ASYMPTOTIC OPTIMAL GROUP SEQUENTIAL STRATEGIES IN TWO-ARMED BANDIT PROBLEMS

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ABSTRACT

Consider designing a r-stage clinical trial. There are two available treatments and N exchangeable patients to be treated as effectively as possible. The stages may be viewed as separate trials. Responses are dichotomous. The problem is to decide how large each stage should be and how many patients should be assigned to each treatment during each stage. Information is updated during after each stage using Bayes' theorem. In planning stage j, responses from selections in stages 1 to $j-1$ are available but responses in stage j are not. We consider $r = 2$ for two situations, when one arm is known and when both arms are unknown. The dominant term for the length of the first stage in an optimal design for general N is found explicitly. In both situations the order of magnitude of the length of the first stage is $N^{1/2}$.

1. INTRODUCTION

In a standard design of a two-armed clinical trial, patients are randomized in a balanced fashion to the two treatment arms. The trial's sample size, n, is chosen to achieve a particular power to distinguish between the null hypothesis of treatment equality of the arms and a hypothesized "clinically significance difference" δ between the arms. A Bayesian decision-theoretic approach is quite different. It considers the consequences of each possible sample size and identifies one to maximize expected utility, or minimize expected loss. Such an approach requires a definition of utility. One that is appealing is the overall health of individuals affected with the disease or condition in question and who will be treated with one of the two arms. Beginning with Anscombe (1963) and Colton (1963), numerous authors have addressed clinical trial design problem by maximizing expected health over this "patient horizon." This approach has been criticized because the size N of this patient horizon is unknown. In particular, it depends on the effectiveness and side effects of both treatments, which are unknown. To our knowledge the notion of a patient horizon has never been used in designing actual trials, at least not in a formal way.

In this article we assume a number N of patients over which the expected number of treatment successes is to be maximized. The N patients are treated in r stages, with updating between stages. Parameter N has one of two possible interpretations. The less problematic interpretation is that N is the size of a clinical trial. The other is that N is the patient horizon discussed above, where a clinical trial is to be conducted on a subset of these patients, and again the clinical trial can be conducted in stages. In the latter interpretation, r is reduced by 1 because the last "stage" is the set of patients treated with one of the treatments in question in clinical practice and based on the results of the $(r-1)$-stage trial. We address the optimal size of these stages when $r = 2$. In the special case $r = 2$ and taking the latter interpretation, this means finding the optimal length of a single-stage clinical trial.

We take N to be fixed, which in the "patient horizon" setting is subject to the criticism cited in the first paragraph. Our principal message is that the order of magnitude of N should be considered in choosing sample sizes of clinical trials, and therefore precision in choosing N is not important. Considering the extremes, diseases or conditions that are very common (large N) call for larger trials than do rare diseases (small N). These two extremes are addressed in the same way when choosing sample sizes via power calculations. (However, any particular sample size corresponds to some combination of power and δ. Applied statisticians may choose lower power and larger δ for diseases that are rare, a strategy that is consistent with our conclusions in this article.) In the Bayesian approach, unknown quantities are regarded as random. Allowing N to have a probability distribution would give results similar to the results of this article upon replacing N with its mean (Witmer 1986, Cheng 1994). In an actual setting, experts could assess the annual size of the patient population and the potential availability of other therapies over the next several years. Patients presenting in the future could be discounted by the probability they will be treated using one of the two treatments involved in the trial and the expected value of N calculated.

Consider two treatments with dichotomous responses: success and failure. The goal is to treat N patients as effectively as possible, which we take to mean maximizing the expected proportion of success. A substantial literature deals with sequential procedures in which assignments depend on all previous assignments and responses. For example, Feldman (1962), Rodman (1978), Gittins (1979), Whittle (1980), Bather (1981), Berry and Fristedt (1985), and Berry and Eick (1995) assume that the outcomes for previously treated patients are known when the current patient arrives. This assumption is not always realistic: responses may be delayed and even if responses are immediate, continual updating may not be possible.

