國立交通大學

統計學研究所

碩士論文

二元滿足點之 Phase II/III 調適性無縫臨床試驗設計

An Adaptive Seamless Phase II/III Design for Binary Endpoints in Clinical Trials

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指導教授：蕭金福　教授

中 華 民 國 一〇一 年 六 月

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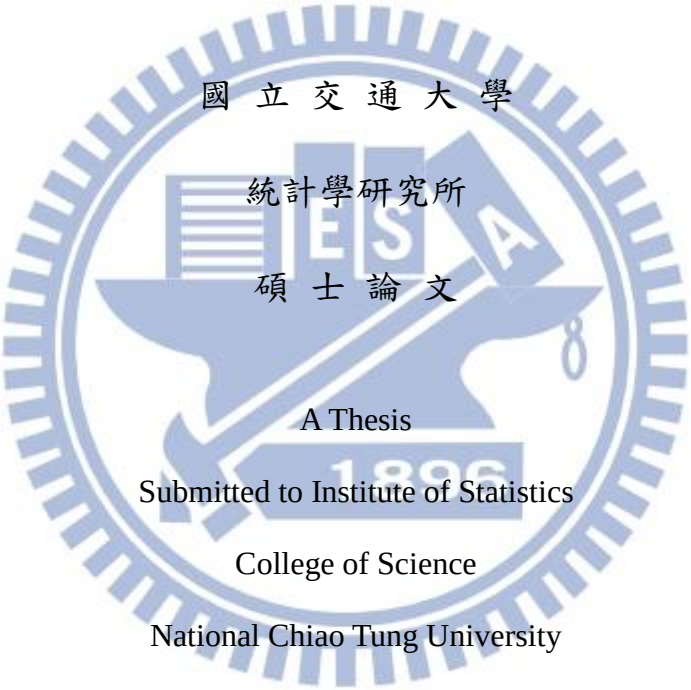

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國立交通大學統計學研究所碩士班

中文摘要

對於製藥發展來說，如何設計一個臨床試驗、分析其數據，以及評估藥物的效益已成為一門重要課題。成功開發新藥物的價格急劇上升，而且在發展過程中有超過一半的時間和費用被使用於臨床試驗中。因此，在新藥開發中減少開支和時間，並且證明新藥的效益是一項挑戰。我們了解儘管在生物醫學研究方面的開支增加，並不能反映藥物開發的成功率增加。目前存在大量的候選藥物以及蓬勃的臨床研究發展，新藥物的研究和開發的成功率仍然令人失望。所以需要發展一種快速、經濟且適當的方法以減少藥物發展的時間與花費。為了減少時間跟成本，對於二元滿足點的臨床試驗，提出了一個 phase II/III 的調適性無縫設計。此研究中，有兩種調適性無縫臨床試驗設計:一種是停止於無效(Design I)以及另一種停止於無效以及有效(Design II)。設計分成兩階段，第一階段即 phase II 的試驗中，幾個不同劑量的試驗藥物與對照組相比，這樣我們可以評估在對照組的試驗藥物劑量的療效。經過第一階段（phase II 階段），我們進行分析是否進行第二階段（phase III 階段）。最後，還給出數值例子來說明我們的設計。

關鍵字：調適性設計、Phase II/III 設計、臨床試驗

An Adaptive Seamless Phase II/III Design for Binary Endpoints in Clinical Trials

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Abstract

How to design a clinical trial, to analyze the data, and to evaluate the benefit of drugs becomes an important course for pharmaceutical development. The price of successfully developing new drugs has risen steeply, and more than half of the time and expense in the development process are spent in clinical trials. Hence, one challenge in the development of new drug is reducing expenses and time, moreover demonstrating the benefits of a new drug. It is recognized that, in spite of increasing spending of biomedical research does not reflect an increase of the success rate of pharmaceutical development. The success rate of researching and developing new drugs is disappointing even though there are many potential candidates and lengthy process of clinical development. Therefore, there is a reason to find ways in which drug development could be expedited and made more efficient. In this thesis, two adaptive seamless phase II/III designs are developed: one permits early stopping only for futility (Design I), and the other allows early stopping for either efficacy or futility (Design II). The resulting designs are in practice two-stage designs. At the stage one (the phase II stage), several doses of an experiment are compared with a control group so that we can evaluate the efficacy of doses of the experiment over the control group. After stage one (phase II stage), an interim analysis is performed and a decision is made on whether to proceed to stage two (phase III stage). Numerical examples are also given to illustrate our designs.

KEY WORDS: Adaptive design, clinical trial, seamless phase II/III design

誌謝

時光飛逝，兩年的時間過去了，在學校的生活告了一個段落，要邁入不同於學生生活的另一個階段。在學校的兩年，要感謝同學們的幫忙與支持，學長姐們的照顧，所上老師們認真的教學與指導，以及學校提供豐富的資源。雖然，只有兩年的時間，卻讓我獲益良多。

此篇論文的完成，最要感謝我的指導教授，蕭金福老師。剛開始時，什麼都還在摸索的階段，蕭老師不厭其煩，耐心的提點。到最後完成時，持續的建議與指導，從中使我循序漸進，學習到研究的精神與其要領，讓我能夠完成論文的撰寫，研究的過程也要感謝黃翁賢學長的幫助，分享他的經驗，使我事半功倍，順利的完成研究。

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袁明駿　謹誌于

國立交通大學統計學研究所

中華民國一〇一年六月

Content

1. Introduction

The development of pharmaceutical products is becoming risky, increasingly challenging, inefficient, time-consuming endeavor and costly. Based on the reports from Economist (2002), a new drug from screening of candidates to regulatory approval for commercial marketing will take more than 12 years on the average between $800 million and $1 billion in US. 70% of the cost of pharmaceutical development has been wasted on drugs that do not even make it to market. Despite of an increasing understanding of disease etiology and advance in medical technology, the success rate of drug development, 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].

One of the many probable reasons is that the method used in the past decades is no longer working for the new century. In March 2004, the US Food and Drug Administration (FDA) announced a white paper designated "Stagnation/Innovation: Challenge and Opportunity on the Critical Path to New Medical Products" (Anonymous, 2004) [2]. The document recognized that nowadays revolution in biomedical science has raised new hope for the cure of many diseases. Nevertheless, it points out that the number of new drug and biologic applications submitted to the FDA has quite declined in the last decade and discusses several potential causes for this decline. Currently, only 10% of investigational new drug (IND) applications to the FDA result in clinically approved agents, and in oncology it is only 5%. The white paper concludes that if the drug development processes do not become more efficient and effective, innovation may continue to stagnate and the biomedical revolution may hard to

achieve its full potential. Consequently, there is an urgent need to develop new concept and methodology to increase the success rate and reduce the cost of money and time in order to take a great benefit to patients and pharmaceutical factories.

