國立交通大學

統計學研究所

碩士論文

連續型變數之貝氏二階段第二期臨床試驗設計

Bayesian Two-Stage Designs for Phase II Clinical Trials with Continuous Endpoints

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中 華 民 國 一〇二 年 六 月

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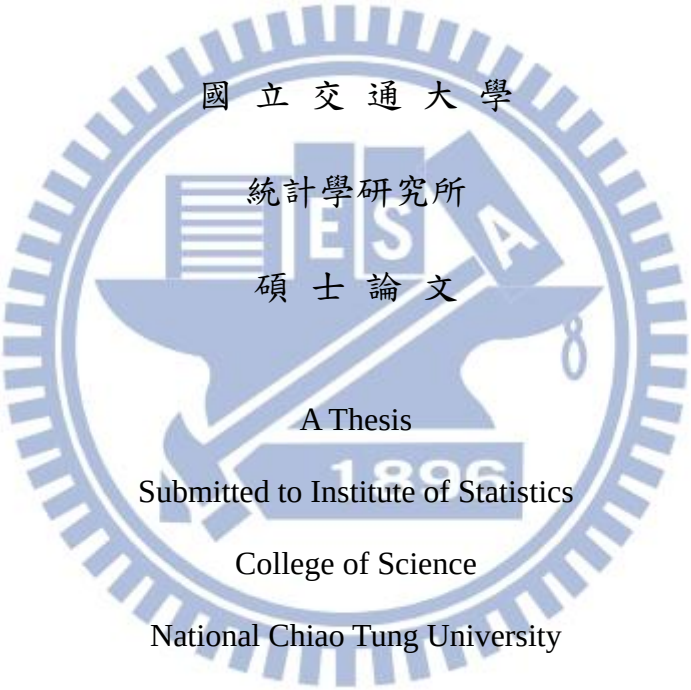

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連續型變數之貝氏二階段第二期臨床試驗設計

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中文摘要

製藥發展是需要長時間和花費的一個過程，而許多機構在執行藥物臨床測試時，藥物在相對較晚的程序中才宣告失敗停止，因此基於在偵測藥物效能上使用較快且可靠的方法並且減少受試者人數和試驗所需時間，研發出新式臨床策略或方法設計，其中的設計是更加有效率不論是在執行上或是花費上在偵測有可能性的藥物，而新設計在製藥發展中有著迫切的需要。在臨床試驗第二階段(phase II clinical trials)，其中兩階段(two-stage)或是多階段(multiple-stage) 無對照組試驗設計多採用 frequentist 的統計方法，另一方面，相對於 frequentist 另有貝氏(Bayesian)統計方法，貝氏方法可將相關的先前資訊納入臨床結果分析之中，可使之更加符合直覺並且對試驗更有幫助。在此篇論文當中，針對連續型變數提出兩種貝氏二階段藥物效用監控設計，並針對此二設計提出數值範例來示範此二貝氏設計並且與 frequentist 的統計方法做出比較。

關鍵字：二階段臨床測試; 貝氏方法

Bayesian Two-Stage Designs for Phase II Clinical Trials with Continuous Endpoints

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Abstract

Pharmaceutical development is a lengthy and expensive process and many of these agents fail relatively late in that process. Hence, there is an urgent need of new strategies and methodology for efficient and cost-effective designs to screen potential candidates based on the idea of the proof of the concept for efficacy in a rapid and reliable manner to minimize the total sample size and hence to shorten the duration of the trials. In phase II clinical trials, two-stage or multiple-stage designs with no control group have been proposed based on frequentist statistical approaches. Alternatively, Bayesian methods incorporating relevant prior information into the analysis of the trial results may be more intuitive and helpful. In this thesis, two Bayesian two-stage screening designs based on continuous efficacy endpoints are proposed. Numerical example is presented to illustrate the Bayesian approach. Comparisons with other frequentist approaches are also made.

KEY WORDS: phase II clinical trials; Bayesian approach; two-stage design

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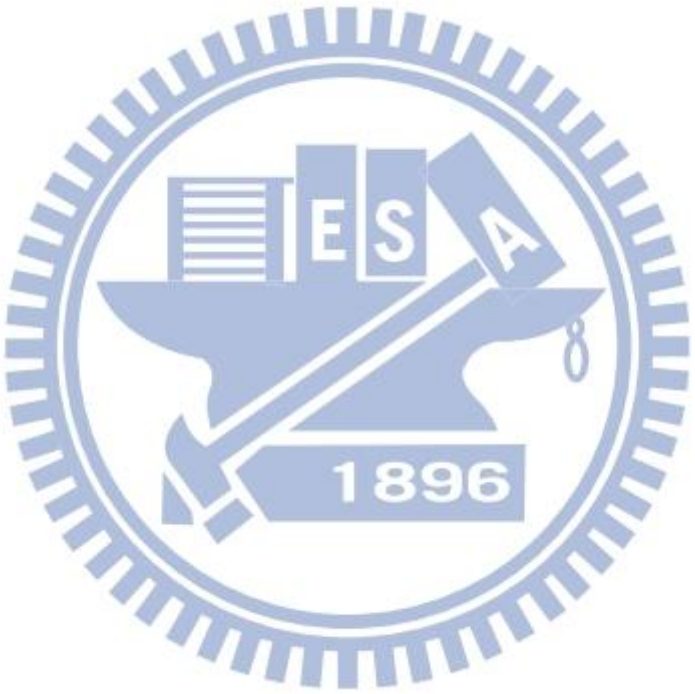
Content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1. Introduction

The development of pharmaceutical products is risky, challenging, slow, costly and time-consuming endeavor. An analysis which takes into account that projects which were neither success nor fair suggests that it usually takes about 10-15 years to develop one new medicine from the time it is discovered to when it is available for commercial marketing and treating patients. The average cost to research and develop each successful drug is estimated to be $800 million to $1 billion and 70% of the cost of pharmaceutical development is wasted on drugs that do not even make it to market. By the time a drug company applies to the Food and Drug Administration (FDA) for marketing approval of a new product, on average it has performed more than 70 clinical studies on at least 4,000 patients. Despite a better understanding of disease etiology and advance in medical technology, there is only 1 out of 10,000 candidates screened in the laboratory that will survive to market launch, and more than 60% of the potential candidates that enter clinical trials fail. Furthermore, the success rate of the phase III stage of the clinical development has fallen by 30% [1]. On the other hand, the development of biomedical science has been raised to cure many diseases nowadays and been full of potential. Nevertheless, the number of the biomedical products and new drugs submitted to the FDA and approved by the FDA does not increase. One of the probable reasons may be that the drug screening process should become more efficient and effective to let the biomedical science fill with full potential. As a result, there is an urgent need of new strategies and methodologies for overall success improving, efficient, and cost-effective designs to screen potential candidates based on the idea of the proof of the concept for efficacy in a rapid and reliable manner to minimize the total sample size and hence to shorten the duration of the trials.

Trials of pharmaceutical agents have been divided into phase Ⅰ－Ⅳ. The drug

first was developed and tested in the laboratory. Once it is done and ready for testing in the human subjects, a phase Ⅰ trial is conducted. The purpose of the phase Ⅰ trial is to examine the drug tolerance, metabolism and study the drug toxicity in human and also identify the best dose to be used. Then, the phase II trial may employ the best dose identified in the phase Ⅰ study to assess the efficacy of the drug and determine whether it should be tested in further phase Ⅲ trial. The phase Ⅲ trial consists of therapeutic confirmatory studies and establishment of the safety profile by comparing the drug with other compound being used to treat the condition. The phase Ⅳ trial consists of the examination the drug in broad or special population and seeking to identify uncommon adverse events, for example Lawrence et al. [2] and Tan and Machin [3].

To evaluate the biological activity or efficacy of the drug, the phase II trial is conducted. Phase II trials can be a single-stage or a multi-stage design. Among two-stage designs, the approaches commonly used are Gehan design, Simon optimal design, and the minimax design. These designs are based on the frequentist statistical approach. For Simon's two-stage design, it requires some specific input, including uninteresting level, target level, type Ⅰ error and type II error. The sample sizes are evaluated subjected to the constraint upon the type Ⅰ error and type II error. The idea of the two-stage approach is presented as follows. When the first stage is completed, the trial would be terminated if the response rate does not exceed some critical value indicating that the drug has low efficacy and is not recommended to the next step of the trial. Otherwise, more patients are enrolled and treated in the second stage. After the second stage is completed, the final analysis is performed with the outcomes of the first and the second stage. The drug would be rejected if the overall response rate is less than some critical level and not be recommended to the phase Ⅲ trial. Otherwise, the drug would be recommended to the phase Ⅲ trial. Simon [4] proposed

the “Optimal two-stage designs for phase II clinical trials” with binary response endpoints. Tsou et al. [5] proposed a two-stage screening design based on continuous efficacy endpoints under the framework of Simon two-stage design.

The main concept of Bayesian approach is the incorporation of the prior distribution which brings in the prior experience or information. So, the Bayesian design in Simon [4] allows for the formal incorporation of relevant information from the other resources of the evidence in the monitoring and analysis of the trial. With a Bayesian approach, we can obtain the posterior distribution of the true response rate. This allows us to compute the probability that the response rate falls within the region of interest. For example, we can derive the interval with a 95 per cent probability of containing the true response rate. On the other hand, the frequentist approach cannot answer this kind of questions.

Several Bayesian designs have been proposed for phase II trials, for example methods proposed by Thall [6], Heitjan [7], and Sylverster [8], while most of these are not the real two-stage design but the continuous monitoring design of the trial. In particular, Thall and Simon proposed a design which involves the continual accrual of patients until the new drug is shown with high posterior probability to be either promising or not promising, or until a predetermined maximum sample size is reached. Their design requires the specifications of an informative clinical prior for the response rate of the standard drug which has been found to be the best so far, and a non-informative clinical prior for the response rate of the new drug [6]. In contrast, instead of the prior for the new drug, Heitjan’s design requires the specification of hypothetical skeptical and enthusiastic priors. Both Thall and Simon’s as well as Heitjan’s designs make use of probability distributions for both the response proportions of the standard drug as well as the new drug. This is unlike the framework of the frequentist designs in which only take account of the response rate of the

standard drug.

Tan and Machin [3] proposed two Bayesian designs for phase II trials which are like the frameworks of designs of Thall [6], Heitjan [7] and Sylverster [8]. The design does not require the specification of a loss or utility function and only need to specify a prior distribution for the response rate of the new drug and not the standard drug as well. It would make the design to be similar to the frequentist approach of two stage phase II clinical trials.

In this thesis, two Bayesian designs for phase II trials with continuous endpoints will be developed. One is the single threshold Bayesian design and another is the dual threshold Bayesian design. These two designs are presented in Section 2 and 3, respectively. The methods to determine the sample size and to determine whether to recommend the drug to the phase Ⅲ trial or not are also proposed. In Section 4, the numerical results of sample sizes and simulation studies are shown. Comparison with Simon design will be given in Section 5. Discussion and conclusion are made in Section 6.

