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OPTIMAL DESIGNS FOR CLINICAL TRIALS IN STAGES

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Abstract

Consider designing a clinical trial in stages; say there are r stages and a total of N patients in the trial. There are two treatments available for use with any of the patients in the trial. Responses are dichotomous. The objective is to maximize the expected number of successes in the trial. The decision problem is to choose a number of patients to allocate to the next stage and to decide how the two treatments should be allocated within this stage as a function of N, r and the current information. Information is updated via Bayes theorem after each stage, and all available information is used in determinng the design for the next stage. Responses from selections in previous stages are available and can be considered, but responses in the current stage are not available until the selections are to be made for the next stage. We show that optimal designs have certain monotonicity properties and characterize the class of optimal strategies for particular N, r and prior distributions.

1. Introduction. In a clinical trial, each patient is assigned to a treatment from the set of treatments under consideration. The assignments are usually made randomly according to some predetermined probability distribution. A large literature concerns sequential

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allocations, assuming that outcomes of previously treated patients are known when the current patient arrives—see Feldman (1962), Rodman (1978), Gittins (1979), Whittle (1980), Bather (1981), Berry and Fristedt (1985) and Simons (1986). This assumption may not be realistic; for example, responses may be delayed, or continual updating may not be possible logistically.

A more realistic assumption is that patient responses are not available immediately but are available in batches or intermittently. Canner (1970), Pocock (1977), Berry & Pearson (1985), Witmer (1986), Thall, Simon, Ellenberg & Shrager (1988), Simon (1989) and Lan & DeMets (1989) consider stagewise selection: all allocations are made simultaneously for the next m patients on the basis of the currently available information.

We consider two treatments, labeled 1 and 2, and dichotomous responses: success and failure. The probabilities of success are ρ and λ. The total number N of patients is arbitrary. These N patients will be treated in a fixed number r of groups (or stages). There are two possible interpretations for N. First, the clinical trial contains all N patients. Second, N is the total number of patients with the disease or condition in question who will be treated with treatment 1 or 2, only some of whom—namely, n, will be in a "clinical trial." In any case, the objective is to maximize *worth*—the overall expected rate of successes among the N patients.

When deciding how many patients to assign to treatment 1 and how many to treatment 2 at a particular stage, responses from selections in previous stages are available and can be considered. However, responses in the current stage are not available until selections are to be made for the next stage.

Using standard terminology, this is a *bandit problem* and treatments are *arms*. Bandit problems involve choosing one from among a set of experiments to observe at each of a number of decision epochs. The language of clinical trials is appealing and the corresponding literature is large, but there are other areas of applications, for example, in an industrial setting, the available experiments are machines or processes.

Pocock (1977) suggested a group sequential design dividing patient entry into a number of equally sized groups. The decision to stop the trial or continue is based on repeated significant tests. Improvements in group sequential procedures from a frequentist perspective allow for groups of arbitrary size [Lan and DeMets (1989)]. There are some advantages to having equally sized groups, and one may reasonably

choose such a design. But we will argue that for the objective we consider, such a design does not come close to maximizing the expected rate of successes over the course of the trial.

In this paper we assume that λ, the probability of success on arm 2, is known and that ρ, the probability of success on arm 1, is unknown (or rather, not completely known). We take a Bayesian approach and regard ρ to be random. Information concerning arm 1 is formulated in terms of a prior distribution, F, on ρ. Observations from the same arm are exchangeable. The pattern of information is $(N, (F, \lambda), r)$ and we call this problem the $(N, (F, \lambda), r)$-bandit.

The optimal allocation avoids the known arm, arm 2, until the last stage. We find that the optimal length (number of subjects) of the first stage has rate $\sqrt{N}$ as $N \to \infty$ when F has a *beta* distribution and λ is rational. We also discuss the magnitude of this rate.

We prove that when there are two stages, and F is not a beta distribution, the rate of the optimal length of the first stage will be no greater than $\sqrt{N}$, if F has a "smooth" density function. Furthermore, if $r = 2$ and the support of F excludes λ, then the rate of optimal length in the first stage cannot be greater than $\log N$.