For this reason, much idea has been given to find ways in which drug development could be expedited and made more efficient without compromising the integrity and validity of the development process. In recent years, the use of adaptive design methods in clinical trials based on accrued data has become popular due to its flexibility and efficiency. One of the adaptive designs is an adaptive seamless phase II/III design which has been considered as one possible way to shorten the drug development time and thus reduce patient exposure needed to discover, develop, and demonstrate the benefits of a new drug [3]. An adaptive seamless design combines into a single trial objectives traditionally addressed in separate trials. And it merges several trials that would implement separately into a single trial. In drug development, clinical trials are divided into three phases. Phases I is the stage where the drug is first tested in human beings and the objective is to determine the safety of the new drug. The typical phase II stage (the learning stage) is to discover whether the drugs have any significant biologic effect, and would compare several treatments with a control. After the completion of phase II stage, it is then decided whether to continue the drug development and which treatments to mover forward to the phase III. The goal of the phase III stage (the confirming stage) is to verify the efficacy of the treatment selected from the last stage, and it is evaluated as stand-alone confirmatory trials, ignoring information from previous phases. In an adaptive seamless phase II/III design, we combine the phase II stage which includes several treatments and concurrent control group and the phase III stage into a single trial, and perform the final analysis based on the data derived from both two stages.

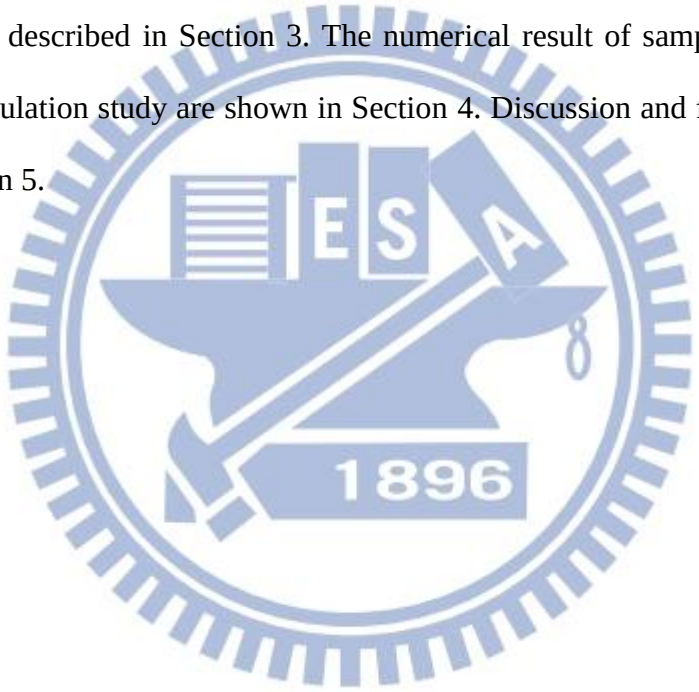
Some of the patients in the learning stage would be monitored continuously until the final analysis, so such a design can help us to get more information of long-term safety effects, and shorten the duration of the trials.

Since we combine phase II into phase III, the adaptive seamless phase II/III design is definitely a two-stage design. A two-stage designs permits early stopping when no new regimens show a minimum pre-indicated advantage or some new regimens show an overwhelming benefit over the standard regimen, and can minimize the number of patients expected to be accrued to the new regimens which do not offer benefit over the standard regimen, subject to the constraints of alpha-error and power. Simon (1989) has proposed an optimal two-stage design which includes one new regimen and one standard therapy for binary endpoints. It minimizes the expected sample size subject to constraints of the type I and II errors if the new regimen has low activity. Tsou et al. (2008) presented a two-stage design for drug screening trials based on continuous endpoints. The proposed two-stage screening design minimize the expected sample size if the new candidate has low efficacy activity subject to the constraint upon the type I and type II error rates.

Similarly, Liu and Pledger (2005) has also proposed a two-stage adaptive design combining phase II and III trials. In the first stage, short-term safety and efficacy are examined, and the trial continues to the next stage with the doses that do not lack efficacy or cause safety concerns. Patients from both the first and second stages are evaluated by a long-term clinical endpoint. At the final analysis, pairwise statistics for two stages are combined to establish dose-response and to identify the lowest effective dose. On the other hand, Maca et al. (2006) have introduced the general concept of adaptive designs, described the current statistical methodologies that relate

to adaptive seamless designs and also discussed the decision process involved with seamless designs.

In this thesis, two adaptive seamless phase II/III designs will be developed: one permits early stopping only for futility (Design I), and the other allows early stopping for either efficacy or futility (Design II). In Section 2. we will present the adaptive seamless phase II/III design which permits early stopping only for futility. The adaptive seamless phase II/III design allowing early stopping for either efficacy or futility will be described in Section 3. The numerical result of sample sizes, critical values and simulation study are shown in Section 4. Discussion and final remarks are made in Section 5.



2. The adaptive seamless phase II/III design permits early stopping only for futility (Design I)

For convention, we consider two-stage designs for a phase II/III adaptive trial for testing an experimental drug with several doses against a control group based on binary response endpoints. At the phase II stage, let K be the number of doses for the experimental drug. Suppose each of the K doses and the control group needs to accrue n_1 patients. Let X_{1i} denote the number of responders among the n_1 patients for i^{th} doses group at the phase II stage, $i = 1, \cdots, K$, and Y_1 denote the number of responders among the n_1 patients for the control group. Let p_0 is the response rate for the control group. For simplicity, we assume that each of doses have the same response rate p_i, where $p_i = p_0 + \Delta, \Delta > 0$. Then X_{1i} and Y_1 are distributed as a binomial distribution. So we can assume that $X_{1i} \sim B(n_1, p_i)$, $Y_1 \sim B(n_1, p_0)$ are independent random variables, where $B(n, p)$ represents a binomial distribution with n trials and a probability of success p. We desired to test the following hypothesis:

$$H_0 : p_i - p_0 \le 0 \ \forall \ i = 1, \ldots K \text{ vs. } H_1 : p_i - p_0 > 0 \text{ for some } i \qquad (1)$$

Large values of $X_{1i} - Y_1$ indicate more responses among the i^{th} doses group than the control group, which supports the hypothesis that the i^{th} doses group is more efficacious than the control group. That is, large values of $X_{1i} - Y_1$ support H_1.So that we can compare the i^{th} doses group with the control group by $X_{1i} - Y_1$.

