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OPTIMUM DESIGNS FOR SELECTING ONE OF TWO MEDICAL TREATMENTS, FIXED SAMPLE SIZE PLAN 2

By

Masahiko Sugimura

Department of Mathematics and Physics, Kumamoto Women's University
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§1. Introduction.

The present question is that how it is possible to design an optimal clinical trial, when a group of patients with a disease are to be treated with one of the two medical treatments, where the responses (i. e., the therapeutic efficacy) are unknown at least for the one of the two medical treatments.

In the planning of medical experiments to assess the therapeutic efficacy of new drugs or treatments, a most important question is how large to make the trial. On the one hand, one wants as few patients as possible to participate so that the number of patients receiving the inferior treatment during the whole trial is minimized, so that the trial is brought to as speedy a conclusion as possible and so that the results are quickly made available to aid in the treatment of many other patients with the disease in question. On the other hand, one wants as many patients as possible to participate so that the number of patients receiving the superior treatment during the whole trial is maximized, and moreover enough patients must participate in the clinical trial so that one can be reasonably certain that the truly superior treatment is selected and its subsequent use is appropriate.

In this situation, an application of Neyman-Pearson principle will lose a active meaning. As an alternative, it seems reasonable to approach the problem from the point of view of the consequences of decisions maid, i. e., to use a cost function. Therefore, we should like to introduce the concepts of the expected loss or the overall expected loss (obtained by integrating over an a priori distribution for a parameter).

In constructing cost (or loss) functions both the consequences of right and wrong decisions and the costs of experimentation may be considered. But, from an ethical point of view, the consequences of right and wrong decisions are our principal concern and so we shall disregard all other costs and concentrate solely on the consequences of treating a patient with the superior or the inferior of the two treatments.

In the case of one sample a clinical trial will be performed on n of the total N patients by administrating one treatment of which efficacy is unknown. In the case of two samples a clinical trial will be performed on $2n$ of the total patients, n on each treatment. And, in the both cases, the remaining $N-n$ or $N-2n$ patients will receive the one treatment selected as the better at the conclusion of the clinical trial.

The problem of the case of known variance has been solved by T. Colton [1]. In this paper, it will be particularly supposed that the variates denoting the individual responses to each treatment have an unknown variance in the both cases. The problem is to determine the optimum value of a parameter (i. e., a sample size or a sampling proportion for a clinical trial) so that the overall expected loss function constructed on the base of the proposed procedure is minimized.

§2. The Case of One Sample.

In the first place, the problem in case of one sample will be investigated in this section, in which only one of the two treatments will be first administered on the n of the N patients and the one or the other of the two treatments will be secondly administered on the remaining $N-n$ patients following the result of the n observations.

2.1 Assumptions.

The assumptions are prepared throughout this section as follows. These are

(1) There are N patients with a disease who are to be treated with one of the two treatments, and the therapeutic efficacy of the one treatment, denoted by A, is known, while the relative superiority or inferiority of the efficacy of the another treatment, denoted by B, for treatment A is unknown. N is fixed and large.

(2) It is assumed that we obtain a quantitative measure of response for each patient by administrating treatments A and B. Let us denote by μ_A the known quantity of the response due to A. The individual response due to B is a normally distributed variate X_B with unkown mean μ_B and unknown variance σ^2. Moreover, it is assumed that higher response is associated with better effect. Then, letting $\delta=\mu_A-\mu_B$, we should like to select treatment A for the trial if δ is positive and treatment B if δ is negative.

(3) The only cost involved is the consequence of treating a patient with the superior or the inferior of the two treatments, and all other costs may be

disregarded. The cost is directly proportional to the difference δ. Then, the loss formulation states that if a patient is treated with the inferior treatment a positive loss proportional to δ is scored.

(4) The difference δ has an *a priori* normal distribution with zero mean and known variance σ_0^2, that is, $\mu_B=\mu_A-\delta$ has an *a priori* normal distribution with mean μ_A and known variance σ_0^2.

