A TWO-STAGE PROCEDURE ON COMPARING SEVERAL EXPERIMENTAL TREATMENTS AND A CONTROL—THE COMMON AND UNKNOWN VARIANCE CASE

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This paper introduces a two-stage selection rule to compare several experimental treatments with a control when the variances are common and unknown. The selection rule integrates the indifference zone approach and the subset selection approach in multiple-decision theory. Two mutually exclusive subsets of the parameter space are defined, one is called the preference zone (PZ) and the other, the indifference zone (IZ). The best experimental treatment is defined to be the experimental treatment with the largest population mean. The selection procedure opts to select only the experimental treatment which corresponds to the largest sample mean when the parameters are in the PZ, and selects a subset of the experimental treatments and the control when the parameters fall in the IZ. The concept of a correct decision is defined differently in these two zones. A correct decision in the preference zone (CD_1) is defined to be the event that the best experimental treatment is selected. In the indifference zone, a selection is called correct (CD_2) if the selected subset contains the best experimental treatment. Theoretical results on the lower bounds for $P(CD_1)$ in PZ and $P(CD_2)$ in IZ are developed. A table is computed for the implementation of the selection procedure.

1. Introduction

This study is motivated by the current clinical trials involving protease inhibitors. Since the delta trial pioneered the research in the combination of drugs (e.g., AZT and ddI; AZT and ddC) as an HIV positive treatment, clinicians have experimented with a variety of HIV positive regimens involving different combinations of drugs. Regimens consisting of the combination of protease inhibitors have shown great potential. For instance, studies had shown that triple combination therapy with Saquinavir, Zidovudine, and Lamivudine reduced a mean viral load by 99% in four weeks. Drugs for HIV infection and AIDS are usually classified into two categories: nucleoside analogs and protease inhibitor. Nucleoside analogs constrain HIV replication by incorporation into the elongating strand of DNA and cause chain termination. Protease inhibitors are new drugs that block the action of the viral protease required for protein processing in the viral cycle. Protease inhibitors

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are usually potent and often used with combination of two nucleoside analogs. Nucleoside analogs include zidovudine (ZVD, AZT), dideoxynosine (ddI, didanosine), dideoxycytidine (ddc, zalcitabine), stavudine (D4T), and so forth. Protease inhibitors include saquinavir, indinavir, ritonavir, and so forth. Many of the combinations show promising results. The best-studied regimens include two nucleoside analog reverse transcriptase inhibitors. The different combinations include zidovudine plus lamivudine, zidovudine plus didanosine, zidovudine plus zalcitabine, stavudine plus didanosine, lamivudine plus stavudine, and didanosine plus lamivudine.

Although many of these treatments are evidently better than the traditional treatments (AZT, AZT, and ddI, or AZT and ddC, etc.), the best treatment is still unknown. This situation is difficult for both the HIV-positive patients and the physicians who are responsible for their well-being. In light of the fact that many protease inhibitors are either approved in the USA or are in advanced clinical testing, it is increasingly important to find the best regimen or a subgroup of equally good regimens. Few studies have been done for this objective. The lack of selection procedures which are designed for this purpose partly contributed to the situation. In addition, among those procedures which can be applied for this purpose, few are communicated effectively to the practitioners in the field. The selection procedure studied in this paper is our attempt to partially address this problem.

The organization of this paper is as follows. In Section 2, we give definitions and state the assumptions and the goal. Section 3 presents the selection procedure. Section 4 reveals the main theoretical results; Section 5 comments on the computation of Table 5.1; Section 6 presents an example and Section 7 gives concluding remarks.

2. Definitions, assumptions, and the goal

We assume that the treatments are normally distributed with different means and a common but unknown variance (i.e., population π_i has distribution $N(\mu_i, \sigma^2)$, $i = 0, 1, \ldots, k$). The normal assumption is usually reasonable for HIV clinical trials. The measure of effectiveness of a regimen could be based on the viral load (the amount of virus in the blood stream), CD_4 (the T cell counts), and the clinical symptoms. The effectiveness could be the average of these measurements and thus validate the normal assumption in general.

We order the experimental treatments by their means. The treatment with mean μ_i is defined to be better than a treatment with mean μ_j if μ_i is greater than μ_j. We denote the ascending ordered means as $\mu_{[1]}, \mu_{[2]}, \ldots, \mu_{[k]}$ and use $\pi_{(i)}$ to denote the population associated with mean $\mu_{[i]}$. The best experimental treatment is then the treatment $\pi_{(k)}$ (the treatment associated with the largest population mean $\mu_{[k]}$). We use μ_0 for the mean of the control treatment. We further assume that the best experimental treatment is better than the control (i.e., $\mu_{[k]} > \mu_0$). This assumption is reasonable for HIV clinical trials. Indeed, many studies have shown that some regimens involving protease inhibitors are better than the traditional treatment.