Our procedure proceeds as follows (cf. Figure 1). The phase II stage needs to recruit n_1 patients for each group. When the study is completed at the phase II stage and if some of the observed values of $X_{1i} - Y_1$ are smaller than a integer $a_1 \in [-n_1, n_1]$, then it says that the i^{th} dose group has futility, and the i^{th} dose group will not be selected to phase III stage. Moreover, if all of observed values of $X_{1i} - Y_1$ are

less than a_1, it indicates that none of the doses of the experimental drug demonstrate a promising result and thus the trial will cease early for futility. Otherwise, the accrual of another n_2 patients will continue to the phase III stage for the control group and dose groups for which $X_{1i} - Y_1 \geq a_1$.

Let X_{2i} denote the number of responders among the n_2 patients for i^{th} doses group continued to the phase III stage, and Y_2 denote the number of responders among the n_2 patients for the control group. Again, X_{2i} and Y_2 are distributed as a binomial distribution. So we can assume that $X_{2i} \sim B(n_2, p_i)$, $Y_2 \sim B(n_2, p_0)$ are independent random variables. After the recruitment of the patients at phase III stage is completed, we then perform the final analysis with the cumulative data $n_1 + n_2$ patients for each group from both stages. Let $X_i = X_{1i} + X_{2i}$ and $Y = Y_1 + Y_2$. At the final stage, we can declare that the i^{th} dose group is confirmed to be superior to the control group if $X_i - Y \geq b_2$, where $b_2 \in [a_1 - n_2, n_1 + n_2]$.

Since every dose group for the experiment drug will be compared to the control group, we use the Bonferroni method for adjusting the overall type I error. Let α be the pairwise type I error for each comparison. As a result, $K\alpha$ is the overall type I error. Also let β be the pairwise type II error. In our design, the probability of "accepting" the i^{th} dose group can be expressed as

$$\varphi(p_i, p_0, n_1, n_2, a_1, b_1)$$

$$= P(X_{1i} - Y_1 \geq a_1, X_i - Y \geq b_2)$$

$$= P(X_{1i} - Y_1 \geq a_1, X_{1i} - Y_1 + X_{2i} - Y_2 \geq b_2)$$

$$= \sum_{x=a_1}^{n_1} P(X_{1i} - Y_1 = x) \times P(X_{2i} - Y_2 \geq b_2 - x \,|\, X_{1i} - Y_1 = x)$$

$$= \sum_{x=a_1}^{n_1} st(x; p_i, p_0, n_1) \times \{1 - ST(b_2 - x - 1; p_i, p_0, n_2)\} \qquad (2)$$

where

$$st(x;p_i,p_0,n)=\left[(1-p_i)(1-p_0)\right]^n\left(\frac{1-p_0}{p_0}\right)^x\cdot\sum_{k=\max(0,x)}^{\min(n,n+x)}\binom{n}{k}\binom{n}{k-x}\left(\frac{p_i}{1-p_i}\right)^k\left(\frac{p_0}{1-p_0}\right)^k,$$

and

$$ST(x;p_i,p_0,n)=\sum_{i=-n}^{x}st(i;p_i,p_0,n),$$

for $-n\le x\le n$. It can be seen that $st(x;p_i,p_0,n)$ is the density function for $S-T$ where S and T are $B(n,p_i)$ and $B(n,p_0)$. Consequently $ST(x;p_i,p_0,n)$ is the cumulative distribution function for $S-T$.

Consequently, under the null hypothesis, the pairwise type I error rate α and the pairwise power can be expressed as

$$\alpha=\varphi(p_0,p_0,n_1,n_2,a_1,$$ (3)

and

$$1-\beta=\varphi(p_i,p_0,n_1,n_2,a_1,$$ (4)

respectively.

By previous assumption, the expected total sample size, EN, under the null hypothesis that $p_i-p_0=0$ for all K comparisons can be calculated as follows:

$$\begin{aligned}\mathrm{EN}&=(K+1)n_1\pi_0+\sum_{j=1}^{K}\left[(j+1)n_2+(K+1)n_1\right]\pi_j\\&=(K+1)n_1+\sum_{j=1}^{K}(j+1)n_2\pi_j\end{aligned}$$ (5)

where π_0 is the probability of stopping accrual at the phase II stage (PET) and π_j $(j=1,2,\cdots,K)$ is the probability that the accruals for j of the dose groups and the control group are continued to the phase III stage. Note that $\pi_0+\sum_{j=1}^{K}\pi_j=1$. More

specifically, π_0 and π_j can be written as follows:

$$\pi_0 = \prod_{i=1}^{K} [P(X_{1i} - Y_1 \le a_1 - 1 | p_0 = p_i)]$$
$$= [\, ST(a_1 - 1; p_0, p_0, n_1)]^K \quad (6)$$

and

$$\pi_j = \binom{K}{j} P(X_{11} - Y_1 \ge a_1 | p_0 = p_i)^j P(X_{11} - Y_1 < a_1 | p_0 = p_i)^{k-j}$$
$$= \binom{K}{j} [1 - ST(a_1 - 1; p_0, p_0, n)]^j [ST(a_1 - 1; p_0, p_0, n)]^{k-j} . \quad (7)$$

For specified values of the treatment effect $\Delta = p_i - p_0$, p_0, α, β and, we can determine n_1, n_2, a_1 and b_2 subject to $n_1 \le n_2$, $a_1 \in [-n_1, n_1]$, $b_2 \in [a_1 - n_2, n_1 + n_2]$, and two constraints of type I and II error rates in (3) and (4), and to minimize the expected total sample size (5) when $p_i - p_0 = 0$. We use exhaustive searches to find values of n_1, n_2, a_1 and b_2 by a C++ program for the phase II/III designs.

3. The adaptive seamless phase II/III design allows early stopping for either efficacy or futility (Design II)

Once again, we consider two-stage designs for a phase II/III adaptive trial for testing an experimental drug with several doses against a control group based on binary response endpoints. In Design II, we will also consider early stopping for efficacy in addition to consider early stopping for futility. We will use all the assumption and notation used in Section 2.