When $r > 2$, we are faced with choosing the optimal lengths for the second stage, third stage and so on. These are random variables that depend on the observations from the previous stages. We discuss some properties of optimal lengths. When $r = 3$ and the prior is *beta* (a,b), we use tables, computed by backwards induction, to show that the rate of optimal length in the first stage is $\sqrt[3]{N}$.

2. Some notation. If $r = 2$, the expected worth of assigning n_1 observations to arm 1 and n_2 to arm 2 in the first stage is

$$\begin{aligned} & W_2(N, (n_1, n_2), (F, \lambda)) \\ &= \frac{1}{N}\{n_1 E(\rho \mid F) + n_2\lambda \\ &\quad + (N - n_1 - n_2) E\{E[\rho \mid (S_1, n_1 - S_1, F)] \vee \lambda\}\}, \end{aligned}$$

where $(S_1, n_1 - S_1, F)$ is the posterior distribution of ρ given S_1 successes and $n_1 - S_1$ failures on arm 1 under prior F. The value of the $(N, (F, \lambda), 2)$-bandit is

(1)
$$V_2(N, (F, \lambda)) = \max_{\substack{0 \le n_1, n_2 \le N \\ n_1 + n_2 \le N}} W_2(N, (n_1, n_2), (F, \lambda)).$$

If n_1 and n_2 achieve the maximum in (1), then n_i is an optimal length for arm i in the first stage.

For any $r = 2, 3, \ldots$ the worth of assignment (n_1, n_2) in the first stage is

$$\begin{aligned} & W_r(N, (n_1, n_2), (F, \lambda)) \\ &= \frac{1}{N}\left[n_1 E(\rho|F) + n_2\lambda\right] \\ &\quad + \frac{N - n_1 - n_2}{N} E\left\{V_{r-1}(N - n_1 - n_2, ((S_1, n_1 - S_1, F), \lambda))\right\} \end{aligned}$$

and the value of the $(N, (F, \lambda), r)$-bandit is

$$V_r(N, (F, \lambda)) = \max_{\substack{0 \le n_1, n_2 \le N \\ n_1 + n_2 \le N}} W_r(N, (n_1, n_2), (F, \lambda))$$

with $V_1(N, (F, \lambda)) = E(\rho|F) \vee \lambda$.

3. General results. Berry and Pearson (1985) proved that for all $N \ge 2$, there exists an n, $0 \le n < N$, such that $(n, 0)$ is an optimal allocation. The proof of this result is based on the idea that allocation $(n_1, 0)$ cannot be worse than allocation (n_1, n_2), and it is usually better. We restrict consideration to allocations of the form $(n, 0)$.

If there is an n and an i, $0 \le i \le n$, such that (i, n, F) is degenerate then arm 1 may become known after a finite number of observations. When this happens, the better arm will be clear. The following is an example.

EXAMPLE 3.1. If $F = 0.5\delta_0 + 0.5\delta_1$ (that is, ρ has a symmetric two-point distribution on $\{0, 1\}$), then we will learn the value of ρ after but one observation: $P(\rho = 1|(1, 0, F)) = 1$ and so $E(\rho|(1, 0, F)) = 1$, and $E(\rho|(0, 1, F)) = 0$. Obviously, arm 1 should be selected for all $N-1$ observations remaining after a success and arm 2 should be selected for all $N - 1$ observations remaining after a failure.

An unknown arm 1 can become a known arm after a finite number of observations only when $P\{\rho \in \{0, 1\}|F\} = 1$ or $P\{\rho \in \{0, x, 1\}|F\} = 1$ for some $x \in (0, 1)$. The complementary case is more interesting. We will study the case in which (i, n, F) is not degenerate for any positive integer n and $0 \le i \le n$. In this case, the support of F contains at least two interior points in the unit interval.

Define

$$d(n, F, \lambda) = E\{E[\rho|(S, n-S, F)] \vee \lambda\}.$$

When the support of F contains at least two interior points in $(0,1)$, $d(n, F, \lambda)$ is nondecreasing in n for given F and λ. This follows from Jensen's inequality.

