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OPTIMUM DESIGNS FOR SELECTING ONE OF TWO MEDICAL TREATMENTS, FIXED SAMPLE SIZE PLAN 3

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1. Introduction

Our present question is that how it is possible to design an optimal clinical trial, when a total of patients with a disease are to be treated with one of the two medical treatments, where the proportion of the therapeutic efficacy is known for one treatment and while unknown for the other.

In the planning of medical experiments to assess the therapeutic efficacy of new drugs or treatments, a most important question is how larg 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 all the trial is minimized, the clinical trial is brought to as speedy a conclusion as possible, and the results are quickly made available to aid in the treatment of the remainder many 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 all the trial is maximized, and enough patients must participate in a clinical trial so that one can be reasonably certain that the truly superior treatment is selected and its subsequent use is appropriate.

In the situation of this kind, an application of Neyman-Pearson principle will lose an 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. There, we should like to introduce the concepts of the expected loss or the expected net gain (moreover, the overall expected loss or the overall expected net gain obtained by integrating over an *a priori* distribution).

In constructing cost functions both the consequences of right and wrong decisions and the costs of experimentation may are considered. But, from an ethical point of view, the consequences of right and wrong decisions are the principal concern for us and so we should like to 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 this paper, the case of one sample and discrete type (i. e., binomial type) will be investigated. Namely, a clinical trial will be performed on n of the total patients by administrating the one treatment that the proportion of the therapeutic efficacy is unknown, and both efficacious proportions of the considered two treatments are compared by observing the number of the patients that the efficacious resposes due to the one treatment were recognized during n administratings.

Thus, the treatment that was selected as the better at the conclusion of the abovementioned clinical trial will be performed on the remainder all patients. Then, the problem is to determine the optimum value of a parameter (i. e., a sample size or a sampling proportion for the considered clinical trial) so that the overall expected loss function constructed on the base of the proposed procedure is minimized or the overall net gain function is maximized.

2. Assumptions

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

(1) There are N patients with a disease who are to be treated with one of the two treatments. The proportion $\mathfrak{P}_A$ of the therapeutic efficacy of the one treatment, denoted by A, is known, while the proportion $\mathfrak{P}_B$ of the therapeutic efficacy of the another treatment, denoted by B, is unknoun. N is fixed and large.

(2) Let us select at random n patients from the all N patients for a clinical trial and perform the one treatment B on the n patients. Then, denote by n_B a variate representing the number of the patients that the assigned efficacious response was recognized. It is assumed that n_B follows a binomial distribution with parameter (i. e., a population proportion) $\mathfrak{P}_B$ and higher proportion is associated with better (i. e., superior) effect. Then, letting $\delta=\mathfrak{P}_A-\mathfrak{P}_B$, 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. Namely, the loss formulation states that if a patient is treated with the inferior

treatment a positive loss proportional to δ is scored.

(3′) Also, the net gain formulation states that if a patient is treated with the superior treatment a positive gain proportional to the true difference δ is scored, while if treated with the inferior treatment a negative gain proportional to the true difference δ is scored.

(4) Let us denote by $f(\mathfrak{P}_B)$ a probability density function of an *a priori* distribution for $\mathfrak{P}_B$ and by $<\Delta_1, \Delta_2>$ a definite interval for $\mathfrak{P}_B$, where $0<\Delta_1 \leqq \mathfrak{P}_B \leqq \Delta_2 < 1$ and $\Delta_1 \leqq \mathfrak{P}_A \leqq \Delta_2$.

3. Procedure

Perform treatment B on n patients chosen at random from N patients. Count the number n_B of the patients that the assigned effective response was observed on n patients.

If $n_B > n_0$, use treatment B on the remaining $N-n$;
If $n_B \leqq n_0$, use treatment A on the remaining $N-n$,
where $n_0 = n\mathfrak{P}_A$.

The proportion $\mathfrak{P}_A$ of the therapeutic efficacy of the treatment A is known, so that we should like to use the treatment A on the remaining if $n_B = n_0$.

4. 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.

$$L_B = C\delta\{n+(N-n)\Pr(n_B > n_0)\}, \tag{4.1}$$

where C is a proportionality factor.