Figure 2 displays the procedure of Design II. After the phase II stage, if all of observed values of $X_{1i} - Y_1$ are less than a integer $a_1 \in [-n_1, n_1]$ a minimal clinical requirement pre-specified by investigators, it indicates that none of the doses of the experimental drug displays a promising result and thus the trial will cease early for futility. If some of the observed values of $X_{1i} - Y_1$ are greater than $b_1 \in [a_1 + 1, n_1]$, then it says that there exists at least one dose of the experimental drug to have overwhelming advantage, and the trial will stop early for efficacy. Otherwise, the accrual of another n_2 patients will continue to the phase III stage for the control group and dose groups for which $a_1 \le X_{1i} - Y_1 \le b_1$.

At the phase III stage, we can declare that the i^{th} dose group is confirmed to be superior to the control group if $X_i - Y \ge b_2 \in [a_1 + 1, n_1 + n_2]$. Just like the Design I, the probability of "accepting" the i^{th} dose group can be expressed as

$$\varphi(p_i, p_0, n_1, n_2, a_1, b_1, b_2)$$

$$= P(X_{1i} - Y_1 \geq b_1 + 1) + P(a_1 \leq X_{1i} - Y_1 \leq b_1, X_i - Y \geq b_2)$$

$$= P(X_{1i} - Y_1 \geq b_1 + 1) + P(a_1 \leq X_{1i} - Y_1 \leq b_1, X_{1i} - Y_1 + X_{2i} - Y_2 \geq b_2)$$

$$= P(X_{1i} - Y_1 \geq b_1 + 1) + \sum_{x=a_1}^{b_1} P(X_{1i} - Y_1 = x) \times P(X_{2i} - Y_2 \geq b_2 - x \,|\, X_{1i} - Y_1 = x)$$

$$= [1 - ST(b_1 - 1; p_i, p_0, n_1)] + \sum_{x=a_1}^{b_1} st(x; p_i, p_0, n_1) \times \{1 - ST(b_2 - x - 1; p_i, p_0, n_2)\}. \quad (8)$$

Consequently, under the null hypothesis, the pairwise type I error rate α and the pairwise power can be expressed as

$$\alpha = \varphi(p_0, p_0, n_1, n_2, a_1, b_1, \quad (9)$$

and

$$1 - \beta = \varphi(p_i, p_0, n_1, n_2, a_1, b_1 \quad (10)$$

respectively.

The expected total sample size EN under the null hypothesis that $p_i - p_0 = 0$ for all *K* comparisons can be calculated as follows:

$$\begin{aligned} \text{EN} &= (K+1) n_1 \pi_0 + \sum_{j=1}^{K} \left[(j+1) n_2 + (K+1) n_1 \right] \pi_j \\ &= (K+1) n_1 + \sum_{j=1}^{K} (j+1) n_2 \pi_j \end{aligned} \quad (11)$$

where π_0 and π_j is shown below,

$$\begin{aligned} \pi_0 &= \prod_{i=1}^{K} [P(X_{1i} - Y_1 \leq a_1 - 1 \,|\, p_0 = p_i)] + 1 - \prod_{i=1}^{K} [P(X_{1i} - Y_1 \leq b_1 \,|\, p_0 = p_i)] \\ &= [\, ST(a_1 - 1; p_0, p_0, n_1)]^K + 1 - [ST(b_1; p_0, p_0, n_1)]^K \end{aligned} \quad (12)$$

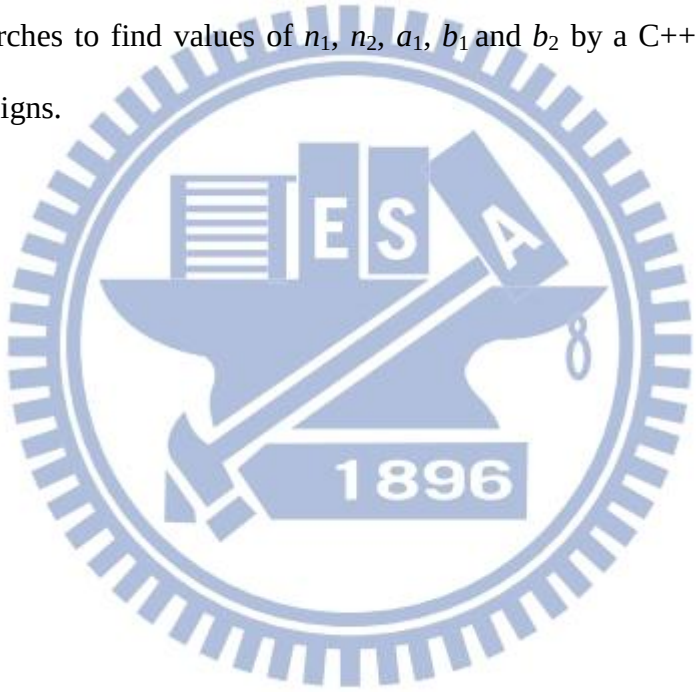
and

$$\pi_j = \binom{K}{j} P(a_1 \le X_{1i} - Y_1 \le b_1 \,|\, p_0 = p_i)^j [1 - P(a_1 \le X_{1i} - Y_1 \le b_1 \,|\, p_0 = p_i)]^{k-j}$$

$$= \binom{K}{j} [1 - ST(b_1; p_0, p_0, n) + ST(a_1 - 1; p_0, p_0, n)]^j \times$$

$$[ST(b_1; p_0, p_0, n) - ST(a_1 - 1; p_0, p_0, n)]^{k-j} \quad (13)$$

For specified values of the treatment effect $\Delta = p_i - p_0$, p_0, α, β and, we can determine n_1, n_2, a_1, b_1 and b_2 subject to $n_1 \le n_2$, $a_1 \in [-n_1, n_1]$, $b_1 \in [a_1 + 1, n_1]$, $b_2 \in [a_1 + 1, n_1 + n_2]$, and the two constraints of type I and II error rates (9) and (10), and to minimize the expected total sample size (11) when $p_i - p_0 = 0$. Again, we use exhaustive searches to find values of n_1, n_2, a_1, b_1 and b_2 by a C++ program for the phase II/III designs.