The parameter space is defined to be the set of all possible values of the population means together with the possible values of the unknown variance ($\Sigma = \{(\mu, \sigma) \mid -\infty < \mu_i < \infty,\ i = 0, 1, \ldots, k;\ 0 < \sigma < \infty;\ \mu_{[k]} > \mu_0\}$).

Two subsets of the parameter space are of particular interest. One is the preference zone (PZ) which is defined to be the set $\{\mu \in \Sigma \mid \mu_{[k]} > \mu_{[k-1]} + \delta^*$ and $\mu_{[k]} > \mu_0 + \delta^*\}$.

The other is the indifference zone (IZ) which is defined to be the set $\{\mu \in \Sigma \mid \mu_{[k]} \leq \mu_{[k-1]} + \delta^* \text{ or } \mu_{[k]} \leq \mu_0 + \delta^*\}$. Here $\delta^* > 0$ is a specified constant.

In PZ, we have an outstanding treatment and therefore, our selection rule will insist on selecting only the best treatment. On the contrary, there is no one treatment which stands out in comparison with the other treatments or the control in the IZ. Thus, we select a subset of treatments that are comparable with the control.

The goal of this study is to derive a selection procedure P_c which selects population $\pi_{(k)}$ if $\mu \in$ PZ or selects a random sized subset containing $\pi_{(k)}$ if $\mu \in$ IZ. Since we assume the common variance of the populations is unknown, we use a two-stage selection procedure in which the first stage is used to estimate the unknown variance.

This goal reflects a conservative "don't rock the boat" philosophy. Conservative approaches are often adopted in clinical trials. Regimens involving protease inhibitors, for instance, often develop resistance and even cross-resistance after a patient stops using the drug for a period of time. Switching to a new regimen involving protease inhibitors should take place only when the new regimen is clearly significantly better than the control treatment. Because a failed regimen involving protease inhibitors will reduce the effectiveness of the other regimens involving different protease inhibitors, it will be in the patients best interest to start with the best possible regimen.

We define a correct selection differently in the PZ and the IZ. We call a decision to be correct (CD_1) if our selection rule selects the population associated with $\pi_{(k)}$ when $\mu \in$ PZ. When $\mu \in$ IZ, a correct decision (CD_2) is defined to be the event that the selected subset contains the best population $\pi_{(k)}$.

The probability requirement is defined to be an ordered pair (P_1^*, P_2^*). We say that a selection rule R satisfies a given probability requirement (P_1^*, P_2^*) if $P(CD_1|R) \geq P_1^*$ and $P(CD_2|R) \geq P_2^*$.

The two-stage selection rule proposed in this paper satisfies any given probability requirement (P_1^*, P_2^*) by allocating a sufficiently large sample size. Since this procedure combines selection and screening, the required sample size will be larger than either the indifference zone approach or the subset selection approach. However, our procedures sample size is smaller than the combined sample sizes of both selection procedures. From this point of view, our procedure is more efficient.

3. The selection procedure P_c

We use $\bar{X}_0$ to denote the sample mean of the control regimen and $\bar{X}_{(i)}$ for the experimental sample mean associated with $\mu_{[i]}$, $i = 1, 2, \ldots, k$. The selection rule is formulated as follows.

(1) Take an initial sample of size n_0 from the populations ($n_0 \geq 2$). Denote the observations by X_{ij} and compute

$$\begin{aligned} \bar{X}_i(n_0) &= \sum_{j=1}^{n_0} \frac{X_{ij}}{n_0}, \quad i = 0, 1, \ldots, k, \\ S_i^2(n_0) &= \frac{1}{n_0 - 1} \sum_{j=0}^{n_0} \left(X_{ij} - \bar{X}_i(n_0)\right)^2, \\ S^2 &= \frac{1}{k+1} \sum_{i=0}^{k} S_i^2. \end{aligned} \tag{3.1}$$

(2) Define

$$n = \max\left\{n_0, \left(\frac{Sh}{\delta^* - c}\right)^2\right\}, \tag{3.2}$$

where $h = \max\{h_2, h_3\}$ and h_1, h_2, and h_3 are chosen to satisfy the probability requirement.

(3) Take $(n - n_0)$ additional observations from each population and compute

$$\bar{X}_i = \sum_{j=1}^{n} \frac{X_{ij}}{n}, \quad i = 0, 1, \ldots, k. \tag{3.3}$$

We have $\bar{X}_{[1]} \le \bar{X}_{[2]} \le \cdots \le \bar{X}_{[k]}$.

(4) If $\bar{X}_{[k]} \ge \bar{X}_{[k-1]} + c$ and $\bar{X}_{[k]} \ge \bar{X}_0 + c$, we select the population which corresponds to $\bar{X}_{[k]}$. Otherwise, we select all populations π_i with sample means satisfying $\bar{X}_i \ge \bar{X}_0 - d$.

Here, $\delta^* > c$ and $\delta^* = ac$, $a > 1$ is chosen by the experimenter. $d = h^{-1}h_1(\delta^* - c)$, h_1 is chosen to satisfy the probability requirement.

