OPTIMUM DESIGNS FOR SELECTING ONE OF TWO MEDICAL TREATMENTS SEQUENTIAL PLAN 1

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OPTIMUM DESIGNS FOR SELECTING ONE OF TWO MEDICAL TREATMENTS SEQUENTIAL PLAN 1

By

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§1. Introduction.

Our present question is 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 while unknown for the other.

In the planning of medical experiments to asses the therapeutic efficacy of new treatments, a most important question is how large to make the clinical 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 of the clinical trial is minimized, the clinical trial is brought to as speedy a conclusion as possible, and the results are quickly made available in the treatment of the many remaining 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 of the clinical trial is maximized, and 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 the situation of this kind, an application of Neyman-Pearson principle will lose its 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, moreover the overall expected loss (obtained by averaging over an *a priori* distribution for a parameter).

In constructing cost functions the consequences of both right and wrong decisions and the costs of experimentation may be considered. But, from an ethical point of view, the former are the principal concern for us and so we should like to disregard all other costs and concentrate solely on the consequence of treating a patient with the superior or the inferior of the two treatments.

In this paper, a sequential plan will be proposed in the case of one sample and discrete type (i.e., binomial type). Namely a clinical trial will be sequentially performed on each patient chosen at random one by one from the total patients by administrating the one treatment of which the proportion of the therapeutic efficacy is unknown, and both efficacious proportions of the considered two treatments will be compared by observing the number of the patients with the preassigned efficacious responses due to this particular treatment from the first patient until n-th, and a decision for selecting one of the two treatments will be finally determined as the result. Thus, the treatment that was selected as the better at the conclusion of the beforementioned clinical trial will be performed on the all remaining patients. The problem therefore is to determine the optimum location of the boundaries so that the overall expected loss function constructed on the base of the proposed procedure is minimized.

The sequential plan has already been investigated by T. Colton [4] on the case of two samples and normal type.

At the end of this paper, the optimum values of the location of the boundaries and the overall expected loss will be evaluated in three cases of numerical examples.

In conclusion, the authors wish to express their heartiest thanks to Professor Dr. T. Kitagawa of Kyushu University, for his kind advice and valuable suggestions in connection with this work.

§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 unknown. N is fixed and large.

(2) We suppose that the clinical trial does not call for a fixed number of participants, but it is performed sequentially on each patient chosen at random one by one from all N patients by administrating treatment B. Let us here denote by n_B the cumulative number of the patients with the preassigned efficacious responses from the first patient until the n–th. It is assumed that n_B is binomially distributed with parameter $\mathfrak{p}_B$ 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 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 from the beforementioned ethical point of view. Moreover, it is supposed that the cost is directly proportional

to the true difference δ, that is, in terms of the loss formulation, if a patient is treated with the inferior treatment a positive loss proportional to δ is scored for him.

(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 defined 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.

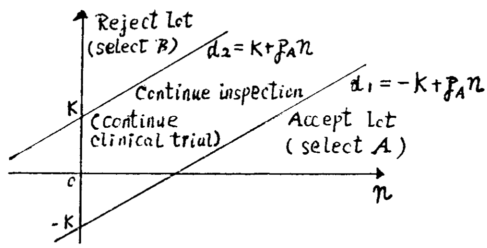
On the basis of the cumulative results that were observed by performing sequentially treatment B on each individual from the first individual until the n–th, a decision is made to select one of the two treatments as the better and use it on all remaining patients or to continue the trial by having an additional individual participant.

Procedure: After the n–th individual,

if $n_B\leqq -K+\mathfrak{p}_A n$, use treatment A on the remaining $(N-n)$;

if $n_B\geqq K+\mathfrak{p}_A n$, use treatment B on the remaining $(N-n)$;

if $-K+\mathfrak{p}_A n<n_B<K+\mathfrak{p}_A n$, continue treatment B with another individual, where K is a parameter and indicates the location of the boudaries that consist of two straight lines parallel mutually. The problem is to determine the parameter K so that the expected loss is minimized.



Let $d_1=-K+\mathfrak{p}_A n$ and $d_2=K+\mathfrak{p}_A n$ briefly.

§4. Construction of Expected Loss Function.