4. Results

In this section, we give some examples for the purpose of illustration. Tables 1－6 illustrate the Designs I for several combinations of parameters with $K=1, K=2, K=3$, $\Delta=0.15$, and $\Delta=0.20$. Also, Tables 7－12 illustrate the Designs II for the same combinations of parameters with $K=1, K=2, K=3$, $\Delta=0.15$, and $\Delta=0.20$. Here we assume that the overall type I rate is 0.05 and $\beta=0.2$ for both designs. The tabulated results contain the critical value a_1 and b_1 for the observed value $X_{1i}-Y_1$ that would permit early stopping at the phase II stage due to the treatment efficacy or futility, the critical value b_2 for the observed value X_i-Y that would not reject the treatment at the phase III stage, the sample size n_1 required at the phase II stage per group , the sample size n_2 required at the phase III stage per group, the expected total sample size EN when there is no difference of efficacy between the dose groups and the control group, the sample sizes n_1' required per group for traditional phase II designs which are evaluated by

$$n_1'=\frac{2\left(Z_\alpha+Z_\beta\right)^2\bar{p}\left(1-\bar{p}\right)}{\Delta_i^{\,2}}$$

where $\bar{p}=\frac{p_i+p_0}{2}$ and $Z_\theta=\Phi^{-1}\left(1-\theta\right)$, $n^j{}_2$ required per group for traditional phase III designs which are evaluated by

$$n^j{}_2=\frac{2\left(Z_{\frac{K\alpha}{j}}+Z_\beta\right)^2\bar{p}\left(1-\bar{p}\right)}{\Delta_i^{\,2}}$$

where $\bar{p}=\frac{p_i+p_0}{2}$, $Z_\theta=\Phi^{-1}\left(1-\theta\right)$, and j denote the number of the doses of the experimental drug selected to the phase III stage and the probability of early termination after the first stage (PET).

For example, the first row in Table 3 displays the results corresponding to $(K\alpha,\beta)=(0.05,0.2)$, $p_i-p_0=0.20$, $K=2$, and $p_0=0.05$ for Designs I, we enroll 10 patients for each group (that is, 30 patients in total) at the phase II stage. When the trial of the phase II stage is completed, if the observed values of $X_{1i}-Y_1$ are all less than 1, it says that no dose group is better than the control group, and hence the study is terminated for futility. Otherwise, we need to enroll another 29 patients for the phase III stage for both the control group and dose groups which satisfy $X_{1i}-Y_1\le 1$. At the final stage, the calculation of the observed value X_i-Y is based on the accumulated data of n_1+n_2 patients from both the phase II and phase III stages. If the observed value X_i-Y is less than or equal 4, we conclude that there is no difference between the dose groups and the control group. On the contrary, we say that the new drug is more effective than the control group if the observed value X_i-Y is more than 4. For this design, the expected total sample size is 59.03, and the probability of early termination after the phase II stage is 0.5354.

Similarly, the first row in Table 9 displays the results corresponding to $(K\alpha,\beta)=(0.05,0.2)$, $p_i-p_0=0.20$, $K=2$, and $p_0=0.05$ for Designs II, we enroll 16 patients for each group (that is, 48 patients in total) at the phase II stage. When the trial of the phase II stage is completed, if the observed values of $X_{1i}-Y_1$ are all less than 2, it says that no dose group is better than the control group, and hence the study is terminated for futility. The trial might be stopped as well if some observed value $X_{1i}-Y_1$ is greater than 3, interpreted as an indication of overwhelming efficacy of the dose of the new drug. Otherwise, we need to enroll extra 33 patients for the phase III stage for both the control group and dose groups which $2\le X_{1i}-Y_1\le 3$. At the final stage, the calculation of the observed value X_i-Y is based on the accumulated data of n_1+n_2 patients from both the phase II

and phase III stages. If the observed value $X_i - Y$ is less than or equal 4, we conclude that there is no difference between the dose groups and the control group. On the contrary, we say that the new drug is more effective than the control group if the observed value $X_i - Y$ is more than 4. For this design, the expected total sample size is 59.34, and the probability of early termination after the first stage is 0.8163.

Obviously, we can observe a phenomenon if the difference between the treatment group and the control group decreases, both the sample size required for each stage and EN increase. It is reasonable since the larger the treatment effect, the smaller the sample size required. Also, comparing the Design I with the Design II, we can find that the required patients for each group at the phase II stage the Design II needs more patients than the Design I. It makes intuitive sense since, in the Design II, it takes more type I error rate and power for early stopping for efficacy. On the other hand, in addition to consider early stopping for futility, the Design II will also consider early stooping for efficacy. Subsequently, the probability of early termination for Design II is general larger than the Design I.

4. Conclusion and Discussion

In this thesis, we propose two adaptive seamless phase II/III designs for evaluation of drugs efficacy based on binary endpoints: one permits early stopping only for futility (Design I), and the other allows early stopping for either efficacy or futility (Design II). Under both design structures, a single trial with the selection and confirmation phases is conducted using the same protocol with the same inclusion/exclusion criteria, the same concurrent control, the same methods for evaluation, and the same efficacy/safety endpoints. Doing so, yields that the data from both the dose selection and confirmation of efficacy are generated within the same study. Another striking feature is that our phase II/III designs would in fact use the data from patients enrolled from the selection stage and from the confirmation stage in the final analysis. With this approach, reduction of the total sample size might be possible. This in term may possibly shorten the total duration of drug development and consequently can save considerably valuable resource and cost.

While early stopping at the phase II stage does not occur, selection of dose level for the confirmation stage will be critical. Of course, one can choose all the dose level meeting with the pre-specified requirement for efficacy. However, the choice of dose level should be determined not only on the efficacy but also on safety. In general, the toxicity might also increase as the dose level increases. In this case, the lowest dose level which meets the efficacy requirement with the best safety profile can be selected for the confirmation stage.

The possibility of shortening the time of development of a new drug is definitely one stimulating feature about the use of an adaptive phase II/III design. As indicated earlier, such a design is not only flexible but also efficient as compared to separate phase II and phase III studies. However, in practice, not all clinical development may be suitable for such a design. For determining the feasibility of the use of an adaptive design in clinical development, Maca et al. [3] proposed a list of criteria. As the use of

an adaptive phase II/III design is to get effective drugs to patients sooner, whether such a design would achieve a reduction in development time would be an important factor for feasibility consideration. When the adaptive phase II/III trial is the only pivotal trial required for regulatory submission, the reduction in clinical development time is clear. On the other hand, if the phase II/III trial is one of two required pivotal trials, then the second pivotal trial should be completed within a reduced time frame that shortens the overall development time. Maca et al. [3] suggestd the second pivotal trial which is more traditionally designed could begin immediately after the phase II analysis so that it is possibly completed close to the time the adaptive phase II/III study is completed. It should be noted that doing so may need more time for planning, development, and health authority review for such a design, and consequently, this extra time must be included into the assessment of the overall development time.