Pearson (1980) proved that $lim_{n\to\infty} d(n, F, \lambda) = E(\rho \vee \lambda|F)$. He adapted a portion of Berk's (1966) proof of a similar result. Pearson also proved that the smallest optimal length of the first stage, $n_1(N, F, \lambda, 2)$, is nondecreasing in N.

A greater number of observations in the first stage enables more informed inferences in the second stage. This is an advantage. But more observations in the first stage means fewer observations in the second stage. This is a disadvantage since there is more potential for payoff in the second stage. The optimal allocation is a compromise between these competing considerations.

In view of above results, it is immediate that for any (F, λ),

$$\lim_{N\to\infty} V_2(N, (F, \lambda)) = E(\rho \vee \lambda|F),$$

and when the support of F contains at least two interior points of $(0,1)$,

$$P(\rho > \lambda|F) > 0,$$

$$P(\rho < \lambda|F) > 0,$$

$$\lim_{N\to\infty} n_1(N, F, \lambda, 2) = \infty,$$

and

$$\lim_{N\to\infty} \frac{n_1(N, F, \lambda, 2)}{N} = 0,$$

where $n_1(N, F, \lambda, 2)$ is the smallest optimal length in the first stage. This implies that equal stage lengths are not optimal. Moreover, the difference between the worth functions under the optimal length and equal length is asymptotically $[E(\rho \vee \lambda|F) - E(\rho|F)]/2$.

4. Main result, two stages. If F is a *beta* (a,b) distribution with $a > 0$, $b > 0$, then the rate of optimal length is determined, and in particular, λ, a and b do not affect the rate. On the other hand, these parameters do affect the magnitude. We can prove [Cheng and Berry (1992)] that when λ is rational,

$$\liminf_{N\to\infty} \frac{n_1(N, beta(a,b), \lambda, 2)}{\sqrt{N}} > 0,$$

$$\limsup_{N\to\infty} \frac{n_1(N, beta(a,b), \lambda, 2)}{\sqrt{N}} < \infty,$$

and if λ is irrational then

(2)

$$\limsup_{N\to\infty} \frac{n_1(N, beta(a,b), \lambda, 2)}{\sqrt{N}} < \infty.$$

Moreover, simulation results show that $n_1(N, beta(a,b), \lambda, 2)$ is nondecreasing in a for given b, λ and N. Also it is nonincreasing in b for given a, λ and N (see tables in next section). The intuition is not obvious. Consider increasing a in which case the probability of success with arm 1 increases. [Indeed, the probability of any number of immediate successes with arm 1 also increases.] So using arm 1 becomes more appealing—recall that in the first stage, arm 1 is used exclusively.

We also believe that

$$\liminf_{N\to\infty} n_1(N, beta(a,b), \lambda, 2)/\sqrt{N} > 0$$

when λ is irrational. However, we cannot prove this inequality so far.

Does there exist a prior distribution for which the rate of the optimal first-stage length is less than $\sqrt{N}$? That is, is

$$\liminf_{N\to\infty} n_1(N, F, \lambda, 2)/\sqrt{N} = 0?$$

The answer is yes. If the support of F excludes λ, then

$$\limsup_{N\to\infty} n_1(N, F, \lambda, 2)/\log N < \infty$$

(see Cheng and Berry, 1992). Moreover, in this case let us define the distance between the two arms to be $\inf\{|x-\lambda| : x \in$ the support of $F\}$. The optimal first-stage length is nonincreasing in the distance between the two arms.

The following example concerns the magnitude.

