Identifying Minimum Effective Dose Under Heteroscedasticity

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Authors’ contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Abstract

We propose a stepwise confidence procedure for identifying minimum effective dose (MED) without multiplicity adjustment. Stepwise procedures strongly control the familywise error rate (FWER) which is a critical requirement for statistical methodologies in identification of MED. The partitioning principle is invoked to validate the control of the FWER. Our simulation study indicates that the FWER was properly controlled in the case with balanced design but failed in some cases of sample sizes for situations of unbalanced design. In addition, the power of the procedure increases with increasing mean of ratio differences and the sample sizes.

Keywords: Balanced design; Fieller; FWER; MED; stepwise procedure; power.

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1 Introduction

In clinical trials, replacing existing active control (reference or standard treatment) with a new treatment is a vital area of research to the pharmaceutical community. In such a trial, we assert the effectiveness of a new treatment with an active control by demonstrating that the new treatment is not worse than the active control by more than a pre-specified margin. In clinical study, where the objective is to investigate whether a new treatment is not inferior to the standard treatment by more than pre-specified margin is known as non-inferiority trial. In other words, a new treatment is considered to be non-inferior to the active control when it retains a sizable portion of the efficacy of the active control. The new treatment is preferred to the active control because it has certain advantages of being easier to administer, less expensive, less toxic and less invasive to the active control. The methodology of designing and analyzing non-inferiority trials is an active area of statistical research. In literature, considerable research effort in statistical methodology for investigating non-inferiority three-arm design have been carried out in about last two decade, [1],[2] and [3]. A typical ‘gold standard’ three-arm trial designs consist of placebo, reference and only one experimental treatment. [4], [5], [6] and [7] extended the gold standard three-arm trial to (k+2)-arm trial in a single step procedure with multiplicity adjustment to study new treatment. However, no multiplicity adjustment is necessary if the experimental groups (new treatments) can be ordered priori according to their treatment effect. Multiple treatments with stepwise procedure without multiplicity has been investigated by these authors but in different settings [8], [9] and [10] are shown to be more powerful than single step procedure. In their papers, they assumed that treatments have the same variances. Meanwhile, in some clinical studies, homogeneous variances assumption are seldom satisfied in practice. In this paper, we put forth a new stepwise procedure and incorporate the procedure proposed by [11] and invoking the partition principle by [12] for a normally distributed data under the assumption of heteroscedasticity settings based on ratio of means. The outline of paper is as follows. In Section 2, the problem is formulated and the corresponding statistical tests are derived. Stepwise confidence based procedure on generalised Fieller’s method for multiple ratio are constructed in Section 3. In Section 4, we proposed and proved that the FWER our procedure can be controlled in strong sense. Simulation studies were conducted to assess the performance of the FWER and the power of our procedure in Section 5. An illustrative example for the formulated problem is demonstrated in Section 6. The conclusion of the article is in Section 7.

2 Testing Procedure

Let $X_{ij}, X_{i2}, \cdots, X_{in_i}$ be efficacy response of a sample data points for the $i$th group ($i = 0, 1, \cdots, k+1$) of a drug compound under study. Consider a one-way model as follows.

$$X_{ij} = \mu_i + \epsilon_{ij} \quad i = 0, 1, 2, \cdots, k+1, \quad j = 1, 2, \cdots, n_i$$  \hspace{1cm} (1)

where $X_{ij}$ represent the efficacy response for the $j$th experimental unit, $j = 1, 2, \cdots, n_i$ in the $(1, 2, \cdots, k)$th treatment group, where $i = 0$ denote the negative control group (or placebo group) and $i = k + 1$ a positive control group ( or reference group) respectively. The justification for the inclusion of a positive control is that if the study fail to detect any significant difference between the positive and negative control groups, which are known to be different, then any lack of observed significant difference between a dose group and negative control group may be the result of failed experimentation rather than closeness of their mean responses [11]. Assume that $X_{ij}$s are mutually independent and follows normal distribution with means $\mu_i$ and unknown variances $\sigma_i^2$, that is $X_{ij} \sim N(\mu_i, \sigma_i^2)$ for $i = 0, 1, \cdots, k+1$. The sample variances and the sample means are denoted as $S_i^2$ and $X_i$ respectively.

