	636	161	219	286	361	102	139	182	230	71	96	125	158
L^*	0.908	1.059	1.211	1.332	1.014	1.184	1.355	1.495	1.037	1.236	1.416	1.585	1.084	1.267	1.449	1.592
L^* as quantile	0.531	0.531	0.531	0.523	0.540	0.541	0.541	0.531	0.526	0.541	0.543	0.539	0.540	0.541	0.542	0.521

Table 1: Minimum sample size N^* and optimal duration L^*.

β_1		1				1.5				2				2.5			
L	λ_1	1.2	1.4	1.6	1.8	1.2	1.4	1.6	1.8	1.2	1.4	1.6	1.8	1.2	1.4	1.6	1.8
$\tilde{L}$*1	*c*=.4	371	478	601	792	213	272	341	448	168	185	228	285	113	138	168	236
	.5	380	482	600	800	218	275	341	452	177	189	230	287	117	141	171	243
	.6	394	488	599	811	226	278	341	457	193	195	234	290	124	147	175	255
	.7	419	499	598	831	240	284	340	466	223	205	239	295	139	159	184	279
	.8	475	521	595	873	272	297	338	485	294	230	251	305	175	187	204	337
$\tilde{L}$*.05	*c*=.4	315	422	544	714	181	241	311	406	129	159	204	258	85	113	144	196
	.5	310	413	533	703	178	237	305	400	130	157	201	254	85	112	143	198
	.6	303	403	520	688	175	232	298	392	132	155	197	250	86	111	141	199
	.7	294	392	507	669	170	225	290	382	135	151	192	243	86	110	139	202
	.8	284	386	504	644	164	220	287	367	142	146	185	234	86	108	135	209
*L**	*c*=.4	292	398	520	670	170	231	301	385	113	151	197	249	78	106	139	178
	.5	288	392	512	656	166	226	295	377	110	147	192	243	76	103	135	175
	.6	286	389	509	643	165	224	292	369	108	144	188	238	74	101	131	172
	.7	285	388	506	640	163	222	290	366	105	142	186	235	73	99	129	168
	.8	284	386	505	638	162	220	288	364	103	141	184	232	72	98	127	162
*L**+0.05	*c*=.4	293	398	519	654	172	234	305	381	112	155	201	252	83	111	145	176
	.5	290	394	514	648	169	229	299	375	109	150	195	246	79	107	138	171
	.6	288	391	510	644	166	226	295	371	107	146	191	240	76	103	134	166
	.7	286	389	507	641	164	223	291	367	105	144	187	236	74	100	131	164
	.8	284	387	505	639	162	221	288	364	104	141	184	233	72	98	128	161
*L**+0.1	*c*=.4	295	401	523	658	176	238	309	387	117	159	207	259	87	117	151	184
	.5	292	396	517	651	171	232	302	379	112	153	199	250	82	110	143	176
	.6	288	392	512	646	167	227	296	373	109	148	193	243	78	105	137	170
	.7	286	389	508	642	164	224	292	368	106	144	188	238	75	101	132	166
	.8	286	386	504	639	162	220	288	364	104	141	184	233	72	98	128	162

Table 2: Total sample size *N* for testing equality using ρ_{tr} α=0.05 and 1-β=0.80.

i. β_2=2.0

λ_2	1.0						1.1					
β_1	1.5			2			1.5			2		
λ_1	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6
N_T^*	316	207	151	153	108	82	715	382	247	290	179	125
L^*	1.152	1.252	1.342	1.232	1.322	1.422	1.145	1.240	1.330	1.220	1.320	1.410

ii. β_2=2.5

λ_2	1.0						1.1					
β_1	1.5			2			1.5			2		
λ_1	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6
N_T^*	357	222	157	161	110	82	948	445	270	333	191	129
L^*	1.165	1.249	1.329	1.229	1.319	1.409	1.135	1.232	1.329	1.224	1.314	1.404

Table 3: Minimum sample size N_T^* and optimal duration *L**.