2.2 Procedure.

Perform treatment B on n patients chosen at random from N patients. Compute the observed mean $\bar{x}_B$ and moreover compute the statistic

(2.1) $$\bar{D}=\frac{\bar{x}_B-\mu_A}{\sqrt{\frac{u^2}{n}}},$$

where u^2 is the unbiased estimate for unknown variance σ^2. The statistic

$$\bar{D}=\left\{\frac{\bar{x}_B-(\mu_A-\delta)}{\sqrt{\frac{\sigma^2}{u}}}+\frac{-\delta}{\sqrt{\frac{\sigma^2}{n}}}\right\}\Big/\sqrt{\frac{u^2}{\sigma^2}}$$

is distributed according to a noncentral t-distribution with $n-1$ degrees of freedom and parameter $\delta_0=-\sqrt{n}\,\delta/\sigma$.

Procedure:

If $\bar{x}_B>\mu_A$ (i. e., $\bar{D}>0$), then use B on the remaining $N-n$;

If $\bar{x}_B\leqq\mu_A$ (i. e., $\bar{D}\leqq 0$), then use A on the remaining $N-n$.

2.3 Construction of Overall Expected Loss Function.

From assumption (3) and the above procedure, if treatment B is inferior to A (i. e., $\delta>0$), then the expected loss L_B due to performing B is as follows.

(2.2) $$L_B=C\delta\{n+(N-n)\Pr.(\bar{D}>0)\},$$

where C is a proportionality factor.

For the same reason, if treatment A is inferior to B (i. e., $\delta<0$), then the expected loss L_A due to performing B is as follows.

(2.3) $$L_B=-C\delta(N-n)\Pr(\bar{D}\leqq 0).$$

Thus, integrating (2.2) and (2.3) over an *a priori* distribution for δ, the overall expected loss $\overline{E\text{ Loss}}$ is obtained as follows.

(2.4) $$\overline{E\text{ Loss}}=\int_{-\infty}^{0}L_A\cdot f(\delta)\,d\delta+\int_{0}^{\infty}L_B\cdot f(\delta)\,d\delta$$

$$=-\int_{-\infty}^{0} C\delta(N-n)\Pr(\bar{D}\leqq 0)f(\delta)\,d\delta$$

$$+\int_{0}^{\infty} C\delta\{n+(N-n)\Pr(\bar{D}>0)\}f(\delta)\,d\delta,$$

where $$f(\delta)=(2\pi)^{-\frac{1}{2}}\sigma_0^{-1}\exp\left[-\delta^2/(2\sigma_0^2)\right].$$

Letting $\delta/\sigma_0=z$ and $n/N=p$, the resulting $\overline{E\,\text{Loss}}/CN$ is as follows.

(2.5) $$\overline{E\,\text{Loss}}/NC=\sigma_0\{(2\pi)^{-\frac{1}{2}}-(1-p)\int_{-\infty}^{\infty} z\varphi(z)F_{n-1}(0)\,dz\},$$

where $$\varphi(z)=(2\pi)^{-\frac{1}{2}}\exp[-z^2/2],\ F_{n-1}(0)=\int_{-\infty}^{0} f_{n-1}(t;\delta_0)\,dt$$

and $$f_{n-1}(t;\delta_0)\,dt=\frac{e-\delta_0^2/2}{\sqrt{\pi}\,\Gamma\left(\frac{n-1}{2}\right)}\sum_{k=0}^{\infty}\frac{\delta_0^k}{k!}2^{\frac{k}{2}}\Gamma\left(\frac{n+k}{2}\right)\frac{(t/(n-1)^{\frac{1}{2}})^k}{(1+t^2/(n-1))^{\frac{n+k}{2}}}\frac{dt}{(n-1)^{\frac{1}{2}}}$$

$(\delta_0=-\sqrt{n}\,\sigma_0 z/\sigma)$.

It may be supposed that the number n of the patients chosen at random from the N patients is more than 6, even from the beforementioned ethical point view. Whence, let us suppose that $n\geqq 6$ (i. e., $n-1\geqq 5$) in the following discussions.

Therefore, the next approximate formulae is obtained.

(2.6) $$F(0)\doteqdot\Phi(\delta_0),$$

where $$\Phi(x)=\int_{-\infty}^{x}\varphi(t)\,dt.$$

Therefore, from (2.5) and (2.6), $\overline{E\,\text{Loss}}/NC$ is approximately expressed as follows.

(2.7) $$\overline{E\,\text{Loss}}/NC=\sigma_0\{(2\pi)^{-\frac{1}{2}}-(1-p)\int_{-\infty}^{\infty} z\varphi(z)\Phi(\delta_0)\,dz\}$$

$$=(2\pi)^{-\frac{1}{2}}\sigma_0\left\{1+\frac{(1-p)\sqrt{2Rp}}{\sqrt{1+2Rp}}\right\},$$

where $R=N\sigma_0^2/2\sigma^2$.