$$H_{0i} : \mu_i - \mu_{k+1} \leq \delta \quad \text{versus} \quad H_{1i} : \mu_i - \mu_{k+1} > \delta \quad \text{for} \quad i = 1, 2, \cdots, k$$ \hspace{1cm} (2)
where \( \delta \) is a relevant efficacy threshold. Pigeot [1], expressed the \( \delta \) value as a fraction of effective size between positive and negative groups by letting \( \delta = (\theta - 1)(\mu_{k+1} - \mu_{0}) \) while the \( \theta \in (0, 1) \) is a fixed retention fraction, [13]. For some ethical reasons a negative control group can be included in trial in Equation (2.1). Therefore, for all \( i = 1, 2, \cdots, k \), let \( \gamma_i \) be the ratio of means differences. Then we have

\[
\gamma_1 = \frac{\mu_1 - \mu_0}{\mu_{k+1} - \mu_0}, \gamma_2 = \frac{\mu_2 - \mu_0}{\mu_{k+1} - \mu_0}, \cdots, \gamma_k = \frac{\mu_k - \mu_0}{\mu_{k+1} - \mu_0}.
\]  

(3)

As a result, the testing problem in Equation (2.1) can be written as:

\[ H_0 : \Gamma = \{\gamma_1, \gamma_2, \cdots, \gamma_k\} \leq \theta \]

for \( i = 1, 2, \cdots, k \).

The validity of statistical procedure in clinical trials is the strong control of the FWER. This is a critical requirement by FDA. For this reason, we employ the partitioning principle proposed by [14], in testing \( H_0 : \gamma_i \leq \theta \). Using the partitioning principle, we have \( 2^k \) parameter space and with \( 2^k - 1 \) null hypotheses to be tested. The \( H_0 : \gamma_i \leq \theta \) hypotheses is decomposed into \( 2^k - 1 \) union of disjoint subspaces and each of these subsets is tested at level \( \alpha \). Only one of these contain the true parameter of interest. In this situation, multiplicity adjustment is needless. For example, letting \( \Gamma = \{\gamma_1, \gamma_2, \gamma_3\} \) for \( k = 3 \), we partition it into eight disjoint parameter subsets:

\[
\Gamma_1 = \{\gamma_1 \leq \theta \text{ and } \gamma_2 \leq \theta \text{ and } \gamma_3 \leq \theta\}
\]

\[
\Gamma_2 = \{\gamma_1 \leq \theta \text{ and } \gamma_2 \leq \theta \text{ and } \gamma_3 > \theta\}
\]

\[
\Gamma_3 = \{\gamma_1 \leq \theta \text{ and } \gamma_2 \leq \theta \text{ and } \gamma_3 < \theta\}
\]

\[
\vdots
\]

\[
\Gamma_8 = \{\gamma_1 > \theta \text{ and } \gamma_2 > \theta \text{ and } \gamma_3 \leq \theta\}
\]

and then testing each of these null hypotheses at the nominal level \( \alpha \).

\[
H_0(123) : \gamma_1 \leq \theta \text{ and } \gamma_2 \leq \theta \text{ and } \gamma_3 \leq \theta
\]

\[
H_0(12) : \gamma_1 \leq \theta \text{ and } \gamma_2 \leq \theta \text{ and } \gamma_3 > \theta
\]

\[
H_0(13) : \gamma_1 \leq \theta \text{ and } \gamma_2 > \theta \text{ and } \gamma_3 \leq \theta
\]

\[
\vdots
\]

\[
H_0(2) : \gamma_1 > \theta \text{ and } \gamma_2 \leq \theta \text{ and } \gamma_3 > \theta
\]

\[
H_0(3) : \gamma_1 > \theta \text{ and } \gamma_2 > \theta \text{ and } \gamma_3 \leq \theta
\]

will guarantee strong control of FWER in a strong sense.