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Listed Tables

Table 1. Designs I for $p_i - p_0 = 0.20$, $K = 1$, $(K\alpha, \beta) = (0.05, 0.2)$

p_0	p_i	EN	PET	n_1	n_2	a_1	b_2	n'_1	n^1_2
0.05	0.25	31.27	0.7317	10	21	1	3	40	40
0.1	0.3	51.27	0.6411	12	38	1	5	50	50
0.2	0.4	77.84	0.7200	21	64	2	8	65	65
0.3	0.5	95.06	0.6855	23	78	2	10	75	75
0.4	0.6	102.55	0.6674	25	79	2	11	78	78
0.5	0.7	99.04	0.6641	25	73	2	11	75	75
0.6	0.8	89.21	0.6614	27	52	2	10	65	65
0.7	0.9	75.48	0.7026	19	63	2	9	50	50

Table 2. Designs I for $p_i - p_0 = 0.15$, $K = 1$, $(K\alpha, \beta) = (0.05, 0.2)$

p_0	p_i	EN	PET	n_1	n_2	a_1	b_2	n'_1	n^1_2
0.05	0.2	57.63	0.6914	14	48	1	4	61	61
0.1	0.25	83.24	0.7409	31	41	2	6	80	80
0.2	0.35	129.58	0.6692	37	84	2	10	110	110
0.3	0.45	165.43	0.7154	46	129	3	13	129	129
0.4	0.55	175.47	0.6899	53	112	3	14	138	138
0.5	0.65	177.87	0.7319	64	93	4	14	135	135
0.6	0.75	168.57	0.7046	45	133	3	14	121	121
0.7	0.85	139.72	0.6589	32	111	2	12	96	96
0.8	0.95	98.98	0.7070	24	87	2	9	61	61

Table 3. Designs I for $p_i - p_0 = 0.20$, $K = 2$, $(K\alpha, \beta) = (0.05, 0.2)$

p_0	p_i	EN	PET	n_1	n_2	a_1	b_2	n'_1	$n^1{}_2$	$n^2{}_2$
0.05	0.25	59.03	0.5354	10	29	1	4	51	40	51
0.1	0.3	95.42	0.3687	20	25	1	6	63	50	63
0.2	0.4	136.10	0.6142	32	49	3	10	83	65	83
0.3	0.5	169.08	0.6557	38	76	4	13	95	75	95
0.4	0.6	182.86	0.6117	42	69	4	14	99	78	99
0.5	0.7	187.50	0.6273	37	97	4	15	95	75	95
0.6	0.8	169.53	0.6401	36	81	4	14	83	65	83
0.7	0.9	138.99	0.6016	26	72	3	12	63	50	63

Table 4. Designs I for $p_i - p_0 = 0.15$, $K = 2$, $(K\alpha, \beta) = (0.05, 0.2)$

p_0	p_i	EN	PET	n_1	n_2	a_1	b_2	n'_1	$n^1{}_2$	$n^2{}_2$
0.05	0.2	97.82	0.7242	24	45	2	5	77	61	77
0.1	0.25	151.04	0.6946	38	58	3	8	101	80	101
0.2	0.35	236.78	0.6343	56	89	4	13	140	110	140
0.3	0.45	297.35	0.6432	67	128	5	17	164	129	164
0.4	0.55	328.31	0.6103	70	143	5	19	174	138	174
0.5	0.65	331.15	0.5933	74	126	5	19	171	135	171
0.6	0.75	307.62	0.6103	70	118	5	18	154	121	154
0.7	0.85	257.29	0.6013	51	123	4	16	122	96	122
0.8	0.95	180.44	0.6087	33	98	3	12	77	61	77

Table 5. Designs I for $p_i - p_0 = 0.20$, $K = 3$, $(K\alpha, \beta) = (0.05, 0.2)$

p_0	p_i	EN	PET	n_1	n_2	a_1	b_2	n'_1	$n^1{}_2$	$n^2{}_2$	$n^3{}_2$
0.05	0.25	93.77	0.7284	16	51	2	5	57	40	51	57
0.1	0.3	129.53	0.4651	23	31	2	7	71	50	63	71
0.2	0.4	200.64	0.6210	35	74	4	12	93	65	83	93
0.3	0.5	245.57	0.5310	38	90	4	15	106	75	95	106
0.4	0.6	267.94	0.5580	49	74	5	16	111	78	99	111
0.5	0.7	267.92	0.5689	45	93	5	17	106	75	95	106
0.6	0.8	246.20	0.5060	37	89	4	16	93	65	83	93
0.7	0.9	203.80	0.5728	32	81	4	14	71	50	63	71

Table 6. Designs I for $p_i - p_0 = 0.15$, $K = 3$, $(K\alpha, \beta) = (0.05, 0.2)$

p_0	p_i	EN	PET	n_1	n_2	a_1	b_2	n'_1	$n^1{}_2$	$n^2{}_2$	$n^3{}_2$
0.05	0.2	144.19	0.6280	23	65	2	6	86	61	77	86
0.1	0.25	220.10	0.5536	42	53	3	9	114	80	101	114
0.2	0.35	344.04	0.5012	57	104	4	15	157	110	140	157
0.3	0.45	430.20	0.4997	72	127	5	19	184	129	164	184
0.4	0.55	477.45	0.5457	77	169	6	22	196	138	174	196
0.5	0.65	482.34	0.5212	82	145	6	22	192	135	171	192
0.6	0.75	447.25	0.5489	76	144	6	21	172	121	154	172
0.7	0.85	372.93	0.5339	62	121	5	18	137	96	122	137
0.8	0.95	266.93	0.5737	42	106	4	14	86	61	77	86

Table 7. Designs II for $p_i - p_0 = 0.20$, $K = 1$, $(K\alpha, \beta) = (0.05, 0.2)$

p_0	p_i	EN	PET	n_1	n_2	a_1	b_1	b_2	n'_1	n^1_2
0.05	0.25	30.67	0.7290	11	16	1	2	3	40	40
0.1	0.3	52.34	0.8298	18	48	2	3	6	50	50
0.2	0.4	76.00	0.7272	26	44	2	5	9	65	65
0.3	0.5	94.61	0.7678	35	53	3	7	11	75	75
0.4	0.6	104.24	0.7622	35	72	3	7	14	78	78
0.5	0.7	103.77	0.8113	40	63	4	8	13	75	75
0.6	0.8	97.03	0.8353	36	76	4	7	14	65	65
0.7	0.9	83.06	0.8667	33	64	4	6	13	50	50