We assume that a decision of selecting one of the two treatments has been made in the n–th stage. Let $L_{\mathfrak{P}_B}$ denote the probability that selects treatment A as the result of the decision made in the beforementioned procedure when the proportion of the efficacy due to treatment B is $\mathfrak{p}_B$. Therefore, $1-L_{\mathfrak{P}_B}$ gives the probability that selects treatment B.

The approximation formula givs

$$L_{\mathfrak{P}_B}=\frac{e^{Kt}}{1+e^{Kt}} \quad \text{and} \quad 1-L_{\mathfrak{P}_B}=\frac{1}{1+e^{Kt}}, \tag{4. 1}$$

where t is any one non-zero real number so that satisfies a relation

$$\mathfrak{p}_B(e^t-1) = e^{\mathfrak{P}_A t}-1,$$

and

$$E_{\mathfrak{P}_B}(n)=\frac{K(2L_{\mathfrak{P}_B}-1)}{\mathfrak{p}_A-\mathfrak{p}_B}, \tag{4. 2}$$

where $E_{\mathfrak{P}_B}(n)$ denotes the A. S. N. (average number of the patients treated in the clinical trial) of the sequential trial and let $E_{\mathfrak{P}_B}(n)=E(n)$ briefly. From assumption (3) and the abovementioned procedure, if treartmet B is inferior to A (i.e., $\delta>0$), then the expected loss $[E\ Loss]_B$ due to performing B becomes as follows.

$$\begin{aligned}(4.\ 3)\qquad [E\ Loss]_B &= C\delta\{E(n)+(N-E(n))P_r(\text{Selecting } B)\}\\ &= C\delta\{E(n)+(N-E(n))(1-L_{\mathfrak{P}_B})\}\\ &= C\delta\{N-(N-E(n))L_{\mathfrak{P}_B}\},\end{aligned}$$

where C denotes a proportionality factor.

In the same reason, if treatment A is inferior to B (i.e., $\delta<0$), then the expected loss $[E\ Loss]_A$ due to performing A becomes as follows.

$$\begin{aligned}(4.\ 4)\qquad [E\ Loss]_A &= -C\delta\{N-E(n)\}P_r(\text{Selecting } A)\\ &= -C\delta\{N-E(n)\}L_{\mathfrak{P}_B}.\end{aligned}$$

Therefore, by averaging over an *a priori* distribution for $\mathfrak{p}_B$, the overall expected loss $\overline{E\ Loss}$ is obtained.

$$\begin{aligned}(4.\ 5)\qquad \overline{E\ Loss}/NC &= \int_{\varDelta_1}^{\mathfrak{P}_A} \delta\Big\{1-\Big(1-\frac{E(n)}{N}\Big)L_{\mathfrak{P}_B}\Big\}f(\mathfrak{p}_B)\,d\mathfrak{p}_B\\ &\quad -\int_{\mathfrak{P}_A}^{\varDelta_2} \delta\Big\{1-\frac{E(n)}{N}\Big\}L_{\mathfrak{P}_B}f(\mathfrak{p}_B)\,d\mathfrak{p}_B.\end{aligned}$$

Assumption (4′); We should like to suppose here upon a uniform probability distribution $f(\mathfrak{p}_B)=\frac{1}{\varDelta_2-\varDelta_1}$ about an *a priori* distribution for $\mathfrak{p}_B$.

Moreover, it may be assumed that $\mathfrak{p}_B=\frac{\mathfrak{p}_A+\varDelta_1}{2}$ for $\delta>0$ and $\mathfrak{p}_B=\frac{\varDelta_2+\mathfrak{p}_A}{2}$ for $\delta<0$ approximately, then $L_{\mathfrak{P}_B}=e^{Kt}/(1+e^{Kt})$ where t is any one non-zero real number so that satisfies a relation $(\mathfrak{p}_A+\varDelta_1)\ (e^t-1)/2=e^{\mathfrak{P}_At}-1$ for $\delta>0$ and a relation $(\varDelta_2+\mathfrak{p}_A)\ (e^t-1)/2=e^{\mathfrak{P}_At}-1$ for $\delta<0$, and then $L_{\mathfrak{P}_B}$ are independent of a parameter $\mathfrak{p}_B$ in both cases.