Given the sample mean estimates as:

\[
\bar{X}_i = \frac{1}{n_i} \sum_{i=1}^{n_i} X_i, i = 1, 2, \cdots, k
\]

\[
\bar{X}_{k+1} = \frac{1}{n_{k+1}} \sum_{k=1}^{n_{k+1}} X_{k+1,k}
\]

and \( \bar{X}_0 = \frac{1}{n_0} \sum_{j=1}^{n_0} X_{0,j} \)

and the test statistics as:

\[
T_i = \frac{\bar{X}_i - \theta \bar{X}_{k+1} - (1 - \theta)\bar{X}_0}{\sqrt{\frac{s^2}{n_i} + \frac{\theta^2 s^2_{k+1}}{n_{k+1}} + \frac{(1-\theta)^2 s^2_0}{n_0}}}
\]

(4)

for \( i = 1, 2, \cdots, k \).

are \( t \)-distributed with degrees of freedom given by

\[
\nu_i = \frac{\left(\frac{s^2}{n_i} + \frac{\theta^2 s^2_{k+1}}{n_{k+1}} + \frac{(1-\theta)^2 s^2_0}{n_0}\right)^2}{\frac{s^2}{n_i^2(n_i-1)} + \frac{\theta^2 s^2_{k+1}}{n_{k+1}^2(n_{k+1}-1)} + \frac{(1-\theta)^2 s^2_0}{n_0^2(n_0-1)}}
\]

(5)

for \( i = 1, 2, \cdots, k \).
where γ is obtained to approximate the degrees of freedom. Note that, the degrees of freedom in this situation are according to [15] and [16]. This is because they rely on unknown group variances. When the assumption of larger values of the endpoints represent better treatment effect is of interest, then efficacy can be concluded if \( H_0 \) is rejected. That is:

\[
T_i > t_{k,1-\alpha(\nu_i)} \quad \text{for} \quad i = 1, 2, \ldots, k
\]

with its corresponding \((1-\alpha)\)-quantiles \( t_{k,1-\alpha(\nu_i)} \) of central \( k \)--variate \( t \)-distribution with degrees of freedom \( \nu_i (i = 1, \ldots, k) \)

In this study, we will construct a confidence set approach for \( \gamma_i \) for \( i = 1, 2, \ldots, k \) without multiplicity adjustment. The concept of Minimum effective dose (MED) for the proof of efficacy was defined as [17]:

\[
MED = \min\{i : \gamma_i > \theta, \quad i = 1, 2, \ldots, k\}
\]

3 Construction of Confidence Intervals for Ratio of Mean Difference

We employed the generalized Fieller’s theorem [18] to construct confidence interval for \( \gamma_i \) for \( i = 1, 2, \ldots, k \). We do this by solving \( k \) quadratic equations and then adapt the following notations from [2] and [19] to obtain:

\[
Z_i = \bar{X}_i - \bar{X}_0, \quad Z_{k+1} = \bar{X}_{k+1} - \bar{X}_0
\]

\[
Y_i = \frac{t^2_{1-\alpha,\nu_i} s_i^2}{n_i}, \quad Y_{k+1} = \frac{t^2_{1-\alpha,\nu_{k+1}} s_{k+1}^2}{n_{k+1}}, \quad Y_0 = \frac{t^2_{1-\alpha,\nu_0} s_0^2}{n_0}
\]

Thus yielding the lower confidence bounds respectively as:

\[
\theta_{i,1-\alpha} = \frac{Z_i Z_{k+1} - Y_0 - \sqrt{(Z_i Z_{k+1} - Y_0)^2 - (Z^2_{k+1} - Y_{k+1} - Y_0)(Z_i^2 - Y_i - Y_0)}}{Z^2_{k+1} - Y_{k+1} - Y_0}
\]

The above confidence limits for one-sided \( 100(1 - \alpha) \% \) confidence interval are only valid as long as 

\[
Z^2_{k+1} > Y_{k+1} - Y_0
\]

by Fieller’s theorem [18].

Definition 1. Suppose that the data \( X \) have a distribution determined by a parameter \( \Gamma = \{\gamma_1, \gamma_2, \ldots, \gamma_k\} \in \Theta \). A confidence set \( C(X) \) for \( \Gamma \) is said to be directed towards a subset of the parameter space \( \Theta^* \subset \Theta \), if for every sample point \( X \), either \( \Theta^* \subset C(X) \) or \( C(X) \subset \Theta^* \).

Therefore Equation (2.2) can be rewritten as a multiple testing problem:

\[
H_{10} : \gamma_i \in \Theta_i \text{ vs. } H_{1i} : \gamma_i \in \Theta_i^c \text{ for } i = 1, \ldots, k
\]

where \( \Theta_i^c = \{\Gamma : \gamma_i > \delta\} \) and \( \Theta_i = \{\Gamma : \gamma_i \leq \delta\} \) for a given sample point \( X \).