EXAMPLE 4.1. Let F =beta(a,b) and $\lambda = 0.5$. We find that

$$\limsup_{N\to\infty} \frac{n_1(N, beta(a,b), \lambda, 2)}{\sqrt{N}}$$

$$\leq \left\{ \frac{1}{2^{a+b}\beta(a,b)[E(\rho \vee \lambda | beta(a,b)) - E(\rho | beta(a,b))]} \right\}^{\frac{1}{2}},$$

$$\liminf_{N\to\infty} \frac{n_1(N, beta(a,b), \lambda, 2)}{\sqrt{N}}$$

$$\geq \left\{ \frac{1}{2^{a+b+1}\beta(a,b)[E(\rho \vee \lambda | beta(a,b)) - E(\rho | beta(a,b))]} \right\}^{\frac{1}{2}}.$$

Therefore, for each given a and b, we may compute the asymptotic upper and lower bounds for the optimal length. The lower bound differs from the upper bound by a factor of $1/\sqrt{2}$.

5. Main result, more than two stages. Consider general r. Optimal allocations for stages 2 through $r-1$ are random since they depend on the results from previous stages. Optimal lengths can be found by dynamic programming. But the focus can reasonably be on the length of the first stage. The decision problem at the current stage is the same as for the first stage, except that F, r and N change from one stage to the next. For instance, stage i, $1 < i < r$, is the first stage of an $(r-i+1)-$stage problem with the current distribution updated based on the previous results. The new bandit problem is $(N^{\{i\}}, (F^{\{i\}}, \lambda), r-i+1)$ where $N^{\{i\}}$ equals N − number of observations in the previous $i-1$ stages; $F^{\{i\}}$ is the conditional distribution of ρ given the results from the previous $i-1$ stages. For the same reason as when $r = 2$, the optimal allocation in the first stage is of the form $(n_1, 0)$. For the $(N, (F, \lambda), r)$-bandit, let $n_i(N, F, \lambda, r)$ be the smallest value among those n_i for which $(n_i, 0)$ is an optimal allocation for the ith stage.

Assume that $P\{\rho > \lambda | F\} > 0$, $P\{\rho < \lambda | F\} < 0$, and the support of F contains at least two interior points of $(0, 1)$. Then

$$\lim_{N\to\infty} \sum_{i=1}^{r-1} E(n_i(N, F, \lambda, r)) = \infty$$

and

$$\lim_{N\to\infty} \frac{n_1(N, F, \lambda, r)}{N} = 0.$$

On average, the total length of the first $r-1$ stages tends to infinity with N. But the proportion of the total of N observations contained in the first stage goes to zero. In particular, the stages should not be of equal length.

Since the optimal lengths of later stages are random, it is difficult to make specific statements at stage one concerning these lengths. But some types of results are possible. An example is the following theorem.

THEOREM. *Suppose* $r = 3$. *Assuming*

$$P\{\rho > \lambda|F\} > 0, \text{ and } \quad P\{\rho < \lambda|F\} > 0$$

and the support of F *contains at least two interior points of* $(0,1)$, *then*

(3)

$$\limsup_{N\to\infty} P\left\{\frac{n_2(N,F,\lambda,3)}{N} > \epsilon\right\} \leq \eta$$

for arbitrary $\epsilon > 0$, *where* $\eta = P\{\rho < \lambda|F\}$.

PROOF. The proof of (3) is in two parts.

(a) If $n_1(N,F,\lambda,3)$ is bounded above, then since n_1 is nondecreasing in N, there exists an n_0 such that $n_1 = n_0$ when $N \geq N_0$ for some N_0. Let s_1 denote the number of successes in the first stage. n_2 obviously depends on s_1. As a consequence of the results in two stages in Section 3, we have

$$\lim_{N\to\infty} \frac{n_2(N,F,\lambda,3)s_1}{N - n_0} = 0$$

and

$$\lim_{N\to\infty} n_2(N,F,\lambda,3)s_1 = +\infty,$$

for all $s_1 = 0, \ldots, n_0$. That is,

(4)

$$\lim_{N\to\infty} \frac{n_2(N,F,\lambda,3)}{N - n_0} = 0 \quad a.s.$$

and

$$\lim_{N\to\infty} n_2(N,F,\lambda,3) = +\infty \quad a.s$$

The properties given by (4) imply that

$$\lim_{N\to\infty} P(n_2(N,F,\lambda,3)/N > \epsilon) = 0$$

for arbitrarily $\epsilon > 0$ and (3) follows.