Thus, if we take into consideration assumption (4′) and the abovementioned approximate condition, then $\overline{E\ Loss}/NC$ results in the next formula (4. 6)

$$\begin{aligned}(4.\ 6)\qquad \overline{E\ Loss}/NC &= \frac{1}{2(\mathfrak{d}_1+\mathfrak{d}_2)}\Big[\mathfrak{d}_1^2\Big\{1-L_1\Big(1-\frac{2K(2L_1-1)}{N\mathfrak{d}_1}\Big)\Big\}\\ &\quad +\mathfrak{d}_2^2\Big\{1+\frac{2K(2L_2-1)}{N\mathfrak{d}_2}\Big\}L_2\Big],\end{aligned}$$

where $\mathfrak{d}_1=\mathfrak{p}_A-\varDelta_1$, $\mathfrak{d}_2=\varDelta_2-\mathfrak{p}_A$, and $L_i=\frac{e^{Kt_i}}{1+e^{Kt_i}}$ $(i=1,\ 2)$ (t_i is any one non-zero real number so that satisfies a relation

$$\frac{\Delta_i + \mathfrak{p}_A}{2}(e^{t_i}-1)=e^{\Delta t_i}-1. \tag{4. 7}$$

Namely,

$$\overline{E\ Loss}/NC=\frac{1}{2(\mathfrak{d}_1+\mathfrak{d}_2)}\left[\mathfrak{d}_1^2\left\{\frac{1}{1+e^{Kt_1}}-\frac{2K}{N\mathfrak{d}_1}\cdot\frac{e^{Kt_1}(1-e^{Kt_1})}{(1+e^{Kt_1})^2}\right\}\right.$$
$$\left.+\mathfrak{d}_2^2\left\{\frac{e^{Kt_2}}{1+e^{Kt_2}}-\frac{2K}{N\mathfrak{d}_2}\cdot\frac{e^{Kt_2}(1-e^{Kt_2})}{(1+e^{Kt_2})^2}\right\}\right]. \tag{4. 8}$$

For the sake of determinating the optimum value K^* of the parameter K so that $\overline{E\ Loss}/NC$ of (4. 8) is minimized, we should like to differentiate (4. 8) and set this derivative equal to zero. Therefore the next relation is obtained.

$$\mathfrak{d}_1\{N\mathfrak{d}_1t_1e^{kt_1}(1+e^{Kt_1})+2e^{Kt_1}(1-e^{2Kt_1})+2Kt_1e^{Kt_1}(1-3e^{Kt_1})\}/(1+e^{Kt_1})^3$$
$$=\mathfrak{d}_2\{N\mathfrak{d}_2t_2e^{Kt_2}(1+e^{Kt_2})-2e^{Kt_2}(1-e^{2Kt_2})$$
$$-2Kt_2e^{Kt_2}(1-3e^{Kt_2})\}/(1+e^{Kt_2})^3. \tag{4. 9}$$

Compute the values t_i obtained from (4. 7) for the given values Δ_1, Δ_2, and $\mathfrak{p}_A$. Secondly, substitute the above t_i for (4. 9) and numerically work at an equation (4. 9) with regard to K. Thus the optimum value K^* of the parameter K so that $\overline{E\ Loss}/NC$ of (4. 8) is minimized will be determined.

§5. Numerical Example.

In the first place two special cases are considered as the numerical examples in accordance with assumption (4′), that is, the case [1°] of the probability density function $f(\mathfrak{p}_B)=\frac{1}{0.5-\Delta_1}$ and the case [2°] of the probability density function $f(\mathfrak{p}_B)=\frac{1}{\Delta_2-0.5}$. Let us $N=100$, $\mathfrak{p}_A=0.5$ in both cases.

Case [1°]: From (4. 8)

$$\overline{E\ Loss}/NC=\frac{\mathfrak{d}_1}{2}\left\{\frac{1}{1+e^{Kt_1}}-\frac{2K}{N\mathfrak{d}_1}\cdot\frac{e^{Kt_1}(1-e^{Kt_1})}{(1+e^{Kt_1})^2}\right\}, \tag{5. 1}$$

and from (4. 9)

$$-\frac{N}{2}\mathfrak{d}_1t_1-1=K\left(1-\frac{4e^{Kt_1}}{1+e^{Kt_1}}\right)t_1-e^{Kt_1}, \tag{5. 2}$$

where $\mathfrak{d}_1=0.5-\Delta_1$.