4 The Proposed Procedure

4.1 Stepwise confidence interval for identifying minimum effective dose based on ratio of mean differences

We identify minimum effective dose via Hsu-Berger [11] stepwise confidence set procedure: In the first step, we establish the assay sensitivity of the procedure by proving that 

\[
Z^2_{k+1} > Y_{k+1} - Y_0.
\]

If
Suppose that the step at which the procedure stops. In such a situation, the sensitivity of experiment is inadequate. We estimate the lower confidence limits in the second step as:

\[
\hat{\theta}_{i,1-\alpha} = \frac{Z_iZ_{k+1} - Y_0 - \sqrt{(Z_iZ_{k+1} - Y_0)^2 - (Z_{k+1}^2 - Y_{k+1} - Y_0)(Z_{k+1}^2 - Y_i - Y_0)}}{Z_{k+1}^2 - Y_{k+1} - Y_0}
\]

for \( i = 1, \cdots, k \)

where \( k \) is the total number of treatment doses to be tested. In step three, we start screening the drug by screening the highest dose (that is at \( i = k \)) for the first effective drug and sequentially screen the subsequent doses for \( i = k - 1, k - 2, \cdots, 1 \) without adjusting the \( \alpha \) levels in each of the steps in descending manner searching for the first integer \( M \); if it exists \( [1 \leq M \leq k] \) such that \( \theta_M > \theta \) and \( \theta_{M-1} \leq \theta \) (this screens the first ineffective dose). In this set up, dose level at step \( M \) is estimated as \( MED \). The lowest estimated effective dose that is not worse than reference doses, such that it and all higher doses at steps \( k, k - 1, \cdots, M + 1 \) are also not worse than the references doses.

Once dose at step \( M \) is estimated as \( MED \) then the lower confidence bound for doses at \( M - 2, M - 3, \cdots, 1 \) steps are needless and should not be computed.

Suppose that our stepwise confidence interval procedure stops at step \( M (1 \leq M \leq k) \), we have the following Proposition.

**Proposition 1.** Suppose that \( \hat{\theta}_{k-i+1} \) for \( i = 1, 2, \cdots, k \) is the lower confidence bound for \( \gamma_{k-i+1} \) with confidence level \( 1 - \alpha \). Then for all \( \Gamma = \{\gamma_1, \gamma_2, \cdots, \gamma_k\} \in \Theta \), we have

\[
Pr\left( \bigcap_{i=1}^{M} \{\gamma_{k-i+1} > \theta\} \cap \{\gamma_{k-M} \leq \theta_{k-M}\} \right) \geq 1 - \alpha
\]

**Proof.** Let \( M = 1 \) be the step at which the procedure stops. In such a situation, the sensitivity of the experiment cannot be assessed and hence no dose can be declared as efficacious.

For \( M (2 \leq M \leq k) \) and for \( j = 1, \cdots, k \), let \( C_j(X) = \{\gamma_{k-j+1} > \theta_{k-j+1}\} \) such that \( \Theta_1 = \{\gamma_k \leq \theta\} \) and \( \Theta_j = \bigcap_{i=1}^{j-1} \{\gamma_{k-i+1} > \theta\} \cap \{\gamma_{k-j+1} \leq \theta\} \) for \( j = 2, \cdots, k \). Then, consider the following sets \( \Theta_1^*, \Theta_2^*, \cdots, \Theta_{k+1}^* \), as partitions of the parameter space \( \Theta \).

Hence

\[
\Theta_1^* = \Theta_1
\]

\[
\Theta_2^* = \Theta_2 \cap \Theta_1^*
\]

\[
\Theta_3^* = \Theta_3 \cap \Theta_2^* \cap \cdots \cap \Theta_{k-2} \cap \Theta_{k-1}^*
\]

\[
\Theta_k^* = \Theta_k \cap \Theta_{k-1}^* \cap \cdots \cap \Theta_{k-2} \cap \Theta_{k-1}^*
\]

\[
\Theta_{k+1}^* = \Theta_{k+1} \cap \Theta_k^* \cap \cdots \cap \Theta_{k-1}^* \cap \Theta_k^*
\]

If \( \Gamma \in \Theta_1^* \) then clearly a \( 100(1 - \alpha)\% \) confidence set for \( \Gamma = \{\gamma_1, \gamma_2, \cdots, \gamma_k\} \) will be

\[
C(X) = \bigcup_{i=1}^{k} (C_i(X) \cap \Theta_i^*).
\]