(b) Suppose

$$\lim_{N\to\infty} n_1(N,F,\lambda,3) = +\infty.$$

Since

$$P\{\rho < \lambda | F\} = \eta > 0,$$

there must exist a δ such that

$$\eta_\delta = P\{\rho < \lambda - \delta | F\} > 0.$$

Where S_i is the number of successes in stage i, we have

(5)

$$\begin{aligned} & V_3(N, (F, \lambda)) \\ & = \frac{n_1}{N} E(\rho|F) + E\left\{\frac{n_2}{N} E(\rho|(S_1, n_1 - S_1, F))\right\} \\ & + E\left\{\frac{N - n_1 - n_2}{N} E\left(E(\rho|(S_1 + S_2, n_1 + n_2 - S_1 - S_2, F)) \vee \lambda | S_1\right)\right\} \\ & = \frac{n_1}{N} E(\rho|F) \\ & + E\left\{\frac{N - n_1}{N} E\left(E(\rho|(S_1 + S_2, n_1 + n_2 - S_1 - S_2, F)) \vee \lambda | S_1\right)\right\} \\ & - E\left\{\frac{n_2}{N} E\left(E(\rho|(S_1 + S_2, n_1 + n_2 - S_1 - S_2, F)) \vee \lambda | S_1\right)\right. \\ & \left. - \frac{n_2}{N} E(\rho|(S_1, n_1 - S_1, F))\right\}. \end{aligned}$$

Considering the right side of (5),we have

(6)

$$\lim_{N \to \infty} \frac{n_1}{N} E(\rho|F) = 0$$

and

$$\lim_{N \to \infty} E\left\{\frac{N - n_1}{N} E\left(E(\rho|(S_1 + S_2, n_1 + n_2 - S_1 - S_2, F)) \vee \lambda | S_1\right)\right\}$$

$$= E(\rho \vee \lambda | F).$$

Therefore since $\lim_{N\to\infty} V_3(N,(F,\lambda)) = E(\rho \vee \lambda|F)$,

(7)

$$\lim_{N\to\infty} -E\left\{\frac{n^2}{N}E\left(E\left(\rho \mid (S_1+S_2, n_1+n_2-S_1-S_2, F)\right) \vee \lambda \mid S_1\right)\right.$$

$$\left. -\frac{n^2}{N}E\left(\rho \mid (S_1, n_1-S_1, F)\right)\right\} = 0.$$

If there exists an $\epsilon > 0$, such that

$$\limsup_{N\to\infty} P\left\{\frac{n_2(N,F,\lambda,3)}{N} > \epsilon\right\} > \eta,$$

then there is subsequence $\{N_k\}$ such that

$$\lim_{k\to\infty} P\{n_2(N_k,F,\lambda,3)/N_k > \epsilon\} > \eta.$$

Define

$$G_N = \left\{\frac{n_2(N,F,\lambda,3)}{N} > \epsilon\right\}$$

and

$$R_N = \{j : E(\rho|(j, n_1-j, F)) < \lambda - \delta,\ j = 0, ..., n_1\}.$$

We have $\lim_{N\to\infty} P\{R_N\} = P\{\rho < \lambda - \delta|F\} = \eta_\delta > 0$. Then

(8)

$$\lim_{k\to\infty} -E\left\{\frac{n_2}{N_k}E\left(E(\rho|(S_1+S_2, n_1+n_2-S_1-S_2, F)) \vee \lambda|S_1\right)\right.$$

$$\left. -\frac{n_2}{N_k}E(\rho|(S_1, n_1-S_1, F))\right\}$$

$$\geq \lim_{k\to\infty} E\left\{\frac{n_2}{N_k}\left(E(\rho|(S_1, n_1-S_1, F)) \vee \lambda - E(\rho|(S_1, n_1-S_1, F))\right)\right\}$$