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

$$L_A = -C\delta(N-n)\Pr(n_B \leqq n_0). \tag{4.2}$$

Thus, integrating (4.1) and (4.2) over an *a priori* distribution for $\mathfrak{P}_B$, the overall expected loss function $\overline{E\text{ Loss}}$ is obtained as follows.

$$\overline{\text{E Loss}} = \int_{\Delta_1}^{\mathfrak{P}_A} L_B f(\mathfrak{P}_B)\, d\mathfrak{P}_B + \int_{\mathfrak{P}_A}^{\Delta_2} L_A f(\mathfrak{P}_B)\, d\mathfrak{P}_B. \tag{4.3}$$

Letting $n/N = a$, $\overline{E\text{ Loss}}/NC$ is given as follows.

$$\text{(4.4)} \quad \overline{E\ \text{Loss}}/NC=\int_{\Delta_1}^{\mathfrak{P}_A}(\mathfrak{P}_A-\mathfrak{P}_B)\{a+(1-a)\Pr(n_B>n_0)\}f(\mathfrak{P}_B)\,d\mathfrak{P}_B$$

$$-\int_{\mathfrak{P}_A}^{\Delta_2}(\mathfrak{P}_A-\mathfrak{P}_B)(1-a)\Pr(n_B\leqq n_0)f(\mathfrak{P}_B)\,d\mathfrak{P}_B$$

$$=\int_{\Delta_1}^{\mathfrak{P}_A}(\mathfrak{P}_A-\mathfrak{P}_B)[a+(1-a)\{1-\Pr(n_B\leqq n_0)\}]f(\mathfrak{P}_B)\,d\mathfrak{P}_B$$

$$-(1-a)\int_{\mathfrak{P}_A}^{\Delta_2}(\mathfrak{P}_A-\mathfrak{P}_B)\Pr(n_B\leqq n_0)f(\mathfrak{P}_B)\,d\mathfrak{P}_B$$

$$=\int_{\Delta_1}^{\mathfrak{P}_A}(\mathfrak{P}_A-\mathfrak{P}_B)f(\mathfrak{P}_B)\,d\mathfrak{P}_B-(1-a)\int_{\Delta_1}^{\Delta_2}(\mathfrak{P}_A-\mathfrak{P}_B)\Pr(n_B\leqq n_0)f(\mathfrak{P}_B)\,d\mathfrak{P}_B.$$

Assumption (4′):

Moreover, we should suppose here upon a uniform probabilily distributio $f(\mathfrak{P}_B)=\dfrac{1}{\Delta_2-\Delta_1}$ about an *a priori* distribution for $\mathfrak{P}_B$ (i. e., assumption (4)).

Then, $\overline{E\ \text{Loss}}/NC$ results in the next formula (4.5).

$$\text{(4.5)} \quad \overline{E\ \text{Loss}}/NC=\frac{1}{\Delta_2-\Delta_1}\Big[\frac{1}{2}(\mathfrak{P}_A-\Delta_1)^2-(1-a)\Big\{\mathfrak{P}_A\sum_{j=0}^{n_0}{}_nC_j\int_{\Delta_1}^{\Delta_2}\mathfrak{P}_B^j(1-\mathfrak{P}_B)^{n-j}\,d\mathfrak{P}_B$$

$$-\sum_{j=0}^{n_0}{}_nC_j\int_{\Delta_1}^{\Delta_2}\mathfrak{P}_B^{j+1}(1-\mathfrak{P}_B)^{n-j}\,d\mathfrak{P}_B\Big\}\Big].$$

Then

$${}_nC_j=\frac{n!}{j!(n-j)!}=\frac{\Gamma(n+1)}{\Gamma(j+1)\Gamma(n-j+1)}=\frac{1}{n+1}\cdot\frac{1}{B(j+1,\ n-j+1)},$$

so that

$$\text{(4.6)} \quad \sum_{j=0}^{n_0}{}_nC_j\int_{\Delta_1}^{\Delta_2}\mathfrak{P}_B^j(1-\mathfrak{P}_B)^{n-j}\,d\mathfrak{P}_B$$

$$=\frac{1}{n+1}\sum_{j=0}^{n_0}\{\int_{\Delta_1}^{\Delta_2}\mathfrak{P}_B^j(1-\mathfrak{P}_B)^{n-j}\,d\mathfrak{P}_B/B(j+1,\ n-j+1)\}$$

$$=\frac{1}{n+1}\sum_{j=0}^{n_0}\{I_{\Delta_2}(j+1,\ n-j+1)-I_{\Delta_1}(j+1,\ n-j+1)\},$$

where $I_x(l,\ m)$ denote an incomplet Beta function.