(7)

For all \( i < M \) (if such \( i \) exists) \( C_i(X) \cap \Theta_i^* = \phi \) since \( \Theta_i^* \subset \Theta_i \). Then

\[
C(X) = \bigcup_{i=M}^{k+1} (C_i(X) \cap \Theta_i^*).
\]

(8)
Similarly, for all $i > M$ (if such $i$ exists) we have $\Theta_{i}^\gamma \subset \Theta_0 \cap \ldots \cap \Theta_{M-1}^\gamma \cap \Theta_M^\gamma$ and equation (4.1) becomes:

$$C(X) = \bigcup_{i=M}^{k+1} (C_i(X) \cap \Theta_i^\gamma)$$

$$\subset (C_M(X) \cap \Theta_M^\gamma) \cup (\Theta_0 \cap \ldots \cap \Theta_{M-1}^\gamma \cap \Theta_M^\gamma)$$

$$= (\Theta_0 \cap \ldots \cap \Theta_{M-1}^\gamma \cap \Theta_M \cap C_M(X)) \cup (\Theta_0 \cap \ldots \cap \Theta_{M-1}^\gamma \cap \Theta_M^\gamma)$$

(9)

If $M < k + 1$, then $\Theta_M^\gamma \subset C_M(X)$ and $C_M(X) \cap \Theta_M^\gamma$ will imply $\Theta_M^\gamma \subset C_M(X)$. Hence

$$C(X) = \bigcup_{i=M}^{k+1} (C_i(X) \cap \Theta_i^\gamma)$$

$$\subset (C_M(X) \cap \Theta_M^\gamma) \cup (\Theta_0 \cap \ldots \cap \Theta_{M-1}^\gamma \cap \Theta_M^\gamma)$$

$$= (\Theta_0 \cap \ldots \cap \Theta_{M-1}^\gamma \cap \Theta_M \cap C_M(X)) \cup (\Theta_0 \cap \ldots \cap \Theta_{M-1}^\gamma \cap \Theta_M^\gamma)$$

$$= (\Theta_0 \cap \ldots \cap \Theta_{M-1}^\gamma \cap \Theta_M \cap C_M(X))$$

(10)

For all $\Gamma = \{\gamma_1, \gamma_2, \ldots, \gamma_k\} \in \Theta_i^\gamma$,

$$P(\Gamma \in C(X)) = P(\Gamma \in (C_i(X) \cap \Theta_i^\gamma))$$

$$= P(\Gamma \in C_i(X)) \geq 1 - \alpha.$$

This completes the proof of Proposition 4.1

Proposition 4.1 indicates that, the FWER can be controlled properly at pre-defined nominal level $\alpha$. In other words, all declarations are guaranteed with probability of $100(1 - \alpha)$.

## 5 Simulation Studies

We conducted simulation studies for case for $k = 2$ experimental treatments. Without lost of generality, take $\theta = 0.8$ and $\alpha = 0.025$. We adopted [2] mean configurations $\mu_{E_i} = 32.66$, $\mu_P = 16.5$, $\mu_R = 36.7$ for $i = 1, 2$ for the simulations. The data set for the simulation was generated from normal distribution with 100,000 replications under the cases of heteroscedasticity using R codes. In these studies, we evaluate the performance of our Method based on FWER and the power.

### 5.1 FWER study

We consider cases of balanced and unbalanced designs to assess the FWER by using Welch method in our construction of confidence intervals, because it approximates the degrees of freedom. This will ensure the control of type I error rate. Result from Table 1 shows that, our procedure performed well for balanced and unbalanced designs at the nominal level of $\alpha = 0.025$. However, in the case of unbalanced design, the procedure failed to control the FWER for sample sizes 4, and at least 16.