finite sample performance of the results derived in Section: Sample Size Calculation, which are based on asymptotic approximation. The simulated powers are given in Table 5. In this study, the simulated powers are computed based on 10000 simulated trials and the nominal power level is 0.8. Results listed in Table 5 show that the simulated powers are much less than 0.80 in most cases. The results suggested that the approximation results derived in Section: Sample Size Calculation are too conservative, which leads to less power to discriminate the null and alternative hypotheses. However, when sample sizes are increased by 50%, most powers are larger than 0.80, especially for $L^* + 0.1$ or *c* not greater than 0.60. The results are listed in Table 6. These result provide

β_2		2												2.5											
		1.0						1.1						1.0						1.1					
β_1		1.5			2			1.5			2			1.5			2			1.5			2		
L	λ_1	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6
L^*0.1	c=.4	493	341	231	236	155	110	1066	661	415	425	273	179	640	404	272	260	175	124	1403	729	499	514	321	205
	.5	473	321	215	224	146	102	1042	619	392	415	259	168	594	388	258	247	166	116	1397	692	479	497	304	195
	.6	457	299	197	212	137	98	1032	580	364	407	244	158	553	363	240	234	155	108	1423	663	448	482	286	183
	.7	456	289	213	206	150	124	1061	551	339	407	231	163	523	333	239	226	156	120	1522	654	413	476	271	176
L^*0.05	c=.4	498	296	206	202	137	100	1320	603	361	420	238	160	592	347	238	233	152	111	2110	790	430	525	280	181
	.5	463	272	188	187	126	91	1235	558	332	393	220	148	555	322	219	217	140	101	2043	748	401	496	262	167
	.6	421	245	172	172	116	89	1121	505	300	362	202	135	503	291	197	198	127	93	1898	685	362	456	240	152
	.7	377	243	195	171	136	122	992	449	282	331	192	148	442	267	199	182	130	108	1695	605	321	409	215	147
L^*	c=.4	389	237	169	177	122	90	925	460	288	353	207	143	429	265	187	195	131	96	1377	573	327	412	235	156
	.5	357	220	157	165	113	84	851	426	267	330	193	133	395	243	170	179	119	87	1245	522	299	382	216	142
	.6	330	208	153	155	109	87	781	397	251	307	182	125	370	226	158	166	110	83	1120	479	278	355	200	131
	.7	320	240	204	175	147	134	728	383	267	290	193	157	357	234	183	167	129	112	1011	449	275	337	193	142
L^*+0.05	c=.4	351	229	165	174	121	91	797	426	273	332	204	141	412	255	178	192	129	95	1093	512	310	398	228	152
	.5	334	217	156	163	113	84	764	407	260	314	192	132	388	238	165	177	118	86	1032	484	291	372	211	140
	.6	322	210	158	155	113	93	741	392	250	301	182	128	370	226	159	165	111	85	996	464	277	353	198	130
	.7	341	265	224	196	164	147	723	398	290	299	212	175	369	252	199	181	143	123	968	449	289	337	204	155
L^*+0.1	c=.4	356	232	167	178	123	92	808	432	277	340	208	143	419	258	180	196	132	96	1103	520	315	409	233	155
	.5	337	218	156	165	113	85	772	410	261	319	194	133	391	240	166	179	119	86	1045	489	293	378	214	141
	.6	322	215	165	159	118	99	744	393	252	302	184	132	370	227	162	166	114	89	1003	465	277	354	199	132
	.7	373	293	244	221	182	161	727	427	318	321	236	194	392	274	217	200	158	135	968	462	309	347	220	170

Table 4: Total sample size N_T for two treatments with α =0.05 and 1- β =0.80.