$$
\begin{aligned}
&\geq \lim_{k\to\infty} E\left\{\frac{\delta n_2}{N_k} I_{R_{N_k}}\right\} \\
&\geq \lim_{k\to\infty} E\left\{\epsilon\delta I_{G_{N_k}} I_{R_{N_k}}\right\} \\
&= \lim_{k\to\infty} \epsilon\delta P\{G_{N_k} \cap R_{N_k}\} \\
&= \lim_{k\to\infty} \epsilon\delta \left(1 - P\{(G_{N_k} \cap R_{N_k})^c\}\right) \\
&\geq \lim_{k\to\infty} \epsilon\delta \left(1 - P\{(G_{N_k})^c\} - P\{(R_{N_k})^c\}\right) \\
&> \epsilon\delta(\eta - \eta_\delta) \\
&\geq 0.
\end{aligned}
$$

Equation (8) contradicts (7). Therefore (3) holds. □

For the rate of $n_1(N, F, \lambda, r)$, if the rate is $\sqrt[x]{N}$, then

$$\lim_{N\to\infty} \log(n_1(N, F, \lambda, r))/\log(N) = 1/x.$$

Tables 1, 2 and 3 give the values of $\log(n_1(N, F, \lambda, r))/\log(N)$, computed by backwards induction method. Where $F = beta(1,1), beta(2,1), beta(1,2)$, $r = 2, 3$; N is the total number of observations, r is the number of stages, and $n_1(N, beta(a,b), \lambda, r)$ is the optimal length for the first stage, the entry in each cell is $\log(n_1(N, F, \lambda, r))/\log(N)$, for various values of λ.

The numerical results are consistent with our theoretical results. For all these combinations of a, b and λ,

$$\lim_{N\to\infty} \log(n_1(N, F, \lambda, r))/\log(N) = 0.5$$

when $r = 2$. Generally speaking, when the prior mean, $a/(a+b)$, of the unknown arm is closer to λ, convergence is faster. For instance, when $a = 1$, $b = 1$ and $\lambda = 0.5$, Table 1 indicates that

$$\log(n_1(10000, beta(1,1), \lambda, 2))/\log(10000) = 0.4967.$$

Considering the results for $r = 3$, when N is 5000 or greater, all entries are smaller than 0.45, and when N is 50000, all entries are smaller than 0.40. This suggests that the rate of the optimal length in the first stage is smaller than $\sqrt{N}$ when r=3. Furthermore it suggests $1/3$ as a possible value for

Table 1.

Ratio of log optimal length and log N ($a = 1$, $b = 1$)

		N						
		50	100	500	1000	5000	10000	50000
$\lambda = 0.3$	$r = 2$	0.5316	0.5396	0.54128	0.5303	0.5309	0.5300	0.5386
	$r = 3$	0.4114	0.4771	0.4461	0.4539	0.4301	0.4180	0.3844
$\lambda = 0.4$	$r = 2$	0.4974	0.4771	0.5114	0.5227	0.5202	0.5189	0.5180
	$r = 3$	0.3544	0.3891	0.3858	0.4101	0.4105	0.3949	0.3784
$\lambda = 0.5$	$r = 2$	0.4114	0.4771	0.4899	0.4875	0.4971	0.4967	0.4997
	$r = 3$	0.1772	0.3495	0.3346	0.3713	0.3825	0.3796	0.3634
$\lambda = 0.6$	$r = 2$	0.3544	0.4225	0.4559	0.4601	0.4747	0.4750	0.4810
	$r = 3$	0.2808	0.2386	0.2883	0.3181	0.33457	0.3459	0.3232
$\lambda = 0.7$	$r = 2$	0.2808	0.2386	0.4128	0.4337	0.4416	0.4498	0.4587
	$r = 3$	0.0000	0.0000	0.2590	0.2817	0.3326	0.3306	0.3011

Table 2.