The various values of Δ_1 are considered as follows, $\Delta_1=0$, .05, .10, .15, .20, .25, .30, .35, .40, .45, .46, .47, .48, and .49. The computed values of K^* and the values of $[\overline{E\ Loss}/NC]_{K^*}$ for K^* are given at Tab. 1.

Table 1. The optimum K^* and $[\overline{E\ Loss}/NC]_{K^*}$
$N=100$, $\Delta_2=\mathfrak{p}_A=0.5$

Δ_1	0	.05	.10	.15	.20	.25	.30
$(\Delta_1+\mathfrak{p}_A)/2$	.25	.275	.3	.325	.35	.375	.4
K^*	1.73	1.83	1.91	1.99	2.05	2.07	2.04
$[\overline{E\ Loss}/NC]_{K^*}$	.02240	.02309	.02455	.02597	.02721	.02797	.02768
Δ_1	.35	.40	.45	.46	.47	.48	.49
$(\Delta_1+\mathfrak{p}_A)/2$	.425	.45	.475	.48	.485	.49	.495
K^*	1.91	1.64	1.07	.90	.70	.49	.25
$[\overline{E\ Loss}/NC]_{K^*}$	.02554	.02050	.01180	.00963	.00733	.00495	.00250

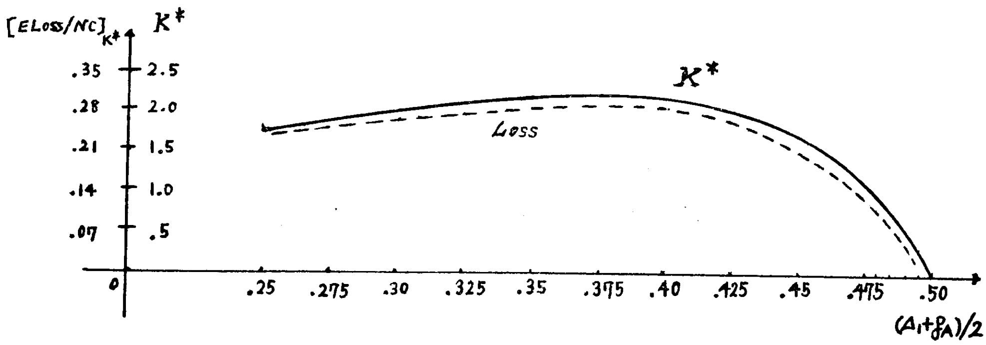


Figure 1. Curves of K^* and $[\overline{E\ Loss}/NC]_{K^*}\times 10$

Case [2°]: From (4. 8),

(5. 1′) $$\overline{E\ Loss}/NC=\frac{\mathfrak{d}_2}{2}\left\{1-\frac{2K}{N\mathfrak{d}_2}\cdot\frac{1-e^{Kt_2}}{1+e^{Kt_2}}\right\}\frac{e^{Kt_2}}{1+e^{Kt_2}},$$

and from (4. 9)

Table 2. The optimum K^* and $[\overline{E\ Loos}/NC]_{K^*}$
$N=100$, $\Delta_1=\mathfrak{p}_A=0.5$

Δ_2	.52	.53	.54	.55	.56	.58	.60
$(\mathfrak{p}_A+\Delta_2)/2$	.51	.515	.52	.525	.53	.54	.55
K^*	23.95	16.65	13.19	11.25	10.25	8.88	8.49
$[\overline{E\ Loss}/NC]_{K^*}$	.00128	.00190	.00216	.00238	.00236	.00219	.00207
Δ_2	.65	.70	.75	.80	.85	.90	1.00
$(\mathfrak{p}_A+\Delta_2)/2$	.575	.60	.625	.65	.675	.70	.75
K^*	9.29	11.23	13.09	15.81	18.19	20.59	25.46
$[\overline{E\ Loos}/NC]_{K^*}$	.00035	.00001	0	0	0	0	0

(5. 2′) $$\frac{N}{2}\mathfrak{d}_2 t_2 - 1 = K\left(1-\frac{4e^{Kt_2}}{1+e^{Kt_2}}\right)t_2 - e^{Kt_2},$$

where $\mathfrak{d}_2 = \Delta_2 - 0.5$.