β_2		2												2.5											
λ_2		1.0						1.1						1.0						1.1					
β_1		1.5			2			1.5			2			1.5			2			1.5			2		
L	λ_1	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6
L^*.1	c=.4	0.736	0.660	0.615	0.588	0.492	0.473	0.832	0.748	0.681	0.741	0.619	0.525	0.753	0.678	0.647	0.642	0.532	0.425	0.847	0.794	0.715	0.786	0.669	0.569
	.5	0.693	0.624	0.614	0.604	0.543	0.509	0.795	0.700	0.654	0.702	0.632	0.570	0.704	0.653	0.632	0.634	0.575	0.514	0.841	0.749	0.671	0.742	0.656	0.600
	.6	0.632	0.626	0.599	0.606	0.573	0.515	0.743	0.652	0.617	0.651	0.610	0.579	0.652	0.623	0.636	0.615	0.601	0.529	0.805	0.689	0.628	0.679	0.620	0.608
	.7	0.591	0.595	0.587	0.575	0.537	0.500	0.660	0.612	0.608	0.603	0.573	0.542	0.617	0.619	0.633	0.607	0.581	0.557	0.738	0.626	0.628	0.622	0.611	0.588
L^*.05	c=.4	0.714	0.672	0.629	0.606	0.485	0.419	0.795	0.733	0.684	0.704	0.621	0.529	0.739	0.681	0.644	0.610	0.524	0.387	0.822	0.764	0.705	0.750	0.649	0.577
	.5	0.676	0.644	0.622	0.607	0.549	0.486	0.760	0.685	0.650	0.688	0.623	0.569	0.688	0.650	0.626	0.622	0.575	0.484	0.810	0.711	0.673	0.712	0.644	0.586
	.6	0.622	0.615	0.601	0.584	0.560	0.495	0.707	0.639	0.626	0.636	0.609	0.560	0.642	0.619	0.623	0.606	0.571	0.525	0.763	0.662	0.634	0.664	0.625	0.594
	.7	0.596	0.583	0.563	0.535	0.548	0.529	0.638	0.610	0.587	0.584	0.546	0.512	0.632	0.620	0.598	0.569	0.540	0.520	0.684	0.622	0.617	0.623	0.597	0.558
L^*	c=.4	0.719	0.685	0.643	0.648	0.554	0.476	0.790	0.741	0.704	0.726	0.664	0.591	0.755	0.711	0.648	0.662	0.580	0.465	0.806	0.766	0.725	0.758	0.696	0.626
	.5	0.677	0.654	0.629	0.647	0.586	0.460	0.757	0.709	0.673	0.709	0.650	0.607	0.715	0.673	0.635	0.661	0.590	0.488	0.787	0.736	0.696	0.734	0.681	0.623
	.6	0.643	0.588	0.567	0.591	0.532	0.444	0.723	0.656	0.629	0.662	0.615	0.574	0.683	0.637	0.578	0.634	0.535	0.428	0.748	0.693	0.649	0.705	0.645	0.577
	.7	0.585	0.553	0.552	0.543	0.506	0.546	0.658	0.603	0.549	0.604	0.548	0.523	0.608	0.584	0.545	0.556	0.521	0.517	0.699	0.640	0.590	0.646	0.572	0.529
L^*+0.05	c=.4	0.759	0.709	0.687	0.710	0.649	0.534	0.779	0.758	0.731	0.760	0.726	0.681	0.764	0.731	0.679	0.736	0.643	0.520	0.785	0.765	0.741	0.777	0.744	0.683
	.5	0.725	0.682	0.633	0.679	0.612	0.470	0.766	0.718	0.701	0.735	0.703	0.655	0.749	0.704	0.642	0.709	0.618	0.476	0.778	0.749	0.714	0.763	0.723	0.672
	.6	0.666	0.605	0.566	0.617	0.528	0.459	0.749	0.699	0.637	0.703	0.642	0.560	0.702	0.620	0.567	0.626	0.500	0.386	0.767	0.720	0.664	0.730	0.681	0.570
	.7	0.581	0.553	0.567	0.537	0.550	0.569	0.694	0.613	0.562	0.613	0.548	0.534	0.637	0.573	0.554	0.547	0.527	0.549	0.730	0.663	0.602	0.667	0.575	0.529
L^*+0.1	c=.4	0.765	0.742	0.703	0.757	0.678	0.577	0.796	0.777	0.750	0.777	0.760	0.713	0.782	0.743	0.696	0.750	0.687	0.561	0.791	0.772	0.757	0.784	0.763	0.724
	.5	0.739	0.696	0.615	0.714	0.597	0.492	0.773	0.754	0.716	0.758	0.729	0.666	0.759	0.709	0.633	0.728	0.629	0.456	0.790	0.766	0.732	0.769	0.735	0.672
	.6	0.686	0.626	0.554	0.606	0.534	0.477	0.756	0.712	0.651	0.718	0.655	0.566	0.731	0.647	0.554	0.640	0.529	0.336	0.774	0.742	0.679	0.751	0.674	0.572
	.7	0.594	0.589	0.598	0.570	0.579	0.609	0.711	0.620	0.577	0.624	0.567	0.568	0.660	0.599	0.613	0.572	0.571	0.588	0.750	0.682	0.616	0.686	0.602	0.560