Table 8. Designs II for $p_i - p_0 = 0.15$, $K = 1$, $(K\alpha, \beta) = (0.05, 0.2)$

p_0	p_i	EN	PET	n_1	n_2	a_1	b_1	b_2	n'_1	n^1_2
0.05	0.2	61.92	0.3706	19	19	0	2	4	61	61
0.1	0.25	82.50	0.7704	30	49	2	4	7	80	80
0.2	0.35	135.30	0.7646	50	75	3	7	12	110	110
0.3	0.45	166.42	0.8257	67	93	5	10	14	129	129
0.4	0.55	185.32	0.8015	74	94	5	11	16	138	138
0.5	0.65	188.52	0.7994	74	101	5	11	17	135	135
0.6	0.75	174.75	0.8181	67	115	5	10	17	121	121
0.7	0.85	148.34	0.8432	61	84	5	9	14	96	96
0.8	0.95	105.69	0.8698	41	91	4	6	12	61	61

Table 9. Designs II for $p_i - p_0 = 0.20$, $K = 2$, $(K\alpha, \beta) = (0.05, 0.2)$

p_0	p_i	EN	PET	n_1	n_2	a_1	b_1	b_2	n'_1	$n^1{}_2$	$n^2{}_2$
0.05	0.25	59.34	0.8163	16	30	2	3	4	51	40	51
0.1	0.3	91.07	0.6446	20	41	2	4	7	63	50	63
0.2	0.4	141.41	0.7523	35	70	4	7	12	83	65	83
0.3	0.5	174.37	0.7506	45	75	5	9	15	95	75	95
0.4	0.6	195.75	0.7051	50	73	5	10	17	99	78	99
0.5	0.7	200.75	0.7798	51	103	6	10	20	95	75	95
0.6	0.8	184.82	0.7870	50	78	6	10	17	83	65	83
0.7	0.9	153.64	0.7839	40	74	5	8	16	63	50	63

Table 10. Designs II for $p_i - p_0 = 0.15$, $K = 2$, $(K\alpha, \beta) = (0.05, 0.2)$

p_0	p_i	EN	PET	n_1	n_2	a_1	b_1	b_2	n'_1	$n^1{}_2$	$n^2{}_2$
0.05	0.2	103.87	0.4312	24	25	1	3	5	77	61	77
0.1	0.25	159.78	0.8191	45	66	4	6	9	101	80	101
0.2	0.35	250.65	0.7987	69	104	6	10	15	140	110	140
0.3	0.45	314.11	0.7160	81	118	6	12	20	164	129	164
0.4	0.55	350.45	0.7837	94	151	8	14	23	174	138	174
0.5	0.65	358.75	0.7787	94	165	8	14	25	171	135	171
0.6	0.75	337.76	0.7837	94	123	8	14	22	154	121	154
0.7	0.85	287.79	0.7843	81	99	7	12	19	122	96	122
0.8	0.95	207.60	0.7815	54	99	5	8	17	77	61	77

Table 11. Designs II for $p_i - p_0 = 0.20$, $K = 3$, $(K\alpha, \beta) = (0.05, 0.2)$

p_0	p_i	EN	PET	n_1	n_2	a_1	b_1	b_2	n'_1	$n^1{}_2$	$n^2{}_2$	$n^3{}_2$
0.05	0.25	88.37	0.7386	16	44	2	3	5	57	40	51	57
0.1	0.3	132.00	0.7070	25	51	3	5	8	71	50	63	71
0.2	0.4	207.25	0.6117	40	55	4	8	13	93	65	83	93
0.3	0.5	261.34	0.6920	55	62	6	11	16	106	75	95	106
0.4	0.6	289.36	0.7273	60	84	7	12	19	111	78	99	111
0.5	0.7	295.19	0.7198	60	91	7	12	21	106	75	95	106
0.6	0.8	272.90	0.7589	55	102	7	11	21	93	65	83	93
0.7	0.9	230.27	0.7646	45	99	6	9	20	71	50	63	71

Table 12. Designs II for $p_i - p_0 = 0.15$, $K = 3$, $(K\alpha, \beta) = (0.05, 0.2)$

p_0	p_i	EN	PET	n_1	n_2	a_1	b_1	b_2	n'_1	$n^1{}_2$	$n^2{}_2$	$n^3{}_2$
0.05	0.2	140.46	0.6418	25	51	2	3	7	86	61	77	86
0.1	0.25	230.61	0.7444	45	92	4	6	12	114	80	101	114
0.2	0.35	363.05	0.6880	74	99	6	11	17	157	110	140	157
0.3	0.45	460.91	0.7213	94	141	8	10	17	184	129	164	184
0.4	0.55	518.88	0.7180	107	149	9	16	26	196	138	174	196
0.5	0.65	530.44	0.7109	107	163	7	10	28	192	135	171	192
0.6	0.75	497.32	0.7789	107	147	10	16	25	172	121	154	172
0.7	0.85	423.79	0.7491	87	140	8	13	24	137	96	122	137
0.8	0.95	305.98	0.8135	67	96	7	10	17	86	61	77	86