In this selection procedure, for a specified δ^*, the experimenter has the freedom to select a different size for c by selecting an appropriate value of a. The probability of selecting one best population increases as a increases (i.e., as c decreases). However, the value of d increases as a increases, thus the subset size increases. The tradeoff between selecting one regimen or the size of a subset of regimens subset size is controlled by a.

4. The main theorem

We need to specify n, c, and d such that the procedure P_c will satisfy a given probability requirement (P_1^*, P_2^*). To derive lower bounds for the probability of correct decisions, we first investigate the infimum of $P(\mathrm{CD}_1|P_c)$ in the PZ (denoted as the least favorable configuration, LFC) and $P(\mathrm{CD}_2|P_c)$ in the IZ (denoted as the worst configuration, WC).

The monotonicity of $P(\mathrm{CD}_1|P_c)$ in the PZ is easily seen. Under the assumption that the best experimental treatment is better than the control, the monotonicity of $P(\mathrm{CD}_2|P_c)$ in the IZ can be shown in a similar way to that of Chen [1]. We state the result in the following lemma.

Lemma 4.1. *Given $k+1$ normal populations $N(\mu_i, \sigma^2)$, $i = 0, 1, \ldots, k$, then for any fixed σ,*

$$\begin{aligned} LFC|P_c &= \{\mu \in PZ \mid \mu_{[k]} - \mu_{[i]} = \delta^*,\ \forall i \ne k\}, \\ WC|P_c &= \{\mu \in IZ \mid \mu_{[k]} = \mu_{[i]},\ \forall i \ne k\}. \end{aligned} \tag{4.1}$$

Using Lemma 4.1, we evaluate the lower bounds of the $P(\mathrm{CD}_1|P_c)$ in the PZ and the $P(\mathrm{CD}_2|P_c)$ in the IZ. These bounds are used to compute h_1, h_2, and h_3 which are used to compute c, d, and n. The following is the main theorem of this paper (the proof of the theorem is given in Appendix 7).

Theorem 4.2. *The values of h_1, h_2, and h_3 which simultaneously satisfy*

$$\begin{aligned}
&\int_{-\infty}^{\infty}\int_{0}^{\infty}\Phi^{k+1}\left(z+\frac{h_3}{\sqrt{N}}x\right)f(x)\phi(x)dx\,dz \geq P_1^*,\\
&\frac{1}{k+1}+\int_{-\infty}^{\infty}\int_{0}^{\infty}\Phi^{k-1}(x)\left[\Phi\left(x+\frac{h_1}{\sqrt{N}}y\right)-\Phi(x)\right]dF(y)d\Phi(x)\\
&\quad+(k-1)\int_{-\infty}^{\infty}\int_{0}^{\infty}\Phi^{k-2}(x)\left[\Phi\left(x+\frac{h_2}{(a-1)\sqrt{N}}y\right)-\Phi(x)\right]\Phi\left(x+\frac{h_1}{\sqrt{N}}y\right)dF(y)d\Phi(x)\\
&\quad+(k-1)\int_{-\infty}^{\infty}\int_{0}^{\infty}\Phi^{k-2}(x)\\
&\quad\times\left\{\int_{x}^{x+h_1N^{-1/2}y}\left[\Phi\left(z+\frac{h_2}{(a-1)\sqrt{N}}y\right)-\Phi\left(x+\frac{h_2}{(a-1)\sqrt{N}}y\right)\right]d\Phi(z)\right\}dF(y)d\Phi(x)\\
&\quad+(k-1)(k-2)\int_{-\infty}^{\infty}\int_{0}^{\infty}\Phi^{k-3}(x)\left[\Phi\left(x+\frac{h_2}{(a-1)\sqrt{N}}y\right)-\Phi(x)\right]\\
&\quad\times\left[\int_{-\infty}^{x+h_1N^{-1/2}y}\left\{\int_{z-h_1N^{-1/2}y}^{x}d\Phi(z_k)\right\}d\Phi(z)\right]d\Phi(x)dF(y)\\
&\quad+(k-1)(k-2)\int_{-\infty}^{\infty}\int_{0}^{\infty}\Phi^{k-3}(x)\left[\int_{x}^{\infty}\left\{\int_{x+(h_2/(a-1)\sqrt{N})y}^{z+(h_2/(a-1)\sqrt{N})y}d\Phi(z_i)\right\}d\Phi(z)\right]\\
&\quad\times\left[\int_{-\infty}^{x+h_1N^{-1/2}y}\left\{\int_{z-h_1N^{-1/2}y}^{x}d\Phi(z_k)\right\}d\Phi(z)\right]d\Phi(x)dF(y)\geq P_1^*
\end{aligned}\tag{4.2}$$

are the values for the selection rule P_c to satisfy a given probability requirement (P_1^*, P_2^*). Here Φ and F are the distribution functions for the standard normal and $X=\sqrt{Y}$ variables, respectively; Y has Chi-square distribution with $N=(k+1)(n_0-1)$ degree of freedom.