Table 5: Simulated power for two treatments using the sample size N_T.

valuable insights to practitioners to choose a larger L ($> L^*$) and smaller c (<0.60) if possible.

Conclusion

In this study, statistical analysis of count data collected from a two-

β_2		2												2.5											
λ_2		1.0						1.1						1.0						1.1					
β_1		1.5			2			1.5			2			1.5			2			1.5			2		
L	λ_1	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6	1.4	1.5	1.6
$L\tilde{*}0.1$	c=.4	0.931	0.873	0.814	0.851	0.774	0.700	0.962	0.941	0.886	0.942	0.876	0.810	0.944	0.891	0.838	0.883	0.806	0.739	0.968	0.956	0.914	0.955	0.902	0.822
	.5	0.897	0.807	0.775	0.821	0.761	0.711	0.963	0.906	0.837	0.911	0.831	0.776	0.909	0.840	0.787	0.840	0.779	0.727	0.968	0.940	0.865	0.938	0.869	0.800
	.6	0.824	0.761	0.730	0.768	0.726	0.689	0.946	0.848	0.772	0.866	0.779	0.738	0.853	0.771	0.740	0.792	0.749	0.710	0.971	0.900	0.811	0.902	0.808	0.749
	.7	0.755	0.703	0.687	0.692	0.651	0.657	0.888	0.765	0.726	0.794	0.700	0.674	0.772	0.734	0.727	0.735	0.701	0.674	0.948	0.817	0.735	0.825	0.744	0.704
$L\tilde{*}0.05$	c=.4	0.910	0.854	0.810	0.830	0.774	0.693	0.947	0.921	0.875	0.910	0.859	0.810	0.919	0.877	0.837	0.861	0.782	0.720	0.960	0.938	0.896	0.928	0.884	0.832
	.5	0.865	0.810	0.780	0.808	0.762	0.704	0.939	0.880	0.831	0.884	0.833	0.775	0.883	0.820	0.783	0.823	0.773	0.723	0.957	0.909	0.848	0.904	0.843	0.789
	.6	0.801	0.754	0.726	0.752	0.708	0.679	0.899	0.828	0.774	0.839	0.783	0.736	0.818	0.766	0.747	0.778	0.728	0.700	0.944	0.857	0.792	0.863	0.797	0.753
	.7	0.741	0.703	0.685	0.686	0.637	0.670	0.830	0.754	0.725	0.756	0.679	0.657	0.746	0.738	0.726	0.714	0.683	0.659	0.887	0.779	0.746	0.790	0.732	0.687
L^*	c=.4	0.900	0.866	0.832	0.861	0.809	0.763	0.924	0.912	0.884	0.906	0.873	0.832	0.912	0.882	0.851	0.869	0.825	0.757	0.937	0.920	0.893	0.917	0.886	0.841
	.5	0.864	0.825	0.791	0.831	0.780	0.728	0.919	0.886	0.846	0.887	0.851	0.807	0.892	0.849	0.800	0.843	0.795	0.730	0.933	0.898	0.868	0.903	0.866	0.819
	.6	0.822	0.772	0.728	0.777	0.714	0.667	0.890	0.842	0.796	0.847	0.791	0.741	0.848	0.794	0.747	0.796	0.733	0.675	0.914	0.863	0.813	0.875	0.819	0.761
	.7	0.737	0.713	0.702	0.685	0.671	0.723	0.845	0.761	0.719	0.760	0.714	0.675	0.786	0.734	0.711	0.718	0.683	0.711	0.869	0.789	0.751	0.814	0.741	0.693
L^*+0.05	c=.4	0.905	0.889	0.863	0.890	0.857	0.818	0.919	0.906	0.889	0.909	0.891	0.866	0.907	0.898	0.867	0.895	0.866	0.817	0.922	0.910	0.901	0.917	0.895	0.886
	.5	0.879	0.858	0.812	0.863	0.821	0.742	0.912	0.891	0.869	0.897	0.871	0.844	0.896	0.878	0.829	0.883	0.835	0.745	0.914	0.904	0.882	0.908	0.886	0.850
	.6	0.848	0.802	0.757	0.799	0.748	0.714	0.899	0.868	0.813	0.867	0.816	0.770	0.869	0.821	0.766	0.828	0.749	0.692	0.908	0.882	0.846	0.893	0.858	0.787
	.7	0.781	0.753	0.765	0.745	0.741	0.782	0.871	0.808	0.758	0.803	0.754	0.724	0.833	0.775	0.755	0.775	0.730	0.750	0.895	0.839	0.786	0.841	0.787	0.736
L^*+0.1	c=.4	0.907	0.897	0.880	0.901	0.882	0.840	0.921	0.912	0.901	0.915	0.902	0.892	0.912	0.907	0.873	0.907	0.884	0.830	0.923	0.916	0.909	0.916	0.910	0.892
	.5	0.901	0.868	0.827	0.883	0.827	0.755	0.917	0.906	0.888	0.905	0.889	0.854	0.911	0.890	0.846	0.893	0.848	0.742	0.923	0.913	0.894	0.914	0.900	0.874
	.6	0.860	0.821	0.785	0.828	0.781	0.734	0.912	0.880	0.845	0.884	0.849	0.798	0.888	0.848	0.793	0.848	0.790	0.697	0.916	0.894	0.858	0.900	0.865	0.813
	.7	0.818	0.803	0.801	0.792	0.804	0.814	0.881	0.842	0.800	0.841	0.792	0.794	0.856	0.817	0.802	0.815	0.795	0.800	0.905	0.862	0.822	0.875	0.826	0.788