In the same manner,

$${}_nC_j=\frac{(j+1)}{(n+1)(n+2)}\cdot\frac{\Gamma(n+3)}{\Gamma(j+2)\Gamma(n-j+1)}=\frac{1}{(n+1)(n+2)}\cdot\frac{(j+1)}{B(j+2,\ n-j+1)},$$

so that

$$\text{(4.7)} \quad \sum_{j=0}^{n_0}{}_nC_j\int_{\Delta_1}^{\Delta_2}\mathfrak{P}_B^{j+1}(1-\mathfrak{P}_B)^{n-j}\,d\mathfrak{P}_B$$

$$=\frac{1}{(n+1)(n+2)}\sum_{j=0}^{n_0}(j+1)\{I_{\Delta_2}(j+2,\ n-j+1)-I_{\Delta_1}(j+2,\ n-j+1)\}.$$

Substituting (4.6) and (4.7) into (4.5), we obtain

$$\text{(4.8)}\qquad \overline{E\ \text{Loss}}/NC=\frac{1}{\Delta_2-\Delta_1}\Big[\frac{1}{2}(\mathfrak{P}_A-\Delta_1)^2$$

$$-\frac{(1-a)}{(n+1)(n+2)}\sum_{j=0}^{n_0}\{(n+2)\mathfrak{P}_A\cdot[I_x(j+1,\ n-j+1)]_{\Delta_1}^{\Delta_2}$$

$$-(j+1)[I_x(j+2,\ n-j+1)]_{\Delta_1}^{\Delta_2}\}\Big].$$

5. Construction of Overall Expected Net Gain Function

The expected net gain formulations based on assumption (3) are mutually identical, even though A is superior (i. e., $\delta>0$) or B is superior (i. e., $\delta<0$). Therefore, without loss of generality we can take δ as positive. From assumption (3) and the procedure in section 3, we then obtain the expected net gain E Net Gain for all N individuals.

$$\text{(5.1)}\qquad E\ \text{Net Gain}=-G\delta n+G\delta(N-n)\{\Pr(\text{Selecting }A)-\Pr(\text{Selecting }B)\}$$

$$=-G\delta n+G\delta(N-n)\{2\Pr(\text{Selecting }A)-1\}$$

$$=-G\delta n+G\delta(N-n)\{2\Pr(n_B\leqq n_0)-1\}$$

$$=G\delta\{-N+2(N-n)\Pr(n_B\leqq n_0)\},$$

where G is a proportionality factor.

From assumption (4), integrating (5.1) over an *a priori* distribution for $\mathfrak{P}_B$, the overall expected net gain function $\overline{E\ \text{Net Gain}}$ is obtained as follows.

$$\text{(5.2)}\qquad \overline{E\ \text{Net Gain}}/NG=2(1-a)\int_{\Delta_1}^{\Delta_2}(\mathfrak{P}_A-\mathfrak{P}_B)\Pr(n_B\leqq n_0)f(\mathfrak{P}_B)\,d\mathfrak{P}_B$$

$$-\int_{\Delta_1}^{\Delta_2}(\mathfrak{P}_A-\mathfrak{P}_B)f(\mathfrak{P}_B)\,d\mathfrak{P}_B.$$

From (4.4)

$$\text{(5.3)}\qquad 2(1-a)\int_{\Delta_1}^{\Delta_2}(\mathfrak{P}_A-\mathfrak{P}_B)\Pr(n_B\leqq n_0)f(\mathfrak{P}_B)\,d\mathfrak{P}_B$$

$$=2\int_{\Delta_1}^{\mathfrak{P}_A}(\mathfrak{P}_A-\mathfrak{P}_B)f(\mathfrak{P}_B)\,d\mathfrak{P}_B-2\overline{E\ \text{Loss}}/NC.$$

Substituting (5.3) into (5.2), the connection between $\overline{E\text{ Loss}}/NC$ and $\overline{E\text{ Net Gain}}/NG$ is obtained as follows.

$$(5.4)\qquad \overline{E\text{ Net Gain}}/NG=\int_{\Delta_1}^{\mathfrak{P}_A}(\mathfrak{P}_A-\mathfrak{P}_B)f(\mathfrak{P}_B)\,d\mathfrak{P}_B-\int_{\mathfrak{P}_A}^{\Delta_2}(\mathfrak{P}_A-\mathfrak{P}_B)f(\mathfrak{P}_B)\,d\mathfrak{P}_B$$
$$-2\,\overline{E\text{ Loss}}/NC.$$

Whence, if the probability density function $f(\mathfrak{P}_B)$ of an *a priori* distribution for $\mathfrak{P}_B$ is symmetrical with respect to $\mathfrak{P}_B=\mathfrak{P}_A$, then the connection between $\overline{E\text{ Loss}}/NC$ and $\overline{E\text{ Net Gain}}/NG$ gets to the next simple formula.

$$(5.5)\qquad \overline{E\text{ Net Gain}}/NG=-2\,\overline{E\text{ Loss}}/NC.$$

From assumption (4′) connected with an *a priori* distribution for $\mathfrak{P}_B$ $\overline{E\text{ Net Gain}}/NG$ (5.4) results finally in the next formula.

$$(5.6)\qquad \overline{E\text{ Net Gain}}/NG=\frac{1}{2(\Delta_2-\Delta_1)}\{(\mathfrak{P}_A-\Delta_1)^2+(\Delta_2-\mathfrak{P}_A)^2\}-2\,\overline{E\text{ Loss}}/NC,$$

where $\overline{E\text{ Loss}}/NC$ is equal to (4.8).