2. Single Threshold Design

We consider a two-stage design for a phase II clinical trial for testing an experimental drug based on continuous response endpoints. In our design, let n_1 be the number of patients recruited and treated in the first stage and (possibly) further n_2 be the number of additional patients recruited at stage 2. Let X_1^i denote the response of the i^{th} patient among the n_1 patients in stage 1, $i = 1,...,n_1$ and X_2^j denote the responses of the j^{th} patient among the n_2 patients in stage 2, $j = 1,...,n_2$. Total sample size would be $N = n_1 + n_2$. Because most continuous efficacy endpoints or their log transformation follow normal or approximately normal distributions, we assume that X_1^i and X_2^j are normally distributed with a mean of μ and a known variance of σ^2. Hence, $X_1^1,....,X_1^{n_1}$, $X_2^1,....,X_2^{n_2}$ are i.i.d. random variables with common distribution $N(\mu,\sigma^2)$. Suppose σ^2 is known. For convenience of notations, we denote $\overline{X_1}$ and $\overline{X_2}$ the sample means of the responses in the stage 1 and 2, respectively. We also define a pair of variables $Y_1 = \overline{X_1}$, $Y_2 = \frac{X_1^1 + ... + X_1^{n_1} + X_2^1 + ... + X_2^{n_2}}{n_1 + n_2} = \frac{n_1\overline{X_1} + n_2\overline{X_2}}{n_1 + n_2}$ which are beneficial for following calculation in two designs. By some algebra (the detail was described in Appendix 1), we know that $\overline{X_1}$ is distributed as $N(\mu, \frac{\sigma^2}{n_1})$ and $\overline{X_2}$ is distributed as $N(\mu, \frac{\sigma^2}{n_2})$.

Considering the single threshold design (STD), we let μ_U be the target response mean and μ be the true mean for testing the drug. Then the prior distribution of μ is assumed as a normal distribution with mean θ and variance τ^2. Furthermore, let λ_1 and λ_2 (with $0 < \lambda_1 < \lambda_2 < 1$) be the minimum desired

threshold probabilities, at the interim stage and at the end of the trial, respectively. Now, suppose that the (hypothetical) response mean underlying Y_1 and Y_2 are just larger than the pre-specified μ_U, that is $\mu_U + \varepsilon_U$, where ε_U is some preselected small value (say between 0 and 0.1).

To find the suitable minimum total sample size for this trial design, we enable two constraints to find the smallest sample size. We enable the posterior probability of μ over the target response mean μ_U at the end of stage 1, $\Pr(\mu > \mu_U \mid Y_1)$, to be at least λ_1. Moreover, the posterior probability of μ over the target response mean μ_U at the end of trial, $\Pr(\mu > \mu_U \mid Y_1, Y_2)$, is at least λ_2. We can express two inequalities as

$$\Pr(\mu > \mu_U \mid Y_1) \geq \lambda_1 \tag{1}$$

and

$$\Pr(\mu > \mu_U \mid Y_1, Y_2) \geq \lambda_2. \tag{2}$$

According to the Bayesian principal, we obtain that the posterior distribution of μ given Y_1 is a normal distribution as (the details are given in Appendix 2).

$$\mu \mid Y_1 \sim N\left(\left(\frac{\tau^2}{\tau^2 + \frac{\sigma^2}{n_1}}\right) y_1 + \left(\frac{\frac{\sigma^2}{n_1}}{\tau^2 + \frac{\sigma^2}{n_1}}\right)\theta \,,\, \frac{\frac{\sigma^2}{n_1}\cdot\tau^2}{\tau^2 + \frac{\sigma^2}{n_1}}\right) \tag{3}$$

$$\sim N\left((1-r)y_1 + r\theta, r\tau^2\right), \text{ where } r = \frac{\frac{\sigma^2}{n_1}}{\tau^2 + \frac{\sigma^2}{n_1}}.$$

By the result of (3), the constraint (1) becomes

$$\int_{\mu_U}^{\infty} \frac{1}{\sqrt{2\pi}\cdot\sqrt{r\tau^2}} \exp\left\{-\frac{\left(\mu - \left[(1-r)y_1 + r\theta\right]\right)^2}{2\cdot r\tau^2}\right\} d\mu \geq \lambda_1. \tag{4}$$

Furthermore, by the following computation, we would like to find the posterior distribution of μ given Y_1 and Y_2 that enable us to simplify the constraint (2) and find the suitable minimum sample size for the design.

We get the joint distribution of Y_1 and Y_2 given μ from the joint distribution

of $\overline{X_1}$ and $\overline{X_2}$ given μ by multiplying a Jacobian factor $|J|$. Then we substitute $\overline{X_1} = Y_1$, $\overline{X_2} = \frac{n_1+n_2}{n_2} Y_2 + \frac{n_1}{n_2} Y_1$ into expression (5) to get expression (6). The joint distribution of Y_1 and Y_2 given μ can be derived as follows,

$$f(y_1, y_2 \mid \mu)$$

$$= f(\overline{x_1}, \overline{x_2} \mid \mu) \cdot |J| \quad \text{, where } |J| = \begin{vmatrix} 1 & 0 \\ \frac{-n_1}{n_2} & \frac{n_1+n_2}{n_2} \end{vmatrix} = \frac{n_1+n_2}{n_2}$$

$$= f(\overline{x_1} \mid \mu) \cdot f(\overline{x_2} \mid \mu) \cdot |J|$$

$$= \frac{1}{2\pi \cdot \frac{\sigma^2}{\sqrt{n_1 n_2}}} \exp\left\{ -\frac{(\overline{x_1}-\mu)^2}{2 \cdot \frac{\sigma^2}{n_1}} - \frac{(\overline{x_2}-\mu)^2}{2 \cdot \frac{\sigma^2}{n_2}} \right\} \cdot \frac{n_1+n_2}{n_2} \tag{5}$$

$$= \frac{1}{2\pi \cdot \frac{\sigma^2}{\sqrt{n_1 n_2}}} \exp\left\{ -\frac{(y_1-\mu)^2}{2 \cdot \frac{\sigma^2}{n_1}} - \frac{(\frac{n_1+n_2}{n_2} y_2 - \frac{n_1}{n_2} y_1 - \mu)^2}{2 \cdot \frac{\sigma^2}{n_2}} \right\} \cdot \frac{n_1+n_2}{n_2} . \tag{6}$$

We then get the joint distribution of Y_1, Y_2 and μ by multiplying the joint distribution of Y_1 and Y_2 given μ and the prior distribution of μ that is $\pi(\mu)$, that is

$$f(y_1, y_2, \mu)$$

$$= f(y_1, y_2 \mid \mu) \cdot \pi(\mu)$$

$$= \frac{1}{2\pi \cdot \frac{\sigma^2}{\sqrt{n_1 n_2}}} \cdot \frac{n_1+n_2}{n_2} \exp\left\{ -\frac{(y_1-\mu)^2}{2 \cdot \frac{\sigma^2}{n_1}} - \frac{(\frac{n_1+n_2}{n_2} y_2 - \frac{n_1}{n_2} y_1 - \mu)^2}{2 \cdot \frac{\sigma^2}{n_2}} \right\} \cdot \frac{1}{\sqrt{2\pi}\tau} \exp\left\{ -\frac{(\theta-\mu)^2}{2\tau^2} \right\}$$

$$= \frac{1}{(2\pi)^{3/2}\dfrac{\sigma^2\tau}{\sqrt{n_1 n_2}}} \cdot \frac{n_1+n_2}{n_2} \exp\left\{ -\frac{(y_1-\mu)^2}{2\cdot\dfrac{\sigma^2}{n_1}} - \frac{(\dfrac{n_1+n_2}{n_2}y_2 - \dfrac{n_1}{n_2}y_1 - \mu)^2}{2\cdot\dfrac{\sigma^2}{n_2}} - \frac{(\theta-\mu)^2}{2\tau^2} \right\}. \qquad (7)$$

By integrating (7) with respect to μ, we get the joint p.d.f. of Y_1 and Y_2 as in (8). Expanding three terms of exponential and also separating the terms irrelevant to μ out of the integration in expression (8), we get expression (9).

$$f(y_1, y_2)$$

$$= \frac{1}{(2\pi)^{3/2}\dfrac{\sigma^2\tau}{\sqrt{n_1 n_2}}} \cdot \frac{n_1+n_2}{n_2} \int_{-\infty}^{\infty} \exp\left\{ -\frac{(y_1-\mu)^2}{2\cdot\dfrac{\sigma^2}{n_1}} - \frac{(\dfrac{n_1+n_2}{n_2}y_2 - \dfrac{n_1}{n_2}y_1 - \mu)^2}{2\cdot\dfrac{\sigma^2}{n_2}} - \frac{(\theta-\mu)^2}{2\tau^2} \right\} d\mu \qquad (8)$$

$$= \frac{1}{(2\pi)^{3/2}\dfrac{\sigma^2\tau}{\sqrt{n_1 n_2}}} \cdot \frac{n_1+n_2}{n_2} \cdot c \cdot$$

$$\int_{-\infty}^{\infty} \exp\left\{ -\frac{1}{2}\left(\frac{n_1}{\sigma^2}\mu^2 + \frac{n_2}{\sigma^2}\mu^2 + \frac{1}{\tau^2}\mu^2 - 2\frac{n_1}{\sigma^2}y_1\mu + 2\frac{n_2}{\sigma^2}\frac{n_1}{n_2}y_1\mu - 2\frac{n_2}{\sigma^2}\frac{n_1+n_2}{n_2}y_2\mu - 2\frac{1}{\tau^2}\mu\theta \right) \right\} d\mu \qquad (9)$$

$$= \frac{1}{(2\pi)^{3/2}\dfrac{\sigma^2\tau}{\sqrt{n_1 n_2}}} \cdot \frac{n_1+n_2}{n_2} \cdot c \cdot$$

$$\int_{-\infty}^{\infty} \exp\left\{ -\frac{1}{2}\left[\frac{n_1}{\sigma^2} + \frac{n_2}{\sigma^2} + \frac{1}{\tau^2} \right] \left[\mu^2 - 2\mu \frac{\dfrac{n_1}{\sigma^2}y_1 - \dfrac{n_1}{\sigma^2}y_1 + \dfrac{n_1+n_2}{\sigma^2}y_2 + \dfrac{1}{\tau^2}\theta}{\dfrac{n_1}{\sigma^2} + \dfrac{n_2}{\sigma^2} + \dfrac{1}{\tau^2}} \right] \right\} d\mu \,, \qquad (10)$$

where

$$c = \exp\left\{ -\frac{n_1}{2\sigma^2}{y_1}^2 - \frac{n_2}{2\sigma^2}\left(\frac{n_1+n_2}{n_2}\right)^2 {y_2}^2 - \frac{n_2}{2\sigma^2}\left(\frac{n_1}{n_2}\right)^2 {y_1}^2 + \frac{n_2}{2\sigma^2}\cdot 2\cdot\frac{n_1+n_2}{n_2}\cdot\frac{n_1}{n_2}y_1 y_2 + 2\cdot\frac{1}{\tau^2}\theta^2 \right\}.$$