We regard the N patients as being treated in a fixed number of r groups, or stages. The decision problem is to choose the size of each stage (number of patients), and the number of patients assigned to each treatment in each stage. When making these decisions, responses from selections in the previous stages are available and can be considered but responses in the current stage are not available until the next group of selections is made.

The two arms can be represented as Bernoulli processes with success probabilities θ_1 and θ_2. We regard θ_1 and θ_2 to be random and having prior distribution $\pi(\theta_1, \theta_2)$. Observations from the same arm are exchangeable.

There is a literature concerning bandit problems in stages. Berry & Pearson (1985) considered several scenarios, including one in which both arms are unknown with a special kind of prior distribution under which θ_1 and θ_2 are dependent and all the mass is assigned to two points: (α, β) and (β, α). They find that when $\alpha = 1 - \beta$, a balanced first stage ($n_1 = n_2$) is nearly optimal.

The outline of this paper is as follows. Sections 2 deals with the case in which $P(\theta_2 = \lambda) = 1$, that is, the second arm is known. Every optimal allocation avoids the known arm until the last stage, unless $P(\theta_1 \leq \lambda) = 1$. In the case of $P(\theta_1 \leq \lambda) = 1$, arm 1 should not be used at all. In Section 2, we consider $r = 2$ and find that the dominant term of the optimal length of the first stage is

$$\Big[\frac{0.5\lambda(1-\lambda)\pi(\lambda)}{E(\theta_1 \vee \lambda) - E(\theta_1)}\Big]^{1/2} N^{1/2},$$

when $\pi(\lambda) > 0$, a result that generalizes Example 6 of Berry & Pearson (1985) where π is uniform on $(0, 1)$.

In Section 3, we extend the results of Section 2 to the case in which both arms are unknown and $r = 2$. As in Section 2, the optimal length of the first stage is found to have order $N^{1/2}$, and the proportionate allocations to the two arms are found. The dominant terms of the optimal allocation to arm 1 and arm 2 are

$$n_1^* \sim \Big[\frac{0.5cN}{E(\theta_1 \vee \theta_2|\pi) - E(\theta_1|\pi)}\Big]^{1/2}, \quad n_2^* \sim \Big[\frac{0.5cN}{E(\theta_1 \vee \theta_2|\pi) - E(\theta_2|\pi)}\Big]^{1/2},$$

where c is defined in (3.9).

2. ONE ARM KNOW, TWO STAGES

When $P(\theta_2 = \lambda) = 1$, observing arm 1 gives immediate gain and information. Observing arm 2 gives only immediate gain. So observations on arm 2 have no utility in stage 1. Therefore arm 2 will be used only in the last stage, if used at all. To make the notation simpler, we replace θ_1 by θ. The expected worth of assigning n observations to arm 1 in the first stage is

$$W_2(N, n, \pi, \lambda) = \frac{1}{N}\left\{nE(\theta) + (N-n)E\Big[E(\theta|S_n) \vee \lambda\Big]\right\}, \tag{2.1}$$

where $E(\theta|S_n)$ is the posterior mean of θ given S_n successes under prior π. Let $n(N, \pi, \lambda, 2)$ be the optimal length of the first stage in a two-stage problem. The maximum worth is

$$V_2(N, \pi, \lambda) = \max_{0 \le n \le N} W_2(N, n, \pi, \lambda) = W_2(N, n(N, \pi, \lambda, 2), \pi, \lambda).$$

$\{E(\theta|S_n) \vee \lambda,\ n = 1, 2, ...\}$ is a uniformly integrable submartingale sequence, and it converges to $\theta \vee \lambda$ almost everywhere. According to the Martingale Convergence Theorem,

$$\lim_{n\to\infty} E(E(\theta|S_n) \vee \lambda) = E(\theta \vee \lambda|\pi). \tag{2.2}$$

Expression (2.2) means that the expected proportion of success from the second stage is maximized if full information concerning the success probability θ is obtained in the first stage. It is easy to see that if $0 < P(\theta \leq \lambda) < 1$, then $n(N, \pi, \lambda, 2)$ must satisfy the following:

$$\lim_{N \to \infty} n(N, \pi, \