5. The computation of the tables

The computation of Table 5.1 is carried out using FORTRAN 77. The density functions were programmed using FORTRAN except the normal distribution function which was an IMSL standard function. Integrations were computed using Gaussian quadrature and IMSL subroutines.

There are three parameters in our selection rule that need to be determined, namely, h_1, h_2, and h_3. The parameter h_3 is selected to satisfy the first probability requirement and h_1, h_2 are selected to satisfy the second probability requirement. To simplify the computation, we first find the smallest h_3 that satisfies the first probability requirement. We then set $h_1=h_3$ and search for an $h_2'=h_2(a-1)^{-1}$ value to satisfy the second probability requirement. Table 5.1 was computed for $a=2$. Thus $h_2'=h_2$ and we use the notation h_2 in the table. For other values of a, different tables are necessary. Interested parties can contact the authors to obtain the h_1, h_2, and h_3 values for other values of a.

Table 5.1

Number of Populations: $k = 2$			
Size n_0	Probability (P_2^*)		
	0.90	0.95	0.99
4	h1 = 1.0430 h2 = 2.4464	h1 = 1.5970 h2 = 3.0828	h1 = 3.6850 h2 = 4.5102
5	h1 = 0.8110 h2 = 2.3888	h1 = 1.1830 h2 = 2.9813	h1 = 2.3070 h2 = 4.2545
6	h1 = 0.6860 h2 = 2.3554	h1 = 0.9760 h2 = 2.9232	h1 = 1.7760 h2 = 4.1123
7	h1 = 0.6060 h2 = 2.3336	h1 = 0.8470 h2 = 2.8856	h1 = 1.4790 h2 = 4.0219
8	h1 = 0.5480 h2 = 2.3184	h1 = 0.7580 h2 = 2.8593	h1 = 1.2850 h2 = 3.9595
9	h1 = 0.5050 h2 = 2.3069	h1 = 0.6910 h2 = 2.8398	h1 = 1.1470 h2 = 3.9136
10	h1 = 0.4700 h2 = 2.2982	h1 = 0.6390 h2 = 2.8249	h1 = 1.0420 h2 = 3.8787
15	h1 = 0.3640 h2 = 2.2734	h1 = 0.4850 h2 = 2.7829	h1 = 0.7530 h2 = 3.7816
20	h1 = 0.3080 h2 = 2.2619	h1 = 0.4060 h2 = 2.7634	h1 = 0.6150 h2 = 3.7371
25	h1 = 0.2720 h2 = 2.2553	h1 = 0.3550 h2 = 2.7521	h1 = 0.5320 h2 = 3.7115

Number of Populations: $k = 4$			
Size n_0	Probability (P_2^*)		
	0.90	0.95	0.99
4	h1 = 0.7560 h2 = 2.7700	h1 = 1.5580 h2 = 3.3321	h1 = 15.200 h2 = 4.5234
5	h1 = 0.6220 h2 = 2.7256	h1 = 1.1930 h2 = 3.2590	h1 = 6.0000 h2 = 8.0000
6	h1 = 0.5400 h2 = 2.6996	h1 = 0.9970 h2 = 3.2164	h1 = 5.5500 h2 = 8.0000
7	h1 = 0.4830 h2 = 2.6825	h1 = 0.8720 h2 = 3.1886	h1 = 5.2000 h2 = 5.2000
8	h1 = 0.4410 h2 = 2.6704	h1 = 0.7830 h2 = 3.1689	h1 = 4.6890 h2 = 4.7000
9	h1 = 0.4080 h2 = 2.6614	h1 = 0.7160 h2 = 3.1543	h1 = 4.3150 h2 = 4.5000
10	h1 = 0.3820 h2 = 2.6544	h1 = 0.6630 h2 = 3.1430	h1 = 4.0240 h2 = 4.1054
15	h1 = 0.2990 h2 = 2.6316	h1 = 0.5030 h2 = 3.1112	h1 = 3.1590 h2 = 4.0374
20	h1 = 0.2540 h2 = 2.6254	h1 = 0.4200 h2 = 3.0963	h1 = 2.7460 h2 = 4.0058
25	h1 = 0.2250 h2 = 2.6200	h1 = 0.3680 h2 = 3.0877	h1 = 2.4460 h2 = 3.9877

Table 5.1. Continued.