We multiply and divide a term $\exp\left\{ \dfrac{\left[\dfrac{n_1+n_2}{\sigma^2}y_2 + \dfrac{1}{\tau^2}\theta \right]^2}{2\left(\dfrac{n_1}{\sigma^2} + \dfrac{n_2}{\sigma^2} + \dfrac{1}{\tau^2} \right)} \right\}$ simultaneously to expression (10). Then the joint p.d.f. of Y_1 and Y_2 can be simplified as

$$f(y_1, y_2)$$

$$= \frac{1}{(2\pi)^{3/2}} \frac{\sigma^2\tau}{\sqrt{n_1 n_2}} \cdot \frac{n_1+n_2}{n_2} \cdot c \cdot \exp\left\{ \frac{\left[\frac{n_1+n_2}{\sigma^2} y_2 + \frac{1}{\tau^2}\theta \right]^2}{2\left(\frac{n_1}{\sigma^2} + \frac{n_2}{\sigma^2} + \frac{1}{\tau^2} \right)} \right\} \cdot$$

$$\int_{-\infty}^{\infty} \exp\left\{ -\frac{1}{2}\left[\frac{n_1}{\sigma^2} + \frac{n_2}{\sigma^2} + \frac{1}{\tau^2} \right] \left[\mu^2 - 2\mu \frac{\frac{n_1}{\sigma^2} y_1 - \frac{n_1}{\sigma^2} y_1 + \frac{n_1+n_2}{\sigma^2} y_2 + \frac{1}{\tau^2}\theta}{\frac{n_1}{\sigma^2} + \frac{n_2}{\sigma^2} + \frac{1}{\tau^2}} \right] \right\} \cdot \exp\left\{ -\frac{\left[\frac{n_1+n_2}{\sigma^2} y_2 + \frac{1}{\tau^2}\theta \right]^2}{2\left(\frac{n_1}{\sigma^2} + \frac{n_2}{\sigma^2} + \frac{1}{\tau^2} \right)} \right\} d\mu$$

$$= \frac{1}{(2\pi)^{3/2}} \frac{\sigma^2\tau}{\sqrt{n_1 n_2}} \cdot \frac{n_1+n_2}{n_2} \cdot c \cdot \exp\left\{ \frac{\left[\frac{n_1+n_2}{\sigma^2} y_2 + \frac{1}{\tau^2}\theta \right]^2}{2\left(\frac{n_1}{\sigma^2} + \frac{n_2}{\sigma^2} + \frac{1}{\tau^2} \right)} \right\} \cdot$$

$$\int_{-\infty}^{\infty} \exp\left\{ -\frac{1}{2}\left[\frac{n_1}{\sigma^2} + \frac{n_2}{\sigma^2} + \frac{1}{\tau^2} \right] \left[\mu^2 - 2\mu \frac{\frac{n_1+n_2}{\sigma^2} y_2 + \frac{1}{\tau^2}\theta}{\frac{n_1}{\sigma^2} + \frac{n_2}{\sigma^2} + \frac{1}{\tau^2}} + \left(\frac{\frac{n_1+n_2}{\sigma^2} y_2 + \frac{1}{\tau^2}\theta}{\frac{n_1}{\sigma^2} + \frac{n_2}{\sigma^2} + \frac{1}{\tau^2}} \right)^2 \right] \right\} d\mu$$

$$= \frac{1}{(2\pi)^{3/2}} \frac{\sigma^2\tau}{\sqrt{n_1 n_2}} \cdot \frac{n_1+n_2}{n_2} \cdot c \cdot \exp\left\{ \frac{\left[\frac{n_1+n_2}{\sigma^2} y_2 + \frac{1}{\tau^2}\theta \right]^2}{2\left(\frac{n_1}{\sigma^2} + \frac{n_2}{\sigma^2} + \frac{1}{\tau^2} \right)} \right\} \cdot$$

$$\int_{-\infty}^{\infty} \exp\left\{ -\frac{1}{2}\left[\frac{n_1}{\sigma^2} + \frac{n_2}{\sigma^2} + \frac{1}{\tau^2} \right] \left[\mu - \frac{\frac{n_1+n_2}{\sigma^2} y_2 + \frac{1}{\tau^2}\theta}{\frac{n_1}{\sigma^2} + \frac{n_2}{\sigma^2} + \frac{1}{\tau^2}} \right]^2 \right\} d\mu$$

$$= \frac{1}{(2\pi)^{3/2}} \frac{\sigma^2\tau}{\sqrt{n_1 n_2}} \cdot \frac{n_1+n_2}{n_2} \cdot c \cdot \exp\left\{ \frac{\left[\frac{n_1+n_2}{\sigma^2} y_2 + \frac{1}{\tau^2}\theta \right]^2}{2\left(\frac{n_1}{\sigma^2} + \frac{n_2}{\sigma^2} + \frac{1}{\tau^2} \right)} \right\} \cdot \frac{\sqrt{2\pi}}{\sqrt{\frac{n_1}{\sigma^2} + \frac{n_2}{\sigma^2} + \frac{1}{\tau^2}}} \quad . \qquad (11)$$

By definition, the conditional p.d.f. of μ given Y_1 and Y_2 is to divide the joint p.d.f. of μ, Y_1, and Y_2 by the joint pd.d.f. of Y_1 and Y_2,

$$f(\mu \mid y_1, y_2)$$

$$= \frac{f(y_1, y_2, \mu)}{f(y_1, y_2)}$$

$$= \frac{\exp\left\{-\frac{1}{2}\left[\frac{n_1}{\sigma^2}+\frac{n_2}{\sigma^2}+\frac{1}{\tau^2}\right]\left[\mu^2 - 2\mu\frac{\frac{n_1+n_2}{\sigma^2}y_2+\frac{1}{\tau^2}\theta}{\frac{n_1}{\sigma^2}+\frac{n_2}{\sigma^2}+\frac{1}{\tau^2}}+\left(\frac{\frac{n_1+n_2}{\sigma^2}y_2+\frac{1}{\tau^2}\theta}{\frac{n_1}{\sigma^2}+\frac{n_2}{\sigma^2}+\frac{1}{\tau^2}}\right)^2\right]\right\}}{\frac{\sqrt{2\pi}}{\sqrt{\frac{n_1}{\sigma^2}+\frac{n_2}{\sigma^2}+\frac{1}{\tau^2}}}}$$

$$= \frac{1}{\sqrt{2\pi}\cdot\frac{1}{\sqrt{\frac{n_1}{\sigma^2}+\frac{n_2}{\sigma^2}+\frac{1}{\tau^2}}}}\exp\left\{-\frac{1}{2}\frac{\left(\mu-\frac{\frac{n_1+n_2}{\sigma^2}y_2+\frac{1}{\tau^2}\theta}{\frac{n_1}{\sigma^2}+\frac{n_2}{\sigma^2}+\frac{1}{\tau^2}}\right)^2}{\frac{1}{\frac{n_1}{\sigma^2}+\frac{n_2}{\sigma^2}+\frac{1}{\tau^2}}}\right\}$$

$$\sim N\left(\frac{\frac{n_1+n_2}{\sigma^2}y_2+\frac{1}{\tau^2}\theta}{\frac{n_1}{\sigma^2}+\frac{n_2}{\sigma^2}+\frac{1}{\tau^2}}, \frac{1}{\frac{n_1}{\sigma^2}+\frac{n_2}{\sigma^2}+\frac{1}{\tau^2}}\right). \qquad (12)$$

We then obtain that the posterior distribution of μ given Y_1 and Y_2 is also a normal distribution. By the result of (12), the constraint (2) becomes

$$\int_{\mu_U}^{\infty}\frac{1}{\sqrt{2\pi}\frac{1}{\sqrt{\frac{n_1}{\sigma^2}+\frac{n_2}{\sigma^2}+\frac{1}{\tau^2}}}}\exp\left\{-\frac{\left(\mu-\frac{\frac{n_1+n_2}{\sigma^2}y_2+\frac{1}{\tau^2}\theta}{\frac{n_1}{\sigma^2}+\frac{n_2}{\sigma^2}+\frac{1}{\tau^2}}\right)^2}{2\cdot\frac{1}{\frac{n_1}{\sigma^2}+\frac{n_2}{\sigma^2}+\frac{1}{\tau^2}}}\right\}d\mu \geq \lambda_2 . \qquad (13)$$

Once the sample size has been determined and the trial begins, the n_1 patients are recruited in stage 1 of the trial. At the end of stage 1, we evaluated the posterior probability $\Pr(\mu > \mu_U \mid Y_1)$ (Note that Y_1 now represents the actual data from the stage 1 not the hypothetical data in the design stage). If $\Pr(\mu > \mu_U \mid Y_1)$ is less than λ_1, the trial is terminated and that there is insufficient evidence that the drug is efficacious enough to be recommended for the phase Ⅲ trial. On the other hand, if the

posterior probability $\Pr(\mu > \mu_U \mid Y_1)$ is greater than or equal to λ_1, further n_2 patients would be recruited in stage 2 of the trial. At the end of stage 2, we evaluated the final posterior probability $\Pr(\mu > \mu_U \mid Y_1, Y_2)$. If $\Pr(\mu > \mu_U \mid Y_1, Y_2)$ is less than λ_2, the trial is insufficiently efficacious to be recommended for the phase Ⅲ trial testing. If $\Pr(\mu > \mu_U \mid Y_1, Y_2)$ is greater than or equal to λ_2, the product would be tested in the phase Ⅲ trial.

3. Dual Threshold Design

The dual threshold design (DTD) is similar to the single threshold design (STD) except that the sample size of stage 1 is not determined on the posterior probability of μ exceeding c, but on the probability that μ will be less than the 'no further interest mean response' μ_L. This represents the average response mean below which the investigators would have no further interest in the new drug. The value μ_L acts as the lower threshold of average response mean, as opposed to the upper threshold represented by μ_U. The first constraint of stage 1 becomes

$$\Pr(\mu < \mu_L \mid Y_1) \le \lambda_1 \tag{14}$$

and the constraint of stage 2 is the same as the one in the STD, as in (2),

$$\Pr(\mu > \mu_U \mid Y_1, Y_2) \ge \lambda_2. \tag{15}$$

Now, suppose that the (hypothetical) response mean underlying Y_1 is just smaller than the pre-specified μ_L, that is $\mu_L - \varepsilon_L$ and the (hypothetical) response mean underlying Y_2 is just larger than the pre-specified μ_U, that is $\mu_U + \varepsilon_U$, where ε_L and ε_U are some preselected small values.