Listed Figures

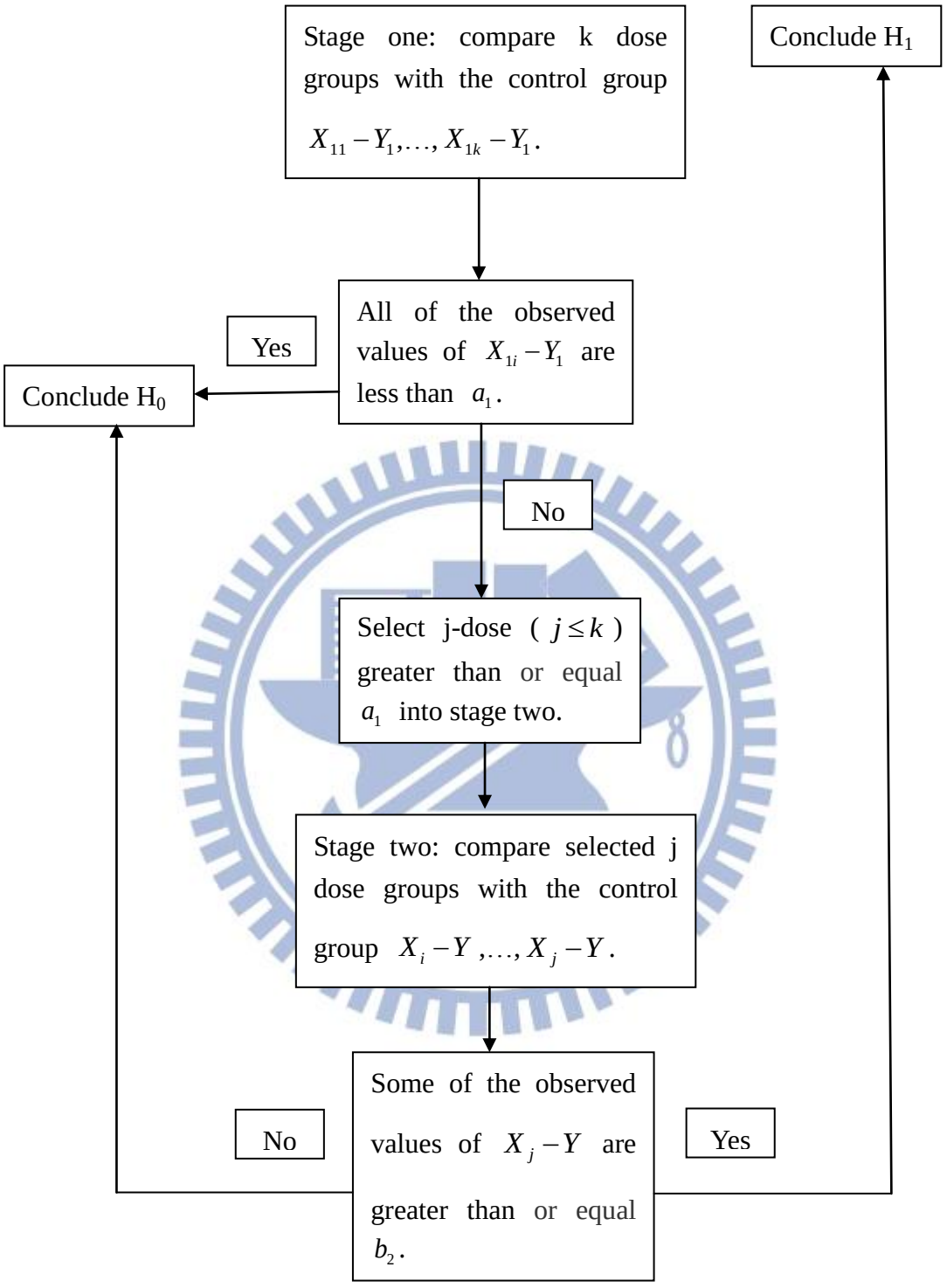

Figure 1. The adaptive seamless phase II/III design permits early stopping only for futility (Design I).

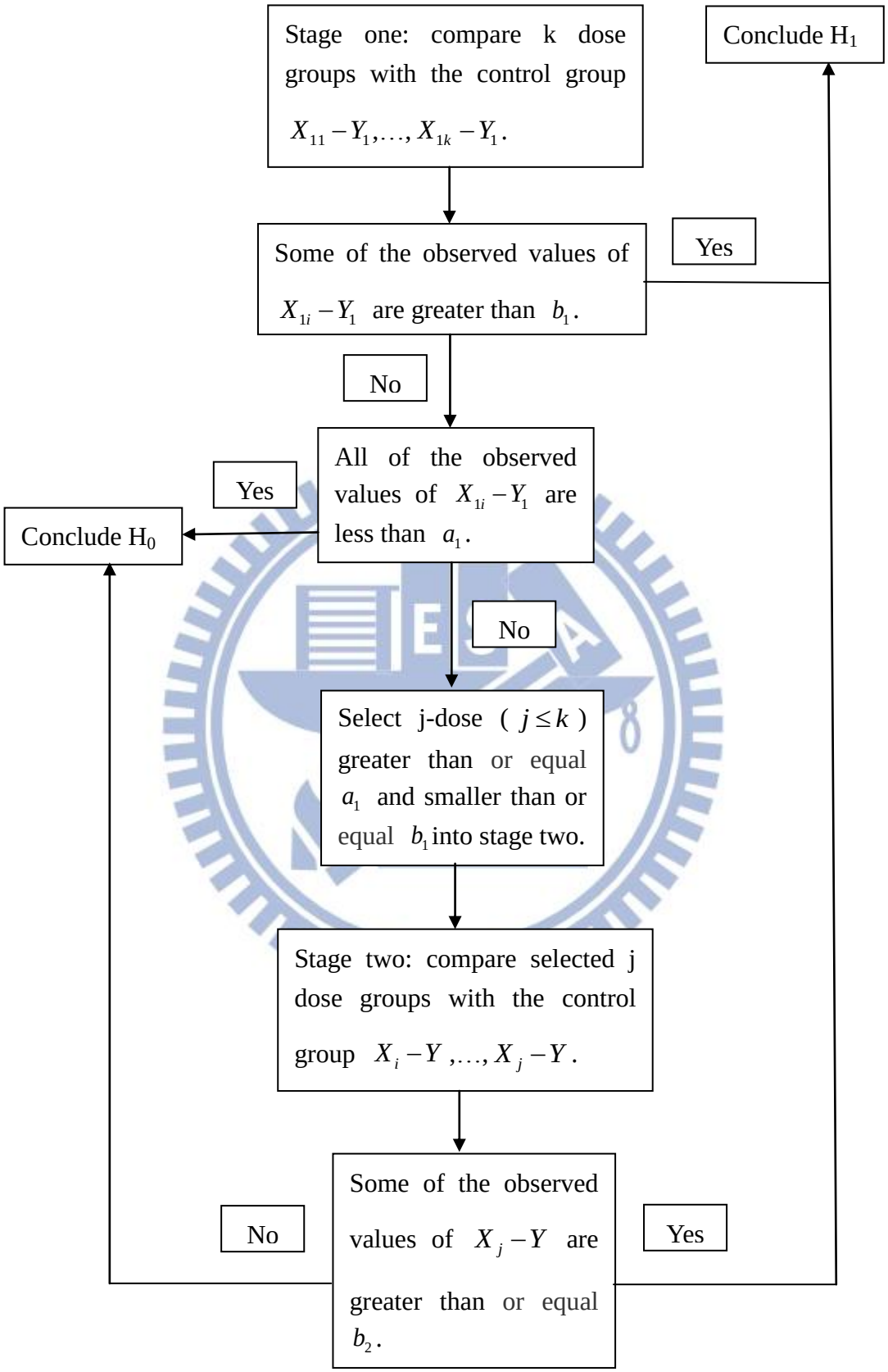

Figure 2. The adaptive seamless phase II/III design allows early stopping for either efficacy or futility (Design II).