Number of Populations: $k = 3$			
Size n_0	Probability (P_2^*)		
	0.90	0.95	0.99
4	h1 = 0.8820	h1 = 1.5050	h1 = 17.000
	h2 = 2.6434	h2 = 3.2348	h2 = 4.0000
5	h1 = 0.7140	h1 = 1.1550	h1 = 15.000
	h2 = 2.5929	h2 = 3.1497	h2 = 4.0000
6	h1 = 0.6150	h1 = 0.9660	h1 = 6.1000
	h2 = 2.5635	h2 = 3.1004	h2 = 7.5000
7	h1 = 0.5480	h1 = 0.8430	h1 = 5.8000
	h2 = 2.5442	h2 = 3.0683	h2 = 5.8000
8	h1 = 0.4990	h1 = 0.7560	h1 = 5.6000
	h2 = 2.5306	h2 = 3.0457	h2 = 5.6000
9	h1 = 0.4610	h1 = 0.6910	h1 = 5.1000
	h2 = 2.5204	h2 = 3.0290	h2 = 5.1000
10	h1 = 0.6390	h1 = 0.6390	h1 = 4.7890
	h2 = 2.5126	h2 = 3.0161	h2 = 4.8000
15	h1 = 0.3350	h1 = 0.4860	h1 = 3.7160
	h2 = 2.4905	h2 = 2.9798	h2 = 3.9342
20	h1 = 0.2840	h1 = 0.4070	h1 = 3.1940
	h2 = 2.4802	h2 = 2.9628	h2 = 3.8973
25	h1 = 0.2510	h1 = 0.3570	h1 = 2.8510
	h2 = 2.4772	h2 = 2.9530	h2 = 3.8760

Number of Populations: $k = 5$			
Size n_0	Probability (P_2^*)		
	0.90	0.95	0.99
4	h1 = 0.4730	h1 = 0.6270	h1 = 0.8860
	h2 = 0.8469	h2 = 1.0725	h2 = 1.6450
5	h1 = 0.3980	h1 = 0.5210	h1 = 0.7220
	h2 = 0.6994	h2 = 0.8686	h2 = 1.2742
6	h1 = 0.3490	h1 = 0.4450	h1 = 0.6220
	h2 = 0.6080	h2 = 0.7460	h2 = 1.0651
7	h1 = 0.3150	h1 = 0.4080	h1 = 0.5540
	h2 = 0.5445	h2 = 0.6627	h2 = 0.9289
8	h1 = 0.2890	h1 = 0.3740	h1 = 0.5040
	h2 = 0.4973	h2 = 0.6017	h2 = 0.8322
9	h1 = 0.2690	h1 = 0.3470	h1 = 0.4650
	h2 = 0.4604	h2 = 0.5546	h2 = 0.7594
10	h1 = 0.2530	h1 = 0.3250	h1 = 0.4340
	h2 = 0.4307	h2 = 0.5169	h2 = 0.7022
15	h1 = 0.2000	h1 = 0.2560	h1 = 0.3380
	h2 = 0.3375	h2 = 0.4010	h2 = 0.5323
20	h1 = 0.1710	h1 = 0.2180	h1 = 0.2860
	h2 = 0.2866	h2 = 0.3389	h2 = 0.4448
25	h1 = 0.1510	h1 = 0.1930	h1 = 0.2530
	h2 = 0.2534	h2 = 0.2988	h2 = 0.3869

6. An example

To implement our selection procedure, an experimenter will follow the following steps.

(1) Specify the parameter δ^* and the value $a > 1$ (please note that a is inversely proportional to the value of c, therefore selecting a larger value of a results in a smaller value of c for a selected δ^*. As a result, the chance of selecting only the best population increases, and at the same time, the possible subset size increases).
(2) Compute $c = \delta^*/a$.
(3) Take an initial sample of size n_0 from all populations.
(4) Compute the sample means, sample variances, and the pooled variance.
(5) Find h_1 and h_2 from Table 5.1 and compute $h_2' = (a-1)^{-1}h_2$ (note that $h_2' = h_2$ when $a = 2$) and $h = \max\{h_2', h_3\}$.
(6) Compute $d = h_1 h^{-1}(\delta^* - c)$.
(7) Compute the overall sample size $n = \max\{n_0, [Sh(\delta^* - c)^{-1}]^2\}$.
(8) Take additional samples of size $(n - n_0)$ from each population.
(9) Compute the combined sample mean for each sample. We have

$$\bar{X}_{[1]} \le \bar{X}_{[2]} \le \cdots \le \bar{X}_{[k]}. \tag{6.1}$$

(10) If $\bar{X}_{[k]} \ge \bar{X}_{[k-1]} + c$ and $\bar{X}_{[k]} \ge \bar{X}_0 + c$, we select the population which corresponds to $\bar{X}_{[k]}$. Otherwise, we select all populations π_i with $\bar{X}_i \ge \bar{X}_0 - d$.

The following is an example which illustrates how to use this procedure. Suppose that we want to compare four experimental regimens with a control and we can assume that all regimens have a common variance. Suppose that it is desired to select the regimen with the largest population mean if $\mu_{[4]} - \mu_{[3]} \ge 2$ and $\mu_{[4]} - \mu_0 \ge 2$, and to guarantee that the probability of correctly choosing the best population is at least 0.95. If $\mu_{[4]} - \mu_{[3]} < 2$ or $\mu_{[4]} - \mu_0 < 2$, the experimenter would want to select a random-sized subset in a way that the probability of the chosen subset contains the population having the largest population mean at least 0.95.