By the same computation in the STD, constraints (14) and (15) become

$$\int_0^{\mu_L} \frac{1}{\sqrt{2\pi}\cdot\sqrt{r\tau^2}} \exp\left\{-\frac{\left(\mu - \left[(1-r)y_1 + r\theta\right]\right)^2}{2\cdot r\tau^2}\right\} d\mu \le \lambda_1 \text{, where } r = \frac{\frac{\sigma^2}{n_1}}{\tau^2 + \frac{\sigma^2}{n_1}} \tag{16}$$

and

$$\int_{\mu_U}^{\infty} \frac{1}{\sqrt{2\pi}\,\frac{1}{\sqrt{\frac{1}{\sigma^2}n_1 + \frac{1}{\sigma^2}n_2 + \frac{1}{\tau^2}}}} \exp\left\{-\frac{\left(\mu - \frac{\frac{1}{\sigma^2}n_1y_1 + \frac{1}{\sigma^2}n_2y_2 + \frac{1}{\tau^2}\theta}{\frac{1}{\sigma^2}n_1 + \frac{1}{\sigma^2}n_2 + \frac{1}{\tau^2}}\right)^2}{2\cdot\frac{1}{\frac{1}{\sigma^2}n_1 + \frac{1}{\sigma^2}n_2 + \frac{1}{\tau^2}}}\right\} d\mu \ge \lambda_2 , \tag{17}$$

respectively, so we can find the minimum required sample size of two stages

according to these two constraints.

Once the sample sizes have been determined and the trial stared, the n_1 patients are recruited in stage 1 of the trial. At the end of stage 1, we evaluated the posterior probability $\Pr(\mu < \mu_L \mid Y_1)$ (Note that Y_1 now represents the actual data from the stage 1 not the hypothetical data in the design stage). If $\Pr(\mu < \mu_L \mid Y_1)$ is greater than or equal to λ_1, the trial is terminated and that there is insufficient evidence that the drug is efficacious enough to be recommended for the phase Ⅲ trial. On the other hand, if the posterior probability $\Pr(\mu < \mu_L \mid Y_1)$ is less than λ_1, further n_2 patients would be recruited in stage 2 of the trial. At the end of stage 2, we evaluated the final posterior probability $\Pr(\mu > \mu_U \mid Y_1, Y_2)$. If $\Pr(\mu > \mu_U \mid Y_1, Y_2)$ is less than λ_2, the trial is insufficiently efficacious to be recommended for the phase Ⅲ trial testing. If $\Pr(\mu > \mu_U \mid Y_1, Y_2)$ is greater than or equal to λ_2, the product would be tested in the phase Ⅲ trial.

4. Result

4.1 Sample size of Single Threshold Design

The purpose of the phase Ⅱ trial is to assess the efficacy of the new drug. Before the trial, we know relatively little information regarding the efficacy of the new drug being test. It makes sense to make a prior distribution in the design stage. Especially, we make the use of the normal distribution which centers on the upper threshold μ_U. We also note that the use of normal distribution allow us easily update the prior distribution from the normal data.

Before the start of the trial, we help the investigators provide some parameters of the normal prior distribution and also the value of ε_U. For suggestion, if the variance of the data is large, we recommend the choice of the larger variance parameter of the prior distribution. Also, the mean of the prior distribution is recommended to be around the target average response rate.

In this section, we give some examples to illustrate our designs. Tables 1－24 demonstrate the Single Threshold Design for several combinations of parameters with $\varepsilon_U = 1.0$, $\varepsilon_U = 0.5$, $\sigma = 6$, $\sigma = 8, \sigma = 13$, $\tau^2 = 1, \tau^2 = 2$, $\tau^2 = 4$, $\tau^2 = 9$. The values of θ are from 8 to 12 centered around μ_U. The rational selections of (λ_1, λ_2) are $(0.6, 0.7)$, $(0.6, 0.8)$ and $(0.7, 0.8)$ as listed in the tables. The tabulated results contain the minimum required sample sizes determined by using a program of numerical technique written in $C++$ corresponding to combinations of ε_U, σ, τ and θ.

For example, as shown in the first row and the first column of the Table 1 displaying the result corresponding to $(\lambda_1, \lambda_2) = (0.6, 0.7)$, $\mu_U = 9$, $\theta = 8$, $\tau^2 = 1$, 112 patients should be enrolled in the stage 1. When the stage 1 trial is completed, if $\Pr(\mu > \mu_U \mid Y_1)$ is less than λ_1, the trial is terminated for futility. Otherwise, we

recruit additional 62 patients (which is $173-112$) in stage 2.

We investigate some properties of the Single Threshold Design. If the difference between center (mean) of the prior distribution θ and target average response rate μ_U increases, both the sample sizes of two stages (stage 1 and stage 2) increase. On the other hand, with regard to the same prior distribution, as μ_U increases, the target becomes harder to reach, thus the sample size N and n_1 increase. Also, from Table 1 and Table 9, if the sample variance σ increases, the both the sample sizes, n_1 and $N-n_1$, increase.

It also can be seen that larger values of λ_2 result in larger sample sizes N. Similarly, larger values of λ_1 result in larger sample sizes n_1. The values of λ_1 and λ_2 are desired success probabilities that the average response rates will exceed the target response value, μ_U, in the interim and the final stage, respectively. Hence, the larger the values of λ_1 and λ_2, the greater the amount evidence from data needed.

We now investigate the connection between the sample size and the value of ε_U. For the selected values of parameters other than ε_U, sample size N decrease as ε_U increase. It make intuitive sense since having data with larger advantage over ε_U means that the threshold probability can be attained with a smaller sample size. For example, the elements in the first row and first column of the Table 1 and Table 2 respectively, the sample size 69 in Table 2 with larger $\varepsilon_U = 1.0$ is smaller than the sample size 173 in Table 1 with smaller $\varepsilon_U = 0.5$.

4.2 Sample size of Dual Threshold Design

In this section, we give some examples to illustrate the Dual Threshold Design. The same vague normal distribution used in the Single Threshold Design is used in the Dual Threshold Design. Also, the suggestions for the prior distribution selection

are the same as those given in the Single Threshold Design. Tables 25－29 illustrate the Dual Threshold Design for several combinations of parameters with $\varepsilon_U = 0.5$, $\varepsilon_L = 0.5$, $\sigma = 6$, $\sigma = 8$, $\tau^2 = 4^2, \tau^2 = 5^2$, $\tau^2 = 6^2$, $\tau^2 = 7^2$, $\tau^2 = 15^2$. The value of θ is from 8 to 12 centered around μ_U. The rational selection of (λ_1, λ_2) are $(0.6, 0.7)$, $(0.6, 0.8)$ and $(0.7, 0.8)$ as listed in the tables. The tabulated results contain the suitable minimum sample size determined by using a program of numerical technique written in $C++$ corresponding to combinations of ε_U, ε_L, σ, τ and θ.

For example, the element in the first row and the first column of the Table 25 displays the result corresponding to $(\lambda_1, \lambda_2) = (0.6, 0.7)$, $\mu_U = 9$, $\theta = 8$, $\tau^2 = 4^2$. The entry is 49(38). That means at least 38 patients required for stage 1 trial. When the stage 1 trial is completed, if $\Pr(\mu < \mu_L \mid Y_1)$ is greater or equal to λ_1, the trial is terminated for futility. Otherwise, we recruit another 11 (which is $49 - 38$) patients in stage 2.

We investigate some properties of the Dual Threshold Design. If the mean of the prior distribution θ increases and the other parameters are fixed, the sample size, n_1, of stage 1 increases but the total sample size N decreases. On the other hand, with regard to the same prior distribution, as μ_U increases, the target becomes harder to reach. Thus, the sample size N increases but the stage 1 sample size n_1 stays the same.

It also can be seen that larger values of λ_2 result in larger sample sizes N. Similarly, larger values of λ_1 result in larger sample sizes n_1. Both Single Threshold Design and Dual Threshold Design have the same trend.

We investigate the connection between the total sample size N and the value

of ε_L. For the selected values of parameters other than ε_L, the total sample size N increases as ε_L increases. To avoid the too large sample size, the values ε_L and ε_U are restricted to 0.5 in the Dual Threshold Design.

5. Comparison with Tsou et al. [5]

5.1 Threshold probabilities

The optimal and minimax designs proposed by Tsou et al. [5] are two commonly used methods in phase Ⅱ two-stage trials with continuous endpoints. We are interest in evaluating the threshold probabilities λ_1 and λ_2 corresponding to these designs and making a comparison with the single threshold design and the dual threshold design.

We choose to work with sample size recommended by Tsou et al. [5] and its decision criteria corresponding to the type Ⅰ and Ⅱ error probabilities of (0.10,0.10), (0.05,0.20) and (0.05,0.10), respectively. We evaluate the value of the probability $\Pr(\mu > \mu_U \mid Y_1, Y_2)$ given the average response rates Y_1 and Y_2 to be overall critical level C_2 recommended by Tsou et al. [5], where if the observed overall sample mean is less than C_2, the trial would be terminated. $\Pr(\mu > \mu_U \mid Y_1, Y_2)$ will give us the desired threshold probability λ_2. The choice of the prior distribution of μ is $N(\mu_U, 2^2)$ for each combination of parameters in the single threshold design because the sample size of $N(\mu_U, 2^2)$ in STD is smaller and much similar to the sample size of Tsou et al. [5]. Also, the choice of the prior distribution of μ in the dual threshold design is $N(\mu_U, 6^2)$ for the same reason.

For the single threshold design, λ_1 is evaluated by $\Pr(\mu > \mu_U \mid Y_1)$ given the average response rate Y_1 to be the critical value of stage 1 C_1 recommended by Tsou et al. [5], where if the observed sample mean is less than C_2, the trial would be terminated. For the dual threshold design, λ_1 is evaluated by $\Pr(\mu < \mu_L \mid Y_1)$ also given the average response rate Y_1 to be the critical value of stage 1 C_1 recommended by Tsou et al. [5].