Table 6: Powers for two treatments with 150% of sample size given in Table 4.2.

stage adaptive seamless design with different durations but with the same study objectives in the two stages is discussed under a Weibull model. In particular, the comparison of the treatments is based on the medians of the distributions. Results corresponding to various types of comparison between two treatments using the combined data observed from the two stages are derived. Furthermore, the required sample sizes for the corresponding tests to achieve a given power level are determined. Since the results are developed based on asymptotic approximation, the simulation study conducted in our study shows that the type I error is well-controlled but the simulated power is less than the nominal level for tests with these sample sizes. However, simulation studies show that the nominal power level can be achieved if the sample sizes are increased by 50%. Thus, results developed in this study provide valuable insights for practitioners to determine the sample sizes in a two-stage design.

References

1. Bauer P, Kieser M (1999) Combining different phases in the development of medical treatments within a single trial. Stat Med 18: 1833-1848.
2. Liu Q, Pledger GW (2005) Phase 2 and 3 Combination Designs to Accelerate Drug Development. Journal of American Statistical Association 100: 493-502.
3. Maca J, Bhattacharya S, Dragalin V, Gallo P, Krams M (2006) Adaptive Seamless Phase II/III Designs-Background, Operational Aspects, and Examples. Drug Information Journal 40: 463-474.
4. Chow SC, Chang M (2007) Adaptive Design Methods in Clinical Trials. Chapman Hall/CRC Press, Taylor and Francis, New York.
5. Tsiatis AA, Mehta C (2003) On The Inefficiency of the Adaptive Design for Monitoring Clinical Trials. Biometrika 90: 367-378.
6. Chow SC, Lu Q, Tse SK (2007) Statistical Analysis for Two-Stage Adaptive Design With Different Study Endpoints. J Biopharm Stat 17: 1163-1176.