In this case, $\delta^* = 2$. If we select $a = 2$, then $c = \delta^* a^{-1} = 1$.

Suppose the experimenter decides to take an initial sample of size $n_0 = 10$. We use MINITAB to generate five random samples of size 10 from the population $N(5, 1.5)$, $N(5.5, 1.5)$, $N(6, 1.5)$, $N(7, 1.5)$, and $N(5.8, 1.5)$ (the control population), respectively. The sample means are

$$\begin{gathered} \bar{X}_1(10) = 5.540, \qquad \bar{X}_2(10) = 4.913, \qquad \bar{X}_3(10) = 6.246, \\ \bar{X}_4(10) = 6.908, \qquad \bar{X}_0(10) = 5.912. \end{gathered} \tag{6.2}$$

The pooled sample variance is $S_p^2 = 2.509$, which is an estimate of σ^2 based on 45 degrees of freedom. Now the experimenter has specified $P_1^* = P_2^* = 0.95$. From Table 5.1 with $k = 4$, $n_0 = 10$, and $P_1^* = P_2^* = 0.95$, the experimenter finds that $h_1 = 0.6630$ and $h_2 = 3.143$. Notice that Table 5.1 is computed assuming that $a = 2$ and $h_2 \ge h_3$.

Therefore, $h = \max\{h_2, h_3\} = h_2 = 3.143$. And

$$d = \frac{0.6630(2-1)}{3.143} = 0.2109. \tag{6.3}$$

Thus,

$$n = \max\left\{10, \left[\frac{\sqrt{2.509}\times 3.143}{2-1}\right]^2\right\} = 25. \tag{6.4}$$

Hence $25 - 10 = 15$ additional observations must be taken from each population. We use MINITAB to generate a second sample of size 15 from populations $N(5, 1.5)$, $N(5.5, 1.5)$, $N(6, 1.5)$, $N(7, 1.5)$, and $N(5.8, 1.5)$, respectively. The overall means are as follows:

$$\begin{gathered} \bar{X}_1(21) = 5.127, \qquad \bar{X}_2(21) = 5.489, \qquad \bar{X}_3(21) = 5.730, \\ \bar{X}_4(21) = 6.838, \qquad \bar{X}_0(21) = 6.019. \end{gathered} \tag{6.5}$$

Since $\bar{X}_{[k]} - \bar{X}_0 = 6.838 - 6.019 = 0.819 < c = 1$, and $\bar{X}_{[k]} - \bar{X}_{[k-1]} = 6.838 - 5.730 = 1.108 > c = 1$, the experimenter will select a subset of good regimens such that $\bar{X}_i > \bar{X}_0 - d = 6.019 - .2109 = 5.808$. Since $\bar{X}_4$ and $\bar{X}_0$ are the only sample means that are greater than 5.808, our procedure selects regimens associated with $\bar{X}_4$ and $\bar{X}_0$.

7. Concluding remarks

Multivariate procedures are seldom used in clinical trials because of the strict conditions they impose (e.g., multivariate normal distribution, etc.). The proposed procedure can be applied to situations when only one measurement variable is compared under different treatment conditions or multiple measurement variables are obtained. When having only one variable, one should check for normality before applying the proposed procedure. In clinical trials, researchers often look at one variable at a time and there is a dominant variable in many studies. When having multiple variables, the proposed procedure requires certain types of averages for these variables. The procedure can be applied when the averages used are normal.

The proposed procedure requires that the populations have common variance. This condition needs to be checked before applying this procedure. It is suggested that clinicians try transformations when normality or common variance assumptions are violated.

Using the result of the main theorem, one can compute the values of (c, d, n) for any given probability requirement. The computation is complicated. One can use FORTRAN to program computation and the IMSL subroutines can be called upon to perform the integrations. The proposed selection procedure can be applied to clinical trials as well as any other applications to compare several experimental treatments with a control when the populations are normally distributed and the variances are common and unknown. The selection of the initial sample size n_0 is important for the accuracy of the procedure. Our suggestion is to select a reasonably large n_0.

The proposed procedure is presented in Table 5.1. We are also currently working on the problem of unknown and unequal variance case.

Appendix

Proof of Theorem 4.2

$$\begin{aligned} P(\mathrm{CD}_1)|P_c) &= P(\bar{X}_{(k)} \geq \bar{X}_{(i)} + c,\ i = 0,1,\ldots,k-1) \\ &\geq \int_{-\infty}^{\infty} E\Phi^k\left(z + \frac{\delta^* - c}{\sigma}\sqrt{N}|S\right) d\Phi(z) \\ &\geq \int_{-\infty}^{\infty} E\Phi^k\left(z + \frac{\delta^* - c}{\sigma} \times \frac{sh_3}{\delta^* - c}|S\right) d\Phi(z) \\ &\geq \int_{-\infty}^{\infty} E\Phi^k\left(z + \frac{h_3}{\sqrt{N}} \times \frac{s}{\sigma} \times \sqrt{N}|S\right) d\Phi(z). \end{aligned} \tag{A.1}$$

Let $Y = \sqrt{N}s\sigma^{-1}$ and $N = (k+1)(n_0 - 1)$, then $Y \sim \sqrt{\chi^2_N}$,

$$P(\mathrm{CD}_1|\mathrm{LFC}) \geq \int_{-\infty}^{\infty}\int_{0}^{\infty} \Phi^{k+1}\left(z + \frac{h_3}{\sqrt{N}}y\right) f(y)\Phi(z)dy\,dz \geq P_1^*. \tag{A.2}$$

To derive the lower bound for $P(\mathrm{CD}_2|P_c)$, we consider the following cases.