Table 30－33 give the values of λ_1 and λ_2 under the single threshold design

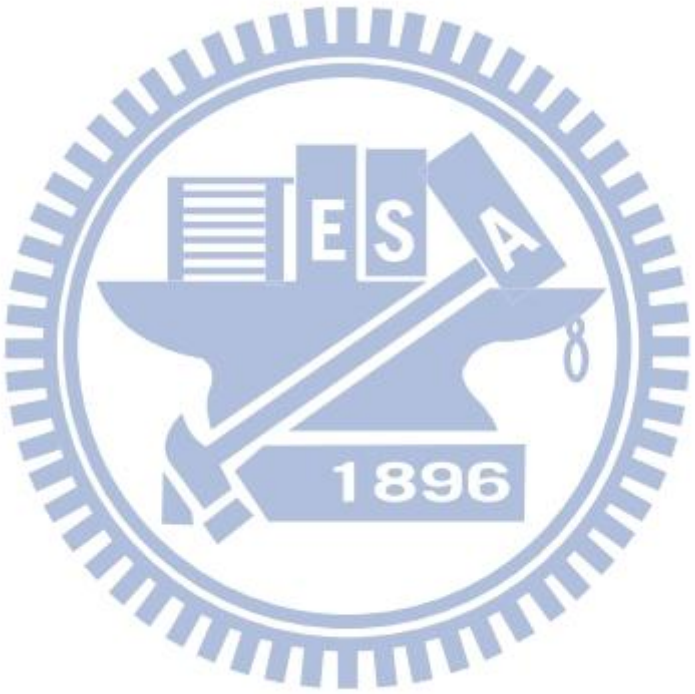
and the dual threshold design, respectively. The values of λ_2 are quite low because the overall critical level C_2 is lower than the target average response rate μ_U although it is higher than μ_L. Thus the drugs recommended to the phase Ⅲ trial have quite low posterior probabilities of μ exceeding the target average response rate μ_U. It also can be seen that the values of λ_1 is quite low for both STD and DTD. It may give us some sense that low λ_1 in the Tsou et al. [5] lower down the chance of early termination of the trial.

5.2 Probabilities of early termination and expected sample sizes

We further compare our designs with the designs of Tsou et al. [5] by evaluating the probability of early termination (PET) and the expected sample size (EN) of the single threshold and the dual threshold design. For the single threshold design, the PET is given by $\Pr\left[Pr\left(\mu > \mu_U \mid Y_1\right) < \lambda_1 \right]$. We take Y_1 as a random variable with the normal distribution $N(\mu, \frac{\sigma^2}{n_1})$. For the dual threshold design, the PET is given by $\Pr\left[Pr\left(\mu < \mu_L \mid Y_1\right) > \lambda_1 \right]$, where Y_1 also follows the normal distribution $N(\mu, \frac{\sigma^2}{n_1})$. As for the expected sample size, EN is given by $n_1 + \left(1 - PET\right) n_2$.

Table 34－35 and 36－37give the values of PET and EN corresponding to STD and DTD, respectively, with $\varepsilon_L = \varepsilon_U = 0.5$ and $(\lambda_1, \lambda_2) = (0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$. The values of PET in STD are in the range 0.20 to 0.35 and suggest not stopping at the end of the stage 1. The values of PET in STD are lower than what they are for the design of Tsou et al. [5]. For the design of Tsou et al. [5], the PET is in the range 0.45 to 0.75. For the DTD, the values of PET are in the range 0.75 to 0.85 and suggest that the design is likely to recommend terminate at the end of stage 1.

For EN, the range is from 40 to 378 for the STD and from 28 to 98 for the DTD. Both generally higher than what they are in Tsou et al. [5]. There is intuitive sense that the value of λ_1 and PET is related because the lower value of λ_1 keeps the lower sample size. So, the STD and the DTD keep the higher sample sizes than sample size of Tsou et al. [5].



6. Conclusion and Discussion

In this thesis, our objective is proposing new Bayesian designs for the phase Ⅱ clinical trial based on continuous efficacy endpoints. Although Bayesian methods are not in general use for its unfamiliarity and difficulty of implementation to investigators, we believe that Bayesian methods can bring much more information to analysis of the phase Ⅱ trial.

To free from complexity of implementation of Bayesian approach, we focus on developing designs which are relatively simple and easy compared to original Bayesian approaches. For example, we do not require specific utility or loss function before the trial. We maintain the adoption of Bayesian designs to process two Bayesian designs for phase II clinical trials. These designs were developed to be familiar to two-stage frequentist phase II clinical trials. The Bayesian approach allows the conjunction of relevant prior information and then the result in that manner is more conservative, informative and accurate.

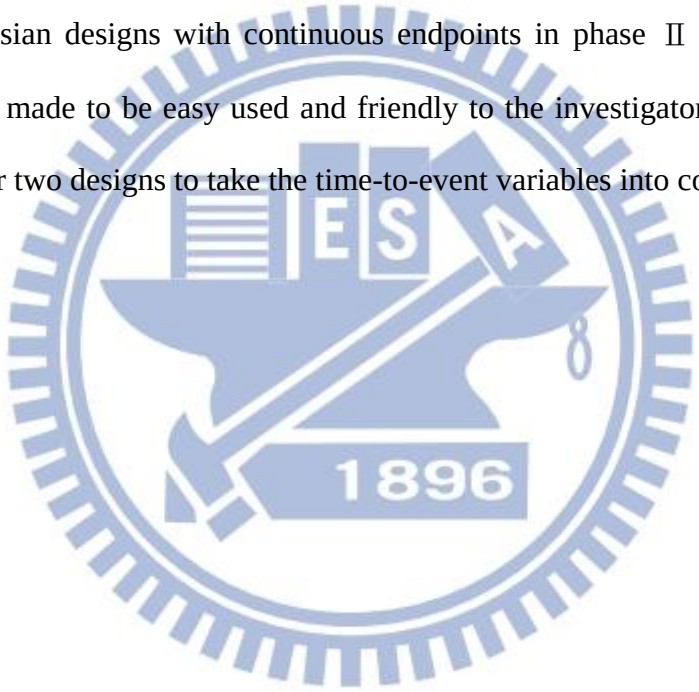
We found that the choice of the variance τ^2 of the prior distribution μ has strong impact on the sample size of the trial. If the variance τ^2 is too small, it would cause a large sample size (larger than general sample size of the phase Ⅱ trial). So, we would suggest investigators choose the variance parameter which is not too small.

The choices of the values of threshold probabilities λ_1 and λ_2 have strong impact on the sample size. As shown in Table 1—29, the higher threshold probabilities, the larger sample sizes. Although we can lower down the threshold probability to pursue smaller sample size for low cost of the trial, we might lower down the probability of detecting the true effect. There is a trade-off between pursuing a smaller sample size and the threshold probabilities not too low for sure the accuracy of the clinical trial.

In the Table 34－37, we found that the sample sizes of our designs are higher

than the sample size of Tsou et al. [5]. However, in the Table 30－33, we know our designs have high threshold probabilities. It shows that our designs is stricter and have higher probability of detecting the true effect. It is a intuitive sense that more information and more accuracy worth higher sample size to ensure the drug efficacy in the clinical trial.

Bayesian method is a good approach alternative to the frquentist approach for phase Ⅱ clinical trials. Bayesian methods incorporating relevant prior information into the analysis of the trial results may be more intuitive and helpful. In this thesis, two new Bayesian designs with continuous endpoints in phase Ⅱ trials have been developed and made to be easy used and friendly to the investigators. Our next step may extend our two designs to take the time-to-event variables into consideration.



Appendix

Lemma 1

Let $X_1^1,....,X_1^{n_1}$ be i.i.d. $N(\mu,\sigma^2)$ random variable. Define Y_1 the sample mean of $X_1^1,....,X_1^{n_1}$.

Then, Y_1 is distributed as $N(\mu,\frac{\sigma^2}{n_1})$.

Proof:

According to the property of the normal distribution, the addition of independent and identically distributed (i.i.d.) normal distributed random variable preserves the normal distribution. Hence, we derive the mean and variance of Y_1 and Y_2 to identify the exact distribution.

$$E(Y_1)=E\left(\frac{X_1^1+...+X_1^{n_1}}{n_1}\right)=\frac{1}{n_1}E\left(X_1^1+...+X_1^{n_1}\right)=\frac{1}{n_1}\left[E\left(X_1^1\right)+...+E\left(X_1^{n_1}\right)\right]$$

$$=\frac{1}{n_1}(\mu+...+\mu)=\frac{1}{n_1}\cdot n_1\cdot\mu=\mu$$

and

$$Var(Y_1)=Var\left(\frac{X_1^1+...+X_1^{n_1}}{n_1}\right)=\frac{1}{n_1^2}Var\left(X_1^1+...+X_1^{n_1}\right)=\frac{1}{n_1^2}\left[Var\left(X_1^1\right)+...+Var\left(X_1^{n_1}\right)\right]$$

$$=\frac{1}{n_1^2}\left(\sigma^2+...+\sigma^2\right)=\frac{1}{n_1^2}\cdot n_1\cdot\sigma^2=\frac{\sigma^2}{n_1}.$$

So, Y_1 is distributed as $N(\mu,\frac{\sigma^2}{n_1})$. □

Lemma 2

Since that $Y\mid\mu$ follows distribution as $N(\mu,\frac{\sigma^2}{n_1})$ and μ is distributed as $N(\theta,\tau^2)$.

The posterior distribution of μ given Y, $\mu|Y$ is $N\left((1-r)y+r\theta\ ,r\tau^2\right)$, where

$$r = \frac{\frac{\sigma^2}{n_1}}{\tau^2 + \frac{\sigma^2}{n_1}}.$$

Proof:

Let $g(Y|\mu)$ and $h(\mu)$ denote the p.d.f. of $N(\mu, \frac{\sigma^2}{n_1})$ and $N(\theta, \tau^2)$, respectively.

Then, the posterior p.d.f. of μ given Y is denoted as $k(\mu|Y)$ which has the following property,

$$k(\mu|Y) \propto g(Y|\mu) \cdot h(\mu)$$

$$\propto \frac{1}{\sqrt{2\pi} \cdot \frac{\sigma}{\sqrt{n_1}}} \cdot \frac{1}{\sqrt{2\pi} \cdot \tau} \exp\left[-\frac{(y-\mu)^2}{2 \cdot \frac{\sigma^2}{n_1}} - \frac{(\mu-\theta)^2}{2 \cdot \tau^2} \right].$$

If we eliminate all constant factors (including factors involving only y), we have

$$k(\mu|Y) \propto \exp\left[-\frac{\left(\tau^2 + \frac{\sigma^2}{n_1}\right)\mu^2 - 2\left(y \cdot \tau^2 + \theta \cdot \frac{\sigma^2}{n_1}\right)\mu}{2\left(\frac{\sigma^2}{n_1}\right)\tau^2} \right].$$

This can be simplified by completing the square to read

$$k(\mu|Y) \propto \exp\left[-\frac{\left(\mu - \left[(1-r)y + r\theta\right]\right)^2}{2r\tau^2} \right], \text{ where } r = \frac{\frac{\sigma^2}{n_1}}{\tau^2 + \frac{\sigma^2}{n_1}}.$$

That is, the posterior p.d.f. of the parameter is obviously normal distribution with

mean $\frac{y \cdot \tau^2 + \theta \cdot \frac{\sigma^2}{n_1}}{\tau^2 + \frac{\sigma^2}{n_1}} = \left(\frac{\tau^2}{\tau^2 + \frac{\sigma^2}{n_1}} \right) y + \left(\frac{\frac{\sigma^2}{n_1}}{\tau^2 + \frac{\sigma^2}{n_1}} \right) \theta$ and variance $\frac{\left(\frac{\sigma^2}{n_1}\right)\tau^2}{\left(\tau^2 + \frac{\sigma^2}{n_1}\right)}$ [10]. □

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Tables

Table 1. Minimum required sample size for single threshold design ($\varepsilon_U = 0.5, \sigma = 6$).