### 5.2 Power calculation

Confidence interval procedures for analyzing clinical trials are insufficient in some situations. For this reason, power estimation is imperative for a well-designed clinical trials. In literature, there are many definitions of power in multiple comparison procedures, but in this study, we will define power in terms of minimum effective dose. The minimum effective dose $\gamma$ is established when $\gamma > \theta$ and
Table 1. FWER study for our procedure. setting

\[ \sigma_k + 1 = 15, \sigma_0 = 5, \sigma_i = 10, \quad i = 1, 2, n_k + 1 = 10, n_0 = 20 \]

| \( n_1 (n_2) \) | Balanced design | Unbalanced design |
|------------------|-----------------|-------------------|
| 4 (5)            | 0.0220 (0.0220) | 0.0256 (0.0240)   |
| 6 (7)            | 0.0236 (0.0235) | 0.0244 (0.0236)   |
| 8 (9)            | 0.0246 (0.0251) | 0.0241 (0.0248)   |
| 10 (11)          | 0.0242 (0.0246) | 0.0247 (0.0241)   |
| 12 (13)          | 0.0240 (0.0249) | 0.0244 (0.0242)   |
| 14 (15)          | 0.0247 (0.0241) | 0.0249 (0.0249)   |
| 16 (17)          | 0.0250 (0.0249) | 0.0247 (0.0248)   |
| 18 (19)          | 0.0244 (0.0249) | 0.0255 (0.0255)   |
| 20 (21)          | 0.0239 (0.0245) | 0.0252 (0.0255)   |
| 22 (23)          | 0.0247 (0.0245) | 0.0255 (0.0255)   |
| 24 (25)          | 0.0243 (0.0239) | 0.0259 (0.0260)   |
| 26 (27)          | 0.0251 (0.0238) | 0.0259 (0.0269)   |
| 28 (29)          | 0.0251 (0.0246) | 0.0269 (0.0255)   |

\( \gamma_{M+1} \leq \theta \) where \( M \) is the first integer at which the stepwise procedure stops. Notice that \( M \) is a random variable because it depends on the sample under consideration. That is

\[
P(M \leq D = i) = P\left( \bigcap_{j=1}^{i} \{ T_j > t_{1-\alpha, \nu_i} \} \cap \{ T_{i+1} \leq t_{1-\alpha, \nu_i} \} \right)
\]  

(11)

However, in our setting, power is defined as the probability of incorrectly rejecting the null hypothesis. Hence Equation (5.1) can be rewritten as:

\[
P(\text{Reject } H_j \text{ for } j = 1, 2, \ldots, i) = P\left( \bigcap_{j=1}^{i} \{ T_j > t_{1-\alpha, \nu_i} \} \right)
\]

(12)

where

\[
\nu_i = \frac{\left( \frac{S_i^2}{\nu_i} + \frac{\sigma_k^2 S_{k+1}^2}{n_k+1} + \frac{(1-\theta)^2 S_0^2}{n_0} \right)^2}{\frac{S_i^4}{\nu_i (\nu_i-1)} + \frac{\sigma_k^2 S_{k+1}^4}{n_k+1 (n_k+1-1)} + \frac{(1-\theta)^2 S_0^4}{n_0 (n_0-1)}}
\]

(13)

Equation (5.3) is based on original ideas of [15] and [16] for a situation of unequal and unknown variances. Therefore Equation (5.2) can be estimated from a \( k \) variate non-central \( t \)-distribution with \( \nu_i \) degrees of freedom. Thus non-centrality parameters for \( i = 1, 2, \ldots, k \) are:

\[
\Theta_i = \frac{\mu_i - \theta \mu_{k+1} - (1-\theta)\mu_0}{\sqrt{\left( \frac{S_i^2}{\nu_i} + \frac{\sigma_k^2 S_{k+1}^2}{n_k+1} + \frac{(1-\theta)^2 S_0^2}{n_0} \right)^2}}
\]

This implies the power calculation must be approximated, since exact power calculation is impossible in this settings. In Table 2, the results of our power estimation are tabulated, it can be generally observed that power increases with increasing in both the ratio of mean differences, the sample sizes. This is consistent with earlier findings [2].
Table 2. Power Estimation of the confidence intervals for $\sigma_i = 10.4 \ i = 1, 2$