6. Numerical Example

It is not analytically feasible to consider the minimization of (4.8) $\overline{E\text{ Loss}}/NC$ with respect to $\mathfrak{P}_B$ by differentiation. Whence the numerical approach adopted is to evaluate $\overline{E\text{ Loss}}/NC$ as given in (4.8) over an assigned value of $a=n/N$ and for a given *a priori* distribution of $\mathfrak{P}_B$, and to choose the minimum by inspection in a certain special case, letting $N=100$, $\mathfrak{P}_A=0.5$.

The five types of *a priori* distribution for $\mathfrak{P}_B$ are chosen as follows in accordance with assumption (4′) and moreover the value of $a=n/N$ of 0.08, 0.10, 0.12, 0.14, 0.16, and 0.18 are considered.

The five types of *a priori* distribution for $\mathfrak{P}_B$.

Type I: $\Delta_1=0.1$, $\Delta_2=0.5$; Type II: $\Delta_1=0.2$, $\Delta_2=0.6$;
Type III: $\Delta_1=0.3$, $\Delta_2=0.7$; Type IV: $\Delta_1=0.4$, $\Delta_2=0.8$;
Type V: $\Delta_1=0.5$, $\Delta_2=0.9$,

where let $N=100$ and $\mathfrak{P}_A=0.5$ for all the types.

The $\overline{E\text{ Loss}}/NC$ in each case is given below.

$\overline{E\ \mathrm{Loss}}/NC$

Type / a	I	II	III	IV	V
0. 08	0. 0241038	0. 0223875	0. 0253713	0. 0255193	0. 0237314
0. 10	0. 0270150	0. 0230373	0. 0238828	0. 0214447	0. 0185248
0. 12	0. 0301452	0. 0242603	0. 0226814	0. 0185301	0. 0150005
0. 14	0. 0335873	0. 0254980	0. 0218367	0. 0163763	0. 0124747
0. 16	0. 0368568	0. 0268820	0. 0213078	0. 0147455	0. 0105838
0. 18	0. 0403671	0. 0283823	0. 0215133	0. 0151114	0. 0091196

By inspecting the above table, the next conclusions are gained. Conclusions;

(1) It seems that when an *a priori* distribution for $\mathfrak{P}_B$ is biased in the left side for $\mathfrak{P}_A=0.5$ (i. e., treatment B is rather inferior to A) $\overline{E\ \mathrm{Loss}}/NC$ decreases as $a=n/N$ decreases and the degree of the decrease of $\overline{E\ \mathrm{Loss}}/NC$ is great as the biase of the distribution from $\mathfrak{P}_A=0.5$ is large. (Types I, II)

(2) While it seems that when an *a priori* distribution for $\mathfrak{P}_B$ is biased in the right side for $\mathfrak{P}_A=0.5$ (i.e., treatment B is rather superior to A) $\overline{E\ \mathrm{Loss}}/NC$ decreases generally as $a=n/N$ increases and the degree of the decrease of $\overline{E\ \mathrm{Loss}}/NC$ is great as the biase of the distribution from $\mathfrak{P}_A=0.5$ is large. (Types IV, V)

(3) Also it may be recognized that when an *a priori* distribution for $\mathfrak{P}_B$ is symmetric for $\mathfrak{P}_A=0.5$ $\overline{E\ \mathrm{Loss}}/NC$ decreases generally as $a=n/N$ increases but the degree of the decrease is rather flat. (Type III)

(4) Note in particular that in the cases of types III and IV the state of decreasing is not monotonious and moreover the minimum value of $\overline{E\ \mathrm{Loss}}/NC$ occurs at $a=n/N=0.16$. Namely, in these types, the optimum value of $a=n/N$ will exist on the neighbourhood of 0.16.

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References

[1] COLTON, T., "A model for Selecting One of Two Medical Treatments", *J. Am. Statist. Assoc.*, **58**, 388-400 (1963).

[2] SUGIMURA, M., "A Preliminary Report on Models for Selecting One of Two Treatments", *J. Kumamoto Women's University*, **18**, 36-49 (1966).

[3] SUGIMURA, M., "Optimum Designs for Selecting One of Two Medical Treatments ——Fixed Sample Size Plan (1)", *Memoirs of the Faculty of General Education, Kumamoto University, Ser. Natural Sciences*, **2** (1967).

[4] SUGIMURA, M., "Optimum Designs for Selecting One of Two Medical Treatments——Fixed Sample Size Plan (2)", *Kumamoto J. Science, Ser.* A, **7**, No. 4 (1967)