2.4 Optimum Value of Parameter *p*.

The problem is to determine the optimum value p^* of p so that $\overline{E\,\text{Loss}}$ of (2.7) is minimized.

Differentiating $\overline{E\,\text{Loss}}$ of (2.7), and equating the derivative to zero gives the quadratic

(2.8) $$4Rp^2+3p-1=0.$$

Solving for p gives

(2.9) $$p^*=\frac{2}{3+\sqrt{9+16R}}.$$

Substituting the p^* of (2.9) into the expression for $\overline{E\text{ Loss}}/NC$ in (2.7) gives

(2.10) $$[\overline{E\text{ Loss}}/NC]_{p^*}=(2\pi)^{-\frac{1}{2}}\sigma_0\left\{1+\frac{1}{4}\left(\frac{64R^2+64R+18-(6+16R)\sqrt{9+16R}}{4R^2+3R+R\sqrt{9+16R}}\right)^{\frac{1}{2}}\right\}.$$

Let us denote by p_0^* the optimum value in the case of two samples where variance σ^2 is known. Eleven values of R are chosen, and p^* and p_0^* are compared for each R.

Table 1. Comparisons of Optimum p

R	0	0. 5	1	2	4	5	10	20	50	100	∞
p_0^*	. 167	. 158	. 152	. 140	. 125	. 119	. 100	. 080	. 057	. 043	0
p^*	. 333	. 281	. 250	. 213	. 173	. 160	. 125	. 095	. 064	. 046	0

From Table 1., it may be concluded that (1) the optimum values p^* in the case of unknown variance are larger than p_0^* in the case of known variance for each R, (2) but the difference $p^*-p_0^*$ approaches zero according as R increases (i. e., σ^2 approaches zero).

§3. The Case of Two Samples.

In this section, the problem in the case of two samples will be investigated, in which a clinical trial will be at first performed on $2n$ of the N individuals, n on each of the two treatments A and B, and secondly the remaining $N-2n$ patients will receive the one treatment selected as the better at the conclusion of the trial.

3.1 Assumptions.

The assumptions are prepared throughout this section as follows. These are

(1) There are N patients with a disease who are to be treated with one of the two treatments, which are unknown on their superiority or inferiority, denoted by A and B. N is fixed and large.

(2) It is assumed that we obtain a quantitative measure of response for each individual. The individual responses to each treatment are respectively normally independently distributed variates x_A, x_B with unknown mean (μ_B for treatment A and μ_B for treatment B) and unknown variance σ^2 (the same for the two treatments). Moreover, we assume that higher response

is associated with better effect. Then, letting $\delta=\mu_A-\mu_B$, we should like t select treatment A for the trial if δ is positive and treatment B if δ negative.

(3) The only cost involved is the consequence of treating a patient with th inferior of two treatments A and B, and all other costs may be disre garded. The loss formulation states that if a patient is treated with th inferior treatment a positive loss proportional to the true mean differenc δ is scored.

(4) The true mean difference δ between the two treatments has an *a prior* normal distribution with zero mean and known variance σ_0^2.

3.2 Procedure.

Perform a clinical trial on $2n$ patients, n on each treatment. Compute th observed difference in sample means, $\bar{d}=\bar{x}_A-\bar{x}_B$ (the notation $\bar{x}_j$ is used to denote the sample mean of the observations given by the j-th treatment where $j=A, B$ Moreover, compute the statistic

$$\bar{D}=\frac{\bar{d}}{\sqrt{\frac{2u^2}{n}}}, \tag{3.1}$$

where u^2 is the unbiased estimate for unknown variance σ^2 $\left(\text{i. e., } u^2=\frac{\sum(x_A-\bar{x}_A)^2+\sum(x_B-\bar{x}_B)^2}{2n-2}\right)$.

The statistic

$$\bar{D}=\left\{\frac{\bar{d}-\delta}{\sqrt{\frac{2\sigma^2}{n}}}+\frac{\delta}{\sqrt{\frac{2\sigma^2}{n}}}\right\}\Big/\sqrt{\frac{u^2}{\sigma^2}}$$

is distributed according to a noncentral t-distribution with $2n-2$ degrees of free dom and parameter $\delta_0=\sqrt{\frac{n}{2}}\cdot\frac{\delta}{\sigma}$.