μ prior / μ_U	N(n_1)				
	N(8,1)	N(9,1)	N(10,1)	N(11,1)	N(12,1)
9	173 (112)	64 (24)	*	*	*
	302 (112)	142 (24)	*	*	*
	302 (173)	142 (64)	*	*	*
10	289 (204)	173 (112)	64 (24)	*	*
	489 (204)	302 (112)	142 (24)	*	*
	489 (289)	302 (173)	142 (64)	*	*
11	410 (302)	289 (204)	173 (112)	64 (24)	*
	729 (428)	489 (204)	302 (112)	142 (24)	*
	729 (410)	489 (289)	302 (173)	142 (64)	*

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 2. Minimum required sample size for single threshold design ($\varepsilon_U = 1.0, \sigma = 6$).

μ prior / μ_U	N(n_1)				
	N(8,1)	N(9,1)	N(10,1)	N(11,1)	N(12,1)
9	69 (51)	25 (11)	*	*	*
	95 (51)	46 (11)	*	*	*
	95 (69)	46 (25)	*	*	*
10	112 (90)	69 (51)	25 (11)	*	*
	144 (90)	95 (51)	46 (11)	*	*
	144 (112)	95 (69)	46 (25)	*	*
11	156 (130)	112 (90)	69 (51)	25 (11)	*
	193 (130)	144 (90)	95 (51)	46 (11)	*
	193 (156)	144 (112)	95 (69)	46 (25)	*

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 3. Minimum required sample size for single threshold design ($\varepsilon_U = 0.5, \sigma = 6$).

μ prior / μ_U	N(n_1)				
	N(8,2)	N(9,2)	N(10,2)	N(11,2)	N(12,2)
9	109 (64)	54(19)	*	*	*
	198(64)	123(19)	*	*	*
	198(109)	123(54)	*	*	*
10	163(108)	109(64)	54(19)	*	*
	278(108)	198(64)	123(19)	*	*
	278(163)	198(109)	123(19)	*	*
11	219(152)	163(108)	109(64)	54(19)	*
	364(152)	278(108)	198(64)	123(19)	*
	364(219)	278(163)	198(109)	123(54)	*

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 4. Minimum required sample size for single threshold design ($\varepsilon_U = 1.0, \sigma = 6$).

μ prior / μ_U	N(n_1)				
	N(8,2)	N(9,2)	N(10,2)	N(11,2)	N(12,2)
9	43(29)	20(8)	*	*	*
	64(29)	38(8)	*	*	*
	64(43)	38(20)	*	*	*
10	65(49)	43(29)	20(8)	*	*
	89(49)	64(29)	38(8)	*	*
	89(65)	64(43)	38(20)	*	*
11	87(69)	65(49)	43(29)	20(8)	*
	113(69)	89(49)	64(29)	38(8)	*
	113(87)	89(65)	64(43)	38(20)	*

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 5. Minimum required sample size for single threshold design ($\varepsilon_U = 0.5, \sigma = 6$).

μ prior / μ_U	N(n_1)				
	N(8,4)	N(9,4)	N(10,4)	N(11,4)	N(12,4)
9	77 (40)	48 (15)	*	*	*
	151 (40)	114 (15)	*	*	*
	151 (77)	114 (48)	75 (8)	*	*
10	104 (62)	77 (40)	48 (15)	*	*
	188 (62)	151 (40)	114 (15)	*	*
	188 (104)	151 (77)	114 (48)	75 (8)	*
11	131 (84)	104 (62)	77 (40)	48 (15)	*
	227 (84)	188 (62)	151 (40)	114 (15)	*
	227 (131)	188 (104)	151 (77)	114 (48)	75 (8)

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 6. Minimum required sample size for single threshold design ($\varepsilon_U = 1.0, \sigma = 6$).

μ prior / μ_U	N(n_1)				
	N(8,4)	N(9,4)	N(10,4)	N(11,4)	N(12,4)
9	29 (17)	16 (6)	*	*	*
	47 (17)	33 (6)	*	*	*
	47 (29)	33 (16)	*	*	*
10	41 (28)	29 (17)	16 (6)	*	*
	60 (28)	47 (17)	33 (6)	*	*
	60 (41)	47 (29)	33 (16)	*	*
11	52 (38)	41 (28)	29 (17)	16 (6)	*
	73 (38)	60 (28)	47 (17)	33 (6)	*
	73 (52)	60 (41)	47 (29)	33 (16)	*

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 7. Minimum required sample size for single threshold design ($\varepsilon_U = 0.5, \sigma = 6$).

μ prior / μ_U	N(n_1)				
	N(8,9)	N(9,9)	N(10,9)	N(11,9)	N(12,9)
9	58(25)	44(13)	*	*	*
	125(25)	108(13)	*	*	*
	125(58)	108(44)	91(28)	*	*
10	71(35)	58(25)	44(13)	*	*
	141(35)	125(25)	108(13)	*	*
	141(71)	125(58)	108(44)	91(28)	*
11	83(46)	71(35)	58(25)	44(13)	*
	158(46)	141(35)	125(25)	108(13)	*
	158(83)	141(71)	125(58)	108(44)	91(28)

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 8. Minimum required sample size for single threshold design ($\varepsilon_U = 1.0, \sigma = 6$).

μ prior / μ_U	N(n_1)				
	N(8,9)	N(9,9)	N(10,9)	N(11,9)	N(12,9)
9	20(10)	*	*	*	*
	36(10)	*	*	*	*
	36(20)	30(13)	22(6)	*	*
10	25(15)	20(10)	*	*	*
	43(15)	36(10)	*	*	*
	43(25)	36(20)	30(13)	22(6)	*
11	31(20)	25(15)	20(10)	*	*
	49(20)	43(15)	36(10)	*	*
	49(31)	43(25)	36(20)	30(13)	22(6)

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 9. Minimum required sample size for single threshold design ($\varepsilon_U = 0.5, \sigma = 8$).

μ prior / μ_U	N(n_1)				
	N(8,1)	N(9,1)	N(10,1)	N(11,1)	N(12,1)
9	307 (199)	113 (42)	*	*	*
	537 (199)	253 (42)	*	*	*
	537 (307)	253 (113)	*	*	*
10	513 (363)	307 (199)	113 (42)	*	*
	869 (363)	537 (199)	253 (42)	*	*
	869 (513)	537 (307)	253 (113)	*	*
11	728 (537)	513 (363)	307 (199)	113 (42)	*
	1296 (537)	869 (363)	537 (199)	253 (42)	*
	1296 (728)	869 (513)	537 (307)	253 (113)	*

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 10. Minimum required sample size for single threshold design ($\varepsilon_U = 1.0$, $\sigma = 8$).

μ prior / μ_U	N(n_1)				
	N(8,1)	N(9,1)	N(10,1)	N(11,1)	N(12,1)
9	122 (90)	44 (19)	*	*	*
	169 (90)	82 (19)	*	*	*
	169 (122)	82 (44)	*	*	*
10	199 (160)	122 (90)	44 (19)	*	*
	255 (160)	169 (90)	82 (19)	*	*
	255 (199)	169 (122)	82 (44)	*	*
11	276 (231)	199 (160)	122 (90)	44 (19)	*
	342 (213)	255 (160)	169 (90)	82 (19)	*
	342 (276)	255 (199)	169 (122)	82 (44)	*

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 11. Minimum required sample size for single threshold design ($\varepsilon_U = 0.5$, $\sigma = 8$).

μ prior / μ_U	N(n_1)				
	N(8,2)	N(9,2)	N(10,2)	N(11,2)	N(12,2)
9	193(114)	95(33)	*	*	*
	352(114)	219(33)	*	*	*
	352(193)	219(95)	*	*	*
10	289(191)	193(114)	95(33)	*	*
	494(191)	352(114)	219(33)	*	*
	494(289)	352(193)	219(95)	*	*
11	389(271)	289(191)	193(114)	95(33)	*
	647(271)	494(191)	352(114)	219(33)	*
	647(389)	494(289)	352(193)	219(95)	*

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 12. Minimum required sample size for single threshold design ($\varepsilon_U = 1.0$, $\sigma = 8$).

μ prior / μ_U	N(n_1)				
	N(8,2)	N(9,2)	N(10,2)	N(11,2)	N(12,2)
9	76(51)	35(14)	*	*	*
	114(51)	67(14)	*	*	*
	114(76)	67(35)	*	*	*
10	115(87)	76(51)	35(14)	*	*
	158(87)	114(51)	67(14)	*	*
	158(116)	114(76)	67(35)	*	*
11	154(122)	115(87)	76(51)	35(14)	*
	201(122)	158(87)	114(51)	67(14)	*
	201(154)	158(116)	114(76)	67(35)	*

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 13. Minimum required sample size for single threshold design ($\varepsilon_U = 0.5$, $\sigma = 8$).

μ prior μ_U	N(n_1)				
	N(8,4)	N(9,4)	N(10,4)	N(11,4)	N(12,4)
9	136 (70)	84 (27)	*	*	*
	268 (70)	202 (27)	*	*	*
	268 (136)	202 (84)	133 (14)	*	*
10	185 (110)	136 (70)	84 (27)	*	*
	334 (110)	268 (70)	202 (27)	*	*
	334 (185)	268 (136)	202 (84)	133 (14)	*
11	233 (149)	185 (110)	136 (70)	84 (27)	*
	402 (149)	334 (110)	268 (70)	202 (27)	*
	402 (233)	334 (185)	268 (136)	202 (84)	133 (14)

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 14. Minimum required sample size for single threshold design ($\varepsilon_U = 1.0$, $\sigma = 8$).

μ prior μ_U	N(n_1)				
	N(8,4)	N(9,4)	N(10,4)	N(11,4)	N(12,4)
9	51 (30)	28 (11)	*	*	*
	84 (30)	58 (11)	*	*	*
	84 (51)	58 (28)	*	*	*
10	72 (49)	51 (30)	28 (11)	*	*
	107 (49)	84 (30)	58 (11)	*	*
	107 (72)	84 (51)	58 (28)	*	*
11	92 (67)	72 (49)	51 (30)	28 (11)	*
	130 (67)	107 (49)	84 (30)	58 (11)	*
	130 (92)	107 (72)	84 (51)	58 (28)	*

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 15. Minimum required sample size for single threshold design ($\varepsilon_U = 0.5$, $\sigma = 8$).