Case 1. When $\bar{X}_{(k)}$ is the largest among the experimental treatments, to have a correct selection, we need one of the following:

(1) $\bar{X}_{(k)} > \bar{X}_0$,

(2) $\bar{X}_{(k)} < \bar{X}_0$ and $\bar{X}_{(k)} > \bar{X}_0 - d$.

Case 2. When $\bar{X}_{(k)}$ is the second largest, assuming that $\bar{X}_{(i)}$ is the largest ($i \neq k$), two possible cases for a correct selection are

(1) $\bar{X}_{(i)} < \bar{X}_{(k)} + c$ and $\bar{X}_{(k)} > \bar{X}_0 - d$,

(2) $\bar{X}_{(i)} > \bar{X}_{(k)} + c$, $\bar{X}_{(i)} < \bar{X}_0 + c$, and $\bar{X}_{(k)} > \bar{X}_0 - d$.

Case 3. When $\bar{X}_{(k)}$ is neither the largest nor the second largest, assuming that $\bar{X}_{(i)}$ is the largest and $\bar{X}_{(j)}$ is the second largest ($i, j \neq k$), the two cases of correct selection are

(1) $\bar{X}_{(i)} < \bar{X}_{(j)} + c$ and $\bar{X}_{(j)} > \bar{X}_{(k)} > \bar{X}_0 - d$,

(2) $\bar{X}_{(i)} > \bar{X}_{(j)} + c$, $\bar{X}_{(i)} < \bar{X}_0 + c$, and $\bar{X}_{(j)} > \bar{X}_{(k)} > \bar{X}_0 - d$.

Then $P(\mathrm{CD}_2|P_c)$ can be expressed as

$$P(\mathrm{CD}_2|P_c) = T_{11} + T_{12} + T_{21} + T_{22} + T_{31} + T_{32}, \tag{A.3}$$

where

$$
\begin{aligned}
T_{11} &= P\big(\bar{X}_{(k)} > \bar{X}_{(m)},\ m = 0,1,\ldots,k-1\big),\\
T_{12} &= P\big(\bar{X}_{(k)} > \bar{X}_{(m)},\ m = 1,\ldots,k-1,\ \bar{X}_{(k)} < \bar{X}_0,\ \bar{X}_{(k)} > \bar{X}_0 + d\big),\\
T_{21} &= \sum_{i=1}^{k-1} P\big(\bar{X}_{(i)} > \bar{X}_{(k)} > \bar{X}_{(m)},\ m = 1,2,\ldots,k-1,\\
&\qquad m \neq i,\ \bar{X}_{(i)} < \bar{X}_{(k)} + c,\ \bar{X}_{(k)} > \bar{X}_0 + d\big),\\
T_{22} &= \sum_{i=1}^{k-1} P\big(\bar{X}_{(i)} > \bar{X}_{(k)} > \bar{X}_{(m)},\ m = 1,2,\ldots,k-1,\\
&\qquad m \neq i,\ \bar{X}_{(i)} > \bar{X}_{(k)} + c,\ \bar{X}_{(i)} < \bar{X}_0 + c, \bar{X}_{(k)} > \bar{X}_0 - d\big),\\
T_{31} &= \sum_{i=1}^{k-1} \sum_{j=1, j\neq i}^{k-1} P\big(\bar{X}_{(i)} > \bar{X}_{(j)} > \bar{X}_{(m)},\ m = 1,2,\ldots,k-1,\\
&\qquad m \neq i,j,\ \bar{X}_{(i)} < \bar{X}_{(j)} + c,\ \bar{X}_{(j)} > \bar{X}_{(k)} > \bar{X}_0 - d\big),\\
T_{32} &= \sum_{i=1}^{k-1} \sum_{j=1, j\neq i}^{k-1} P\big(\bar{X}_{(i)} > \bar{X}_{(j)} > \bar{X}_{(m)},\ m = 1,2,\ldots,k-1,\\
&\qquad m \neq i,j,\ \bar{X}_{(i)} > \bar{X}_{(j)} + c,\ \bar{X}_{(i)} < \bar{X}_0 + c,\ \bar{X}_{(j)} > \bar{X}_{(k)} > \bar{X}_0 - d\big).
\end{aligned}
\tag{A.4}
$$