The various values of Δ_2 are considered as follows, Δ_2=.52, .53, .54, .55, .56, .58, .60, .65, .70, .75, .80, .85, .90, and 1. The computed values of K^* and the values of $[\overline{E\ Loss}/NC]_{K^*}$ for K^* are given at Tab. 2.

(In Tab. 2 $[\overline{E\ Loss}/NC]_{K^*}$ are computed by neglecting the term that contains N.)

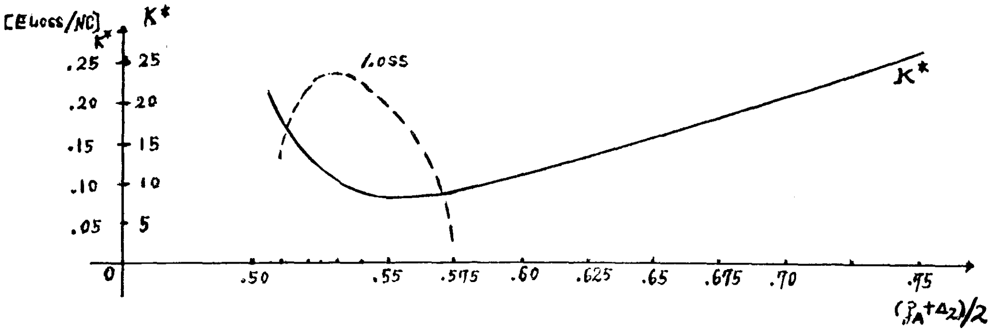


Figure 2. Curves of K^* and $[\overline{E\ Loss}/NC]_{K^*}\times 100$

At the end of this paper, the third case [3°] is considered as more general example than the cases [1°] and [2°] in accordance with assumption (4′).

Case [3°]: Let us $N=100$, $\mathfrak{p}_A=0.5$ like the cases [1°] and [2°], and $f(\mathfrak{p}_B)=\frac{1}{\Delta_2-\Delta_1}$ where $\Delta_2-0.5=0.5-\Delta_1$ (i.e., $\frac{\Delta_2+\Delta_1}{2}=0.5=\mathfrak{p}_A$).

From (4. 8)

(5. 3) $$\overline{E\ Loss}/NC = \frac{\mathfrak{d}}{4}\left\{\frac{1}{1+e^{Kt_1}} - \frac{2Ke^{Kt_1}(1-e^{Kt_1})}{N\mathfrak{d}(1+e^{Kt_1})^2} + \frac{e^{Kt_2}}{1+e^{Kt_2}} - \frac{2Ke^{Kt_2}(1-e^{Kt_2})}{N\mathfrak{d}(1+e^{Kt_2})^2}\right.,$$

where

$$\mathfrak{d} = \Delta_2 - 0.5 = 0.5 - \Delta_1,$$

and from (4. 9)

(5. 4) $$\{N\mathfrak{d}t_1e^{Kt_1}(1+e^{Kt_1}) + 2e^{Kt_1}(1-e^{2Kt_1}) + 2Kt_1e^{Kt_1}(1-3e^{Kt_1})\}/(1+e^{Kt_1})^3$$
$$= \{N\mathfrak{d}t_2e^{Kt_2}(1+e^{Kt_2}) - 2e^{Kt_2}(1-e^{2Kt_2}) - 2Kt_2e^{Kt_2}(1-3e^{Kt_2})\}/(1+e^{Kt_2})^3.$$

The verious values of $<\Delta_1, \Delta_2>$ are considered as follows, $<\Delta_1, \Delta_2>$ = $<0, 1>$, $<.05, .95>$, $<.10, .90>$, $<.15, .85>$, $<.20, .80>$, $<.25, .75>$,

<.30, .70>, <.35, .65>, <.40, .60>, <.45, .55>, <.46, .54>, <.47, .53>, <.48, .52>, and <.49, .51>.

The values of K^* that are numerically computed from (5. 4) and the values of $[\overline{E\ Loss/NC}]_{K^*}$ for K^* are given at Tab. 3.

The curves of K^* and $[\overline{E\ Loss/NC}]_{K^*}\times 10$ for each value of Δ_1 are given at Fig. 3.