μ prior / μ_U	N(n_1)				
	N(8,9)	N(9,9)	N(10,9)	N(11,9)	N(12,9)
9	102(43)	77(22)	*	*	*
	222(43)	192(22)	*	*	*
	222(102)	192(77)	161(49)	*	*
10	126(63)	102(43)	77(22)	*	*
	251(63)	222(43)	192(22)	*	*
	251(126)	222(102)	192(77)	161(49)	*
11	148(81)	126(63)	102(43)	77(22)	*
	280(81)	251(63)	222(43)	192(22)	*
	280(148)	251(126)	222(102)	192(77)	161(49)

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 16. Minimum required sample size for single threshold design ($\varepsilon_U = 1.0$, $\sigma = 8$).

μ prior / μ_U	N(n_1)				
	N(8,9)	N(9,9)	N(10,9)	N(11,9)	N(12,9)
9	35(18)	24(8)	*	*	*
	64(18)	52(8)	*	*	*
	64(35)	52(24)	39(10)	*	*
10	45(26)	35(18)	24(8)	*	*
	76(26)	64(18)	52(8)	*	*
	76(45)	64(35)	52(24)	39(10)	*
11	55(35)	45(26)	35(18)	24(8)	*
	87(35)	76(26)	64(18)	52(8)	*
	87(55)	76(45)	64(35)	52(24)	39(10)

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 17. Minimum required sample size for single threshold design ($\varepsilon_U = 0.5$, $\sigma = 13$).

μ prior / μ_U	N(n_1)				
	N(8,1)	N(9,1)	N(10,1)	N(11,1)	N(12,1)
9	810(524)	297(111)	*	*	*
	1417(524)	666(111)	*	*	*
	1417(810)	666(297)	*	*	*
10	1354(958)	810(524)	297(111)	*	*
	2294(958)	1417(524)	666(111)	*	*
	2294(1354)	1417(810)	666(297)	*	*
11	1923(1417)	1354(958)	810(524)	297(111)	*
	3421(1416)	2294(958)	1417(524)	666(111)	*
	3421(1923)	2294(1354)	1417(810)	666(297)	*

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 18. Minimum required sample size for single threshold design ($\varepsilon_U = 1.0$, $\sigma = 13$).

μ prior / μ_U	N(n_1)				
	N(8,1)	N(9,1)	N(10,1)	N(11,1)	N(12,1)
9	322(236)	115(49)	*	*	*
	446(236)	215(49)	*	*	*
	466(322)	215(115)	*	*	*
10	525(422)	322(236)	115(49)	*	*
	673(422)	446(236)	215(49)	*	*
	673(525)	466(322)	215(115)	*	*
11	729(609)	525(422)	322(236)	115(49)	*
	903(609)	673(422)	446(236)	215(49)	*
	903(729)	673(525)	466(322)	215(115)	*

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 19. Minimum required sample size for single threshold design ($\varepsilon_U = 0.5$, $\sigma = 13$).

μ prior / μ_U	N(n_1)				
	N(8,2)	N(9,2)	N(10,2)	N(11,2)	N(12,2)
9	508(299)	250(87)	*	*	*
	928(299)	577(87)	*	*	*
	928(508)	577(250)	*	*	*
10	764(504)	508(299)	250(87)	*	*
	1303(504)	928(299)	577(87)	*	*
	1303(764)	928(508)	577(250)	*	*
11	1027(714)	764(504)	508(299)	250(87)	*
	1707(714)	1303(504)	928(299)	577(87)	*
	1707(1027)	1303(764)	928(508)	577(250)	*

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 20. Minimum required sample size for single threshold design ($\varepsilon_U = 1.0$, $\sigma = 13$).

μ prior / μ_U	N(n_1)				
	N(8,2)	N(9,2)	N(10,2)	N(11,2)	N(12,2)
9	200(134)	91(37)	*	*	*
	300(134)	177(37)	*	*	*
	300(200)	177(91)	*	*	*
10	304(228)	200(134)	91(37)	*	*
	416(228)	300(134)	177(37)	*	*
	416(304)	300(200)	177(91)	*	*
11	406(321)	304(228)	200(134)	91(37)	*
	530(321)	416(228)	300(134)	177(37)	*
	530(406)	416(304)	300(200)	177(91)	*

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 21. Minimum required sample size for single threshold design ($\varepsilon_U = 0.5$, $\sigma = 13$).

μ prior μ_U	N(n_1)				
	N(8,4)	N(9,4)	N(10,4)	N(11,4)	N(12,4)
9	359(184)	222(70)	*	*	*
	706(184)	532(70)	*	*	*
	706(359)	532(222)	350(37)	*	*
10	487(290)	359(184)	222(70)	*	*
	881(290)	706(184)	532(70)	*	*
	881(487)	706(359)	532(222)	350(37)	*
11	614(393)	487(290)	359(184)	222(70)	*
	1062(393)	881(290)	706(184)	532(70)	*
	1062(614)	881(487)	706(359)	532(222)	350(37)

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 22. Minimum required sample size for single threshold design ($\varepsilon_U = 1.0$, $\sigma = 13$).

μ prior μ_U	N(n_1)				
	N(8,4)	N(9,4)	N(10,4)	N(11,4)	N(12,4)
9	133(79)	74(28)	*	*	*
	220(79)	153(28)	*	*	*
	220(133)	153(74)	*	*	*
10	188(128)	133(79)	74(28)	*	*
	282(128)	220(79)	153(28)	*	*
	282(188)	220(133)	153(74)	*	*
11	242(176)	188(128)	133(79)	74(28)	*
	342(176)	282(128)	220(79)	153(28)	*
	342(242)	282(188)	220(133)	153(74)	*

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 23. Minimum required sample size for single threshold design ($\varepsilon_U = 0.5$, $\sigma = 13$).

μ prior μ_U	N(n_1)				
	N(8,9)	N(9,9)	N(10,9)	N(11,9)	N(12,9)
9	269(114)	204(58)	*	*	*
	585(114)	507(58)	*	*	*
	585(269)	507(204)	426(128)	*	*
10	331(165)	269(114)	204(58)	*	*
	662(165)	585(114)	507(58)	*	*
	662(331)	585(269)	507(204)	426(128)	*
11	389(213)	331(165)	269(114)	204(58)	*
	739(213)	662(165)	585(114)	507(58)	*
	739(389)	662(331)	585(269)	507(204)	426(128)

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 24. Minimum required sample size for single threshold design ($\varepsilon_U = 1.0$, $\sigma = 13$).

μ prior μ_U	N(n_1)				
	N(8,9)	N(9,9)	N(10,9)	N(11,9)	N(12,9)
9	90(46)	61(21)	*	*	*
	169(46)	137(21)	*	*	*
	169(90)	137(61)	101(28)	*	*
10	117(69)	90(46)	61(21)	*	*
	200(69)	169(46)	137(21)	*	*
	200(117)	169(90)	137(61)	101(28)	*
11	144(91)	117(69)	90(46)	61(21)	*
	229(91)	200(69)	169(46)	137(21)	*
	229(144)	200(117)	169(90)	137(61)	101(28)

* : no solution

For each value of μ_U, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 25. Minimum required sample size for dual threshold design ($\varepsilon_L = 0.5$, $\varepsilon_U = 0.5$, $\sigma = 6$).

μ_L	μ prior μ_U	N(n_1)				
		$N(8,4^2)$	$N(9,4^2)$	$N(10,4^2)$	$N(11,4^2)$	$N(12,4^2)$
4	9	49(38)	*	*	*	*
		116(38)	106(42)	97(49)	86(55)	76(59)
		116(73)	106(80)	97(87)	*	*
4	10	58(38)	50(42)	*	*	*
		125(38)	116(42)	106(49)	97(55)	87(59)
		125(73)	116(80)	106(87)	*	*
4	11	66(38)	58(42)	*	*	*
		134(38)	125(42)	116(49)	106(55)	97(59)
		134(73)	125(80)	116(87)	106(93)	*

* : no solution

For each value of μ_U and μ_L, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 26. Minimum required sample size for dual threshold design ($\varepsilon_L = 0.5$, $\varepsilon_U = 0.5$, $\sigma = 6$).

μ_L	μ prior μ_U	N(n_1)				
		$N(8,5^2)$	$N(9,5^2)$	$N(10,5^2)$	$N(11,5^2)$	$N(12,5^2)$
4	9	47(29)	41(32)	*	*	*
		112(29)	106(32)	99(36)	93(40)	87(44)
		112(62)	106(67)	99(71)	93(71)	87(80)
4	10	52(29)	47(32)	41(36)	*(40)	*
		118(29)	112(32)	106(36)	99(40)	93(44)
		118(62)	112(67)	106(71)	99(71)	93(80)
4	11	57(29)	52(32)	47(36)	*	*
		24(29)	118(32)	112(36)	106(40)	99(44)
		124(62)	118(67)	112(71)	106(71)	99(80)

* : no solution

For each value of μ_U and μ_L, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 27. Minimum required sample size for dual threshold design ($\varepsilon_L = 0.5$, $\varepsilon_U = 0.5$, $\sigma = 6$).

μ_L	μ prior μ_U	N(n_1)				
		$N(8,6^2)$	$N(9,6^2)$	$N(10,6^2)$	$N(11,6^2)$	$N(12,6^2)$
4	9	45(24)	41(26)	37(29)	*	*
		109(24)	105(26)	101(29)	96(32)	92(34)
		109(56)	105(69)	101(62)	96(66)	92(69)
4	10	49(24)	45(26)	41(29)	37(32)	*
		113(24)	109(26)	105(29)	101(32)	96(34)
		113(56)	109(59)	105(62)	101(66)	96(69)
4	11	52(24)	49(26)	45(29)	41(32)	*
		118(24)	113(26)	109(29)	105(32)	101(34)
		118(24)	113(59)	109(62)	105(66)	101(69)

* : no solution

For each value of μ_U and μ_L, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 28. Minimum required sample size for dual threshold design ($\varepsilon_L = 0.5$, $\varepsilon_U = 0.5$, $\sigma = 6$).

μ_L	μ prior μ_U	N(n_1) with $\sigma = 6$				
		$N(8,7^2)$	$N(9,7^2)$	$N(10,7^2)$	$N(11,7^2)$	$N(12,7^2)$
4	9	44(21)	41(23)	38(25)	35(27)	*(
		108(21)	105(23)	102(25)	98(27)	95(29)
		108(52)	105(54)	102(57)	98(59)	95(62)
4	10	46(21)	44(23)	41(25)	38(27)	35(29)
		111(21)	108(23)	105(25)	102(27)	98(29)
		111(52)	108(54)	105(57)	102(59)	98(62)
4	11	49(21)	46(23)	44(25)	41(27)	38(29)
		114(21)	111(23)	108(25)	105(27)	102(29)
		114(52)	111(54)	108(57)	105(59)	102(62)

* : no solution

For each value of μ_U and μ_L, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 29. Minimum required sample size for dual threshold design ($\varepsilon_L = 0.5$, $\varepsilon_U = 0.5$, $\sigma = 8$).