Procedure:

If $\bar{d}>0$ (i. e., $\bar{D}>0$), then use treatment A on the remaining $(N-2n)$;
If $\bar{d}\leqq 0$ (i. e., $\bar{D}\leqq 0$), then use treatment B on the remaining $(N-2n)$.

2.3 Construction of Overall Expected Loss Function.

The expected loss formulations based on assumption (3) are identical, eve though B is inferior (i. e., $\delta>0$) or A is inferior (i. e., $\delta<0$). Therefore, withou loss of generality we can take δ as positive. We then obtain the expected loss fo all of the N individuals,

(3.2) $$E\text{ Loss} = C\delta\{n+(N-2n)\Pr(\text{Selecting the inferior})\}$$
$$= C\delta\{n+(N-2n)\Pr(\text{Selecting } B)\}$$
$$= C\delta\{n+(N-2n)\Pr(\bar{D}\leqq 0)\},$$

where C is a proportionality factor. Thus, letting $\delta/\sigma_0 = z$ and $n/N = p$, and integrating (3.2) over an *a priori* distribution for z, the overall expected loss $\overline{E\text{ Loss}}$ is obtained as follows.

(3.3) $$\overline{E\text{ Loss}}/NC = \sigma_0\int_{-\infty}^{\infty} z\{p+(1-2p)F_{2n-2}(0)\}\varphi(z)\,dz$$
$$= \sigma_0(1-2p)\int_{-\infty}^{\infty} z\varphi(z)F_{2n-2}(0)\,dz,$$

where $\varphi(z) = (2\pi)^{-\frac{1}{2}}\exp[-z^2/2]$, $F_{2n-2}(0) = \int_{-\infty}^{0} f_{2n-2}(t;\delta_0)$ and

$$f_{2n-2}(t;\delta_0)\,dt = \frac{e^{-\delta_0^2/2}}{\sqrt{\pi}\Gamma(n-1)}\sum_{k=0}^{\infty}\frac{\delta_0^k}{k!}2^{\frac{k}{2}}\Gamma\left(\frac{2n-1+k}{2}\right)\frac{(t/(2n-2)^{\frac{1}{2}})^k}{(1+t^2/(2n-2))^{\frac{2n-1+k}{2}}}\frac{dt}{(2n-2)^{\frac{1}{2}}}.$$

It may be supposed that the number n of the patients chosen at random from the N patients is more than 4, even from the beforementioned ethical point of view. Whence, let us suppose that $n\geqq 4$ (i. e., $2n-2\geqq 5$) in the following discussions.

Thus the next approximate formulae is obtained.

$$F_{2n-2}(0) \doteqdot \Phi(\delta_0) = \Phi\left(\sqrt{\frac{n}{2}}\,\frac{\sigma_0}{\sigma}z\right),\ \text{where } \Phi(\delta_0) = \int_{-\infty}^{\delta_0}\varphi(x)\,dx.$$

Therefore, from (3.3) and (3.4), $\overline{E\text{ Loss}/NC}$ is approximately expressed as follows.

(3.5) $$\overline{E\text{ Loss}}/NC = \sigma_0(1-2p)\int_{-\infty}^{\infty} z\varphi(z)\Phi\left(\sqrt{\frac{n}{2}}\,\frac{\sigma_0}{\sigma}\,z\right)dz$$
$$= (2\pi)^{-\frac{1}{2}}\sigma_0(1-2p)\sqrt{Rp/(1+Rp)},$$

where $$R = (N\sigma_0^2)/(2\sigma^2).$$

3.4. Optimum Value of Parameter p.

The problem is to determined the optimum value p^* of p so that $\overline{E\text{ Loss}}$ of (3.5) is minimized. Differentiating $\overline{E\text{ Loss}}$ of (3.5), and equating the derivative to zero gives the quadratic

(3.6) $$4Rp^2+6p-1=0.$$

Solving for p gives

(3.7)
$$p^*=\frac{1}{3+\sqrt{9+4R}}.$$

The optimum p^* of (3.7) has the same formula as the optimum p_0^* in case that σ^2 is known. But, in the present case, σ^2 is unknown, so that R is also unknown. Whence, the numerical optimum values p^* must be obtained for various actual values of R (i.e., σ^2), like Table 1. in the above section §2.

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