Table 3. The optimum K^* and $[\overline{E\ Loss/NC}]_{K^*}$

$N=100,\ \mathfrak{p}_A=0.5=\frac{\Delta_1+\Delta_2}{2}$.

$<\Delta_1, \Delta_2>$	<0, 1>	<.05, .95>	<.10, .90>	<.15, .85>	<.20, .80>	<.25, .75>	<.30, .70>
$\mathfrak{d}$	.50	.45	.40	.35	.30	.25	.20
K^*	2.09	2.25	2.42	2.60	2.80	3.01	3.23
$[\overline{E\ Loss/NC}]_{K^*}$	.01254	.01353	.01459	.01572	.01690	.01803	.01886
$<\Delta_1, \Delta_2>$	<.35, .65>	<.40, .60>	<.45, .55>	<.46, .54>	<.47, .53>	<.48, .52>	<.49, .51>
$\mathfrak{d}$	.15	.10	.05	.04	.03	.02	.01
K^*	3.42	3.57	3.64	3.66	3.70	3.78	4.22
$[\overline{E\ Loss/NC}]_{K^*}$	.01871	.01639	.01038	.00866	.00677	.00470	.00246

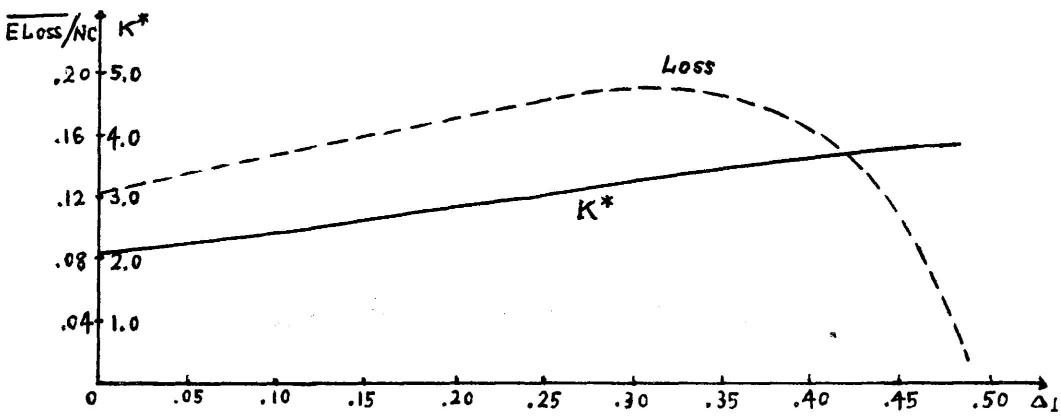


Figure 3. Curves K^* and $[\overline{E\ Loss/NC}]_{K^*}\times 10$

In our sequential method,

(1) When treatment B is inferior to treatment A (i.e., case [1°]), the distance $2K^*$ between an acceptance straight line and a rejection straight line is rather short and the distance approaches zero little by little as the difference $\mathfrak{p}_A-\mathfrak{p}_B$ decreases. This seems to show that when there is little difference between the efficacies of the two treatments, whichever treatment one may select there is no great difference between both decisions.

(2) While, when treatment B is superior to A (i.e., case [2°]), the distance $2K^*$ becomes long as the difference $\mathfrak{p}_B-\mathfrak{p}_A$ approaches zero or

becomes large. This seems to show that when treatment B is greatly superior to treatment A a continuity of tremtment B is advisable rather than performing a decision of selecting A or B.

(3) In the case [3°], the distance $2K^*$ between an acceptance line and a rejection line increases about twofold from 4.18 until 8.44 as the interval $<\Delta_1, \Delta_2>$ of the distribution decreases from $<0, 1>$ until $<0.49, 0.51>$, while $[\overline{E\ Loss/NC}]_{K^*}$ increases little by lIttle as the interval $<\Delta_1, \Delta_2>$ decreases from $<0, 1>$ until $<0.25, 0.75>$ and $[\overline{E\ Loss/NC}]_{K^*}$ gains the maximum value 0.01886 at $<0.30, 0.70>$ and decreases rapidly to zero as $<\Delta_1, \Delta_2>$ decreases from $<0.35, 0.65>$.

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