$\sigma_{k+1} = 13.2, \sigma_0 = 7.5$

| Ratio($\gamma_i$) | $n_{i+1,2}$ | $n_{k+1}$ | $n_0$ | Power  |
|-------------------|-------------|------------|-------|--------|
| 0.70              | 20          | 20         | 20    | 0.0054 |
| 0.70              | 30          | 30         | 30    | 0.0035 |
| 0.70              | 40          | 40         | 40    | 0.0024 |
| 0.70              | 60          | 60         | 60    | 0.0013 |
| 0.80              | 20          | 20         | 20    | 0.0250 |
| 0.80              | 30          | 30         | 30    | 0.0250 |
| 0.80              | 40          | 40         | 40    | 0.0250 |
| 0.80              | 60          | 60         | 60    | 0.0250 |
| 0.90              | 20          | 20         | 20    | 0.0560 |
| 0.90              | 30          | 30         | 30    | 0.1094 |
| 0.90              | 40          | 40         | 40    | 0.1329 |
| 0.90              | 60          | 60         | 60    | 0.1793 |
| 1.00              | 20          | 20         | 20    | 0.2160 |
| 1.00              | 30          | 30         | 30    | 0.3090 |
| 1.00              | 40          | 40         | 40    | 0.3953 |
| 1.00              | 60          | 60         | 60    | 0.5493 |
| 1.10              | 20          | 20         | 20    | 0.4262 |
| 1.10              | 30          | 30         | 30    | 0.5917 |
| 1.10              | 40          | 40         | 40    | 0.7196 |
| 1.10              | 60          | 60         | 60    | 0.8781 |
| 1.20              | 20          | 20         | 20    | 0.6570 |
| 1.20              | 30          | 30         | 30    | 0.8320 |
| 1.20              | 40          | 40         | 40    | 0.9234 |
| 1.20              | 60          | 60         | 60    | 0.9864 |
| 1.30              | 20          | 20         | 20    | 0.8404 |
| 1.30              | 30          | 30         | 30    | 0.9547 |
| 1.30              | 40          | 40         | 40    | 0.9885 |
| 1.30              | 60          | 60         | 60    | 0.9994 |

6 An Example

An inhaled bronchodilators treatments for patients with symptomatic severe and moderate chronic obstructive pulmonary disease (COPD) is the long-term administration of once-daily tiotropium which has been identified as a useful treatment that provides sustained improvements in spirometric and health status [20] and [21]. The once-daily inhaled bronchodilators indacaterol is said to have potential of replacing or as an alternative to existing or the standard tiotropium drug for treatment of patients with moderate to severe COPD. [22], recently conducted non-inferiority clinical trial to compare the bronchodilator efficacy of indacaterol 150$\mu$g ($E_1$) and 300$\mu$g ($E_2$) with an open-label tiotropium 18$\mu$g and a placebo in patients with severe to moderate COPD. The primary endpoint is bronchodilator of efficacy 24-h post-dose (trough) forced expiratory volume in $s(FEV_1$ in mL) after 12 weeks of treatment. The data in Table 3 is a published data obtained from [5]. Note that the sample standard deviations of treatment are somewhat different. A test of equal variance, such as Bartlett test, will reject the equal variances hypothesis at 0.05 level of significance.

From Table 3, we calculate the following values.

$Z_1 = 170, Z_2 = 180, Z_{K+1} = 160$

$Y_1 = 445.3251, Y_2 = 624.2434, Y_0 = 400.9343, Y_{K+1} = 6113650$
Table 3. Trough FEV$_1$ at week 12: changed from baseline (in mL)

| Treatment group | Mean change | Standard deviation | Sample size |
|-----------------|-------------|--------------------|-------------|
| Indacaterol 150µg | 160         | 238                | 346         |
| Indacaterol 300µg | 170         | 285                | 354         |
| Tiotropium      | 150         | 273                | 349         |
| Placebo         | -10         | 213                | 308         |

Hence, the lower confidence bounds for two treatments are given below.

$\theta_{1.0.95} = (0.8775, \infty) \subset \Theta$ significant
$\theta_{2.0.95} = (0.9339, \infty) \subset \Theta$ significant

In Table 3, from our confidence intervals procedures, we assert that, once-daily treatments of indacaterol at 150µg and 300µg are effective doses. Hence we declare that 150µg is the minimum effective indacaterol dose that is not worse than the active control Tiotropium. This conclusion is consistent with [6].

7 Conclusion

Controlling the FWER is a major statistical objective in identifying MED in a pharmaceutical research. We employ stepwise confidence procedure and incorporated the partitioning principle to validate the procedure without multiplicity adjustment. This gives a meaningful guarantee against incorrect decision. Our simulation studies indicate that, the procedure is useful in controlling the FWER for a balanced design than unbalanced design. We observed that, the larger the ratio of mean differences and sample sizes, the larger the power of our procedure.

Competing Interests

Authors have declared that no competing interests exist.

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