μ_L	μ prior μ_U	N(n_1)				
		$N(8,15^2)$	$N(9,15^2)$	$N(10,15^2)$	$N(11,15^2)$	$N(12,15^2)$
4	9	72(26)	71(27)	70(27)	69(28)	68(29)
		186(26)	185(27)	183(27)	182(28)	181(29)
		186(76)	185(77)	183(78)	182(28)	181(80)
4	10	73(26)	72(27)	71(27)	70(28)	69(29)
		187(26)	186(27)	185(27)	183(28)	182(29)
		187(76)	186(77)	185(78)	183(79)	182(80)
4	11	75(26)	73(27)	72(27)	71(28)	70(29)
		188(26)	187(27)	186(27)	185(28)	183(29)
		188(76)	187(77)	186(78)	185(79)	183(80)

* : no solution

For each value of μ_U and μ_L, the first, the second and third rows correspond to (λ_1, λ_2) of $(0.6, 0.7), (0.6, 0.8)$ and $(0.7, 0.8)$, respectively.

Table 30. Single Threshold Design threshold probabilities with $\sigma = 6$ the prior distribution $N(\mu_U, 2^2)$.

μ_L	μ_U	Optimal design				Minimax design			
		n	λ_1	N	λ_2	n	λ_1	N	λ_2
4	9	5	0.328	11	0.206	5	0.328	10	0.222
		4	0.356	11	0.206	4	0.356	10	0.222
		6	0.303	14	0.165	6	0.303	13	0.178
4	10	3	0.333	8	0.166	3	0.333	7	0.191
		3	0.386	7	0.280	4	0.356	7	0.280
		4	0.290	10	0.126	5	0.328	9	0.240
4	11	2	0.344	6	0.151	2	0.344	6	0.150
		2	0.382	6	0.219	1	0.437	5	0.252
		3	0.333	7	0.191	3	0.333	7	0.191

For each value of (μ_L , μ_U), the first, second and third rows correspond to type Ⅰ and Ⅱ error probabilities of (0.10,0.10), (0.05,0.20) and (0.05,0.10), respectively.

Table 31. Single Threshold Design threshold probabilities with $\sigma = 8$ the prior distribution $N(\mu_U, 2^2)$.

μ_L	μ_U	Optimal design				Minimax design			
		n	λ_1	N	λ_2	n	λ_1	N	λ_2
4	9	8	0.342	19	0.211	9	0.326	18	0.220
		6	0.275	19	0.211	7	0.258	17	0.230
		10	0.312	26	0.258	11	0.298	23	0.178
4	10	6	0.316	13	0.183	6	0.375	12	0.285
		5	0.293	13	0.273	5	0.393	12	0.285
		7	0.292	18	0.124	7	0.358	16	0.240
4	11	4	0.369	10	0.231	5	0.342	9	0.250
		3	0.398	10	0.231	3	0.298	9	0.250
		5	0.342	13	0.182	5	0.341	12	0.198

For each value of (μ_L, μ_U), the first, second and third rows correspond to type Ⅰ and Ⅱ error probabilities of (0.10,0.10), (0.05,0.20) and (0.05,0.10), respectively.

Table 32. Dual Threshold Design threshold probabilities with $\sigma = 6$ the prior distribution $N(\mu_U, 6^2)$

μ_L	μ_U	Optimal design				Minimax design			
		n	λ_1	N	λ_2	n	λ_1	N	λ_2
4	9	5	0.150	11	0.145	5	0.238	10	0.157
		4	0.160	11	0.145	4	0.159	10	0.157
		6	0.140	14	0.115	6	0.237	13	0.123
4	10	3	0.208	8	0.091	3	0.252	7	0.108
		3	0.149	7	0.205	4	0.088	7	0.205
		4	0.143	10	0.066	5	0.135	9	0.171
4	11	2	0.172	6	0.029	2	0.187	6	0.049
		2	0.097	6	0.128	1	0.190	5	0.154
		3	0.132	7	0.108	3	0.132	7	0.108

For each value of (μ_L, μ_U), the first, second and third rows correspond to type Ⅰ and Ⅱ error probabilities of (0.10,0.10), (0.05,0.20) and (0.05,0.10), respectively.

Table 33. Dual Threshold Design threshold probabilities with $\sigma = 8$ the prior distribution $N(\mu_U, 6^2)$

μ_L	μ_U	Optimal design				Minimax design			
		n	λ_1	N	λ_2	n	λ_1	N	λ_2
4	9	8	0.237	19	0.149	9	0.238	18	0.156
		6	0.164	19	0.149	7	0.236	17	0.163
		10	0.144	26	0.109	11	0.237	23	0.124
4	10	6	0.211	13	0.102	6	0.286	12	0.209
		5	0.150	13	0.199	5	0.150	12	0.209
		7	0.215	18	0.065	7	0.248	16	0.171
4	11	4	0.132	10	0.137	5	0.185	9	0.152
		3	0.130	10	0.137	3	0.157	9	0.169
		5	0.132	13	0.102	5	0.185	12	0.113

For each value of (μ_L , μ_U), the first, second and third rows correspond to type Ⅰ and Ⅱ error probabilities of (0.10,0.10), (0.05,0.20) and (0.05,0.10), respectively.

Table 34. PET and EN for Single Threshold Design ($\sigma = 6$, $\varepsilon_U = 0.5$).

μ prior	$N(8, 2^2)$		$N(9, 2^2)$		$N(10, 2^2)$		$N(11, 2^2)$		$N(12, 2^2)$	
	PET	EN	PET	EN	PET	EN	PET	EN	PET	EN
9	0.315	65.3	0.346	36.6	*	*	*	*	*	*
	0.315	116.0	0.346	79.7	*	*	*	*	*	*
	0.274	130.7	0.225	99.1	0.518	40.2	*	*	*	*
10	0.256	93.3	0.203	69.4	0.345	36.6	*	*	*	*
	0.256	155.7	0.203	128.4	0.345	79.8	*	*	*	*
	0.240	38.6	0.179	137.7	0.255	99.1	0.519	40.2	*	*
11	0.133	124.7	0.162	97.2	0.203	69.5	0.345	36.6	*	*
	0.133	207.9	0.162	167.6	0.203	128.4	0.345	79.8	*	*
	0.135	214.0	0.155	174.9	0.179	137.7	0.225	99.2	0.519	40.2

* : no solution

For each value of μ_U , the first, second and third rows correspond to $(\lambda_1, \lambda_2) = (0.6, 0.7), (0.6, 0.8) and (0.7, 0.8)$, respectively.

Table 35. PET and EN for Single Threshold Design ($\sigma = 8$, $\varepsilon_U = 0.5$).

μ / prior	$N(8, 2^2)$		$N(9, 2^2)$		$N(10, 2^2)$		$N(11, 2^2)$		$N(12, 2^2)$	
	PET	EN	PET	EN	PET	EN	PET	EN	PET	EN
9	0.206	122.4	0.343	64.4	*	*	*	*	*	*
	0.206	227.2	0.343	141.9	*	*	*	*	*	*
	0.180	244.2	0.227	175.2	0.522	70.8	*	*	*	*
10	0.162	172.8	0.205	122.4	0.343	64.4	*	*	*	*
	0.162	306.0	0.205	227.3	0.343	141.9	*	*	*	*
	0.155	319.3	0.180	244.2	0.227	175.2	0.522	70.8	*	*
11	0.138	221.4	0.162	172.8	0.205	122.4	0.343	64.4	*	*
	0.138	366.9	0.162	297.6	0.205	227.2	0.343	141.9	*	*
	0.138	378.5	0.155	310.8	0.180	244.2	0.227	175.2	0.522	70.8

* : no solution

For each value of μ_U, the first, second and third rows correspond to $(\lambda_1, \lambda_2) = (0.6, 0.7), (0.6, 0.8) and (0.7, 0.8)$, respectively.

Table 36. PET and EN for Dual Threshold Design ($\sigma = 6$, $\varepsilon_L = \varepsilon_U = 0.5$).

μ prior / μ_L		$N(8, 6^2)$		$N(9, 6^2)$		$N(10, 6^2)$		$N(11, 6^2)$		$N(12, 6^2)$	
		PET	EN	PET	EN	PET	EN	PET	EN	PET	EN
4	9	0.807	28.1	0.814	28.7	0.825	30.4	0.834	*	0.839	*
		0.807	40.7	0.814	40.6	0.825	40.5	0.834	42.6	0.839	43.3
		0.842	64.3	0.846	66.0	0.850	67.8	0.855	70.3	0.858	72.2
4	10	0.807	28.8	0.814	29.5	0.825	31.8	0.834	32.8	0.839	*
		0.807	41.2	0.814	41.4	0.825	42.3	0.834	43.4	0.839	43.9
		0.842	64.9	0.846	66.6	0.850	68.5	0.855	71.1	0.858	72.8
4	11	0.807	28.5	0.814	30.3	0.825	31.8	0.834	33.5	0.839	*
		0.807	39.3	0.814	42.2	0.825	43.0	0.834	44.1	0.839	44.8
		0.842	65.8	0.846	67.3	0.850	69.1	0.855	71.6	0.858	73.5

* : no solution

For each value of μ_U, the first, second and third rows correspond to $(\lambda_1, \lambda_2) = (0.6, 0.7), (0.6, 0.8) and (0.7, 0.8)$, respectively.

Table 37. PET and EN for Dual Threshold Design ($\sigma = 8$, $\varepsilon_L = \varepsilon_U = 0.5$).

μ prior / μ_L	μ_U	$N(8,15^2)$		$N(9,15^2)$		$N(10,15^2)$		$N(11,15^2)$		$N(12,15^2)$	
		PET	EN	PET	EN	PET	EN	PET	EN	PET	EN
4	9	0.745	37.7	0.751	37.9	0.750	37.7	0.756	37.9	0.761	38.3
		0.745	66.7	0.751	66.3	0.750	65.8	0.756	66.5	0.761	65.3
		0.819	95.9	0.820	96.4	0.821	96.7	0.822	97.2	0.824	97.7
4	10	0.745	37.9	0.751	38.2	0.750	38.0	0.756	38.2	0.761	38.5
		0.745	67.0	0.751	66.6	0.750	66.5	0.756	65.8	0.761	65.5
		0.819	96.1	0.820	96.6	0.821	97.1	0.822	97.5	0.824	97.9
4	11	0.745	38.5	0.751	38.5	0.750	38.2	0.756	38.5	0.761	38.8
		0.745	67.3	0.751	66.8	0.750	66.8	0.756	66.3	0.761	65.3
		0.819	96.3	0.820	96.8	0.821	97.3	0.822	97.8	0.824	98.1

* : no solution

For each value of μ_U, the first, second and third rows correspond to $(\lambda_1, \lambda_2) = (0.6, 0.7), (0.6, 0.8) and (0.7, 0.8)$, respectively.