Ratio of log optimal length and log N ($a = 2$, $b = 1$)

		N						
		50	100	500	1000	5000	10000	50000
$\lambda = 0.3$	$r = 2$	0.6922	0.6712	0.6448	0.6325	0.6110	0.6016	0.5890
	$r = 3$	0.6130	0.5880	0.5418	0.5227	0.4469	0.4463	0.3990
$\lambda = 0.4$	$r = 2$	0.6557	0.6276	0.6052	0.5998	0.5851	0.5810	0.5683
	$r = 3$	0.4974	0.5207	0.5045	0.4875	0.4416	0.4390	0.3927
$\lambda = 0.5$	$r = 2$	0.5886	0.5731	0.5766	0.5720	0.5621	0.5576	0.5519
	$r = 3$	0.4114	0.4515	0.4651	0.4539	0.4240	0.4203	0.3829
$\lambda = 0.6$	$r = 2$	0.5316	0.5207	0.5361	0.5376	0.5359	0.5350	0.5311
	$r = 3$	0.3544	0.3891	0.4247	0.4184	0.4105	0.4001	0.3616
$\lambda = 0.7$	$r = 2$	0.4114	0.4771	0.4974	0.5017	0.5130	0.5123	0.5093
	$r = 3$	0.2895	0.3495	0.3705	0.3920	0.3731	0.3796	0.3409
$\lambda = 0.8$	$r = 2$	0.3543	0.3495	0.4358	0.4660	0.4787	0.4811	0.4845
	$r = 3$	0.1777	0.1505	0.3346	0.3471	0.3575	0.3404	0.3080

Table 3.

Ratio of log optimal length and log N ($a = 1$, $b = 2$)

		N						
		50	100	500	1000	5000	10000	50000
$\lambda = 0.3$	$r = 2$	0.5316	0.5396	0.5418	0.5304	0.5309	0.5301	0.5256
	$r = 3$	0.3544	0.3495	0.4247	0.4263	0.4105	0.4084	0.3720
$\lambda = 0.4$	$r = 2$	0.4508	0.4515	0.4899	0.4971	0.4954	0.4978	0.5010
	$r = 3$	0.1772	0.3495	0.3705	0.3713	0.3912	0.3763	0.3578
$\lambda = 0.5$	$r = 2$	0.1772	0.3010	0.4247	0.4475	0.4639	0.4673	0.4736
	$r = 3$	0.0000	0.1505	0.3131	0.3010	0.3457	0.3451	0.3233
$\lambda = 0.6$	$r = 2$	*	*	0.3858	0.4031	0.4271	0.4311	0.4470
	$r = 3$	0.0000	0.0000	0.2590	0.2594	0.3011	0.2940	0.2814
$\lambda = 0.7$	$r = 2$	*	*	*	0.3181	0.3779	0.3860	0.4149
	$r = 3$	*	*	0.1115	0.2007	0.2441	0.2698	0.2671

* indicates that $n_1(N, beta(1,2), \lambda, r) = 0$.

$$\lim_{N\to\infty} \log(n_1(N, beta(a,b), \lambda, r))/\log(N).$$

This is easier to see when λ is slightly bigger than $a/(a+b)$, for instance, when $a = 1$, $b = 2$ and $\lambda = 0.5$,

$$\log(n_1(50000, beta(1,2), \lambda, 3))/\log(50000) = 0.3233.$$

Therefore, the rate of the optimal length in the first stage may well be $\sqrt[3]{N}$ when $r = 3$ and F is beta. We conjecture that the rate optimal length in the first stage is $\sqrt[r]{N}$ for general r and beta priors. It seems reasonable to expect in any case that the greater the number of stages, the smaller the rate of $n_1(N, beta(a,b), \lambda, r)$.

6. Conclusion. We have addressed the design of a clinical trial in stages, focusing on the case of two stages. There are two distinct applications. One is the usual group sequential setting in which the N patients in the trial are divided in two. In the other application, the "first stage" is really the entire trial containing N patients and the "second stage" is the clinical setting in which knowledge obtained during the trial is used to treat patients effectively.

The goal is to maximize the expected number of successes over the course of the trial. The length of the first stage is proportional to $\sqrt{N}$ in many cases, and we believe that its rate is never greater than $\sqrt{N}$, when $r = 2$. For r greater than two, our study suggests that the length of the first stage is asymptotically proportional to $\sqrt[r]{N}$ with beta priors on the unknown arm.

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