Conditioning on the sample standard deviation S, applying Lemma 4.1 simultaneously to T_{ij}, $i = 1,2,3$; $j = 1,2$, estimating n using (3.2), and choosing d such that $n = (Sh_1d^{-1})^2$, we have the following inequalities simultaneously:

$$
\begin{aligned}
T_{11} &\geq \frac{1}{k+1},\\
T_{12} &\geq \int_{-\infty}^{\infty}\int_{0}^{\infty} \Phi^{k-1}(x)\left[\Phi\left(x + \frac{h_1}{\sqrt{N}}y\right) - \Phi(x)\right] dF(y)\,d\Phi(x),\\
T_{21} &\geq (k-1)\int_{-\infty}^{\infty}\int_{0}^{\infty} \Phi^{k-2}(x)\left[\Phi\left(x + \frac{h_2}{(a-1)\sqrt{N}}y\right) - \Phi(x)\right]\Phi\left(x + \frac{h_1}{\sqrt{N}}y\right) dF(y)\,d\Phi(x),\\
T_{22} &\geq (k-1)\int_{-\infty}^{\infty}\int_{0}^{\infty} \Phi^{k-2}(x) P\Big(x + \frac{h_2}{(a-1)\sqrt{N}}y < Z_{(i)} < Z_0\\
&\qquad\qquad + \frac{h_2}{(a-1)\sqrt{N}}y,\ Z_0 < x + \frac{h_1}{\sqrt{N}}y\Big) dF(y)\,d\Phi(z)\\
&\geq (k-1)\int_{-\infty}^{\infty}\int_{0}^{\infty} \Phi^{k-2}(x)\left\{\int_{x}^{x+(h_1/\sqrt{N})y}\left[\int_{x+(h_2/(a-1)\sqrt{N})y}^{z+(h_2/(a-1)\sqrt{N})y} d\Phi(w)\right] d\Phi(z)\right\} dF(y)\,d\phi(x)\\
&\geq (k-1)\int_{-\infty}^{\infty}\int_{0}^{\infty} \Phi^{k-2}(x)\left\{\int_{x}^{x+(h_1/\sqrt{N})y}\left[\Phi\left(z + \frac{h_2}{(a-1)\sqrt{N}}y\right)\right.\right.\\
&\qquad\qquad \left.\left. - \Phi\left(x + \frac{h_2}{(a-1)\sqrt{N}}y\right)\right] d\Phi(z)\right\} dF(y)\,d\phi(x),
\end{aligned}
$$

$$
\begin{aligned}
T_{31} &\geq (k-1)(k-2)\int_{-\infty}^{\infty}\int_{0}^{\infty}\Phi^{k-3}(x)P\Bigg(x < Z_{(i)} < x + \frac{h_2}{(a-1)\sqrt{N}}y, \\
&\qquad\qquad x > Z_{(k)} > Z_0 - \frac{h_1}{\sqrt{N}}y\Bigg)d\Phi(x)dF(y) \\
&\geq (k-1)(k-2)\int_{-\infty}^{\infty}\int_{0}^{\infty}\Phi^{k-3}(x)\left[\Phi\left(x + \frac{h_2}{(a-1)\sqrt{N}}y\right) - \Phi(x)\right] \\
&\qquad\qquad \times\left[\int_{-\infty}^{x+(h_1/\sqrt{N})y}\left\{\int_{z-(h_1/\sqrt{N})y}^{x} d\Phi(z_k)\right\}d\Phi(z)\right]d\Phi(x)dF(y), \\
T_{32} &\geq (k-1)(k-2)\int_{-\infty}^{\infty}\int_{0}^{\infty}\Phi^{k-3}(x)P\Bigg(Z_0 + \frac{h_2}{(a-1)\sqrt{N}}y > Z_{(i)} > x \\
&\qquad\qquad + \frac{h_2}{(a-1)\sqrt{N}}y,\ x > Z_{(i)} > Z_0 + \frac{h_1}{\sqrt{N}}y\Bigg), \\
d\Phi(x)dF(y) &\geq (k-1)(k-2) \\
&\qquad \times\int_{-\infty}^{\infty}\int_{0}^{\infty}\Phi^{k-3}(x)\left[\int_{x}^{\infty}\left\{\int_{x+(h_2/(a-1)\sqrt{N})y}^{z+(h_2/(a-1)\sqrt{N})y} d\Phi(z_i)\right\}d\Phi(z)\right] \\
&\qquad\qquad \times\left[\int_{-\infty}^{x+(h_1/\sqrt{N})y}\int_{z-(h_1/\sqrt{N})y}^{x} d\Phi(z_k)\,d\Phi(z)\right]d\Phi(x)dF(y).
\end{aligned}
\tag{A.5}
$$

The sample size n is minimum when $n = (hS/(\delta^* - c))^2 = (h_1 S/d)^2$, thus $d = h_1(\delta^* - c)/h$.

References

[1] P. Chen, *On choosing among several experimental treatments and a control*, Biom. J. **36** (1994), no. 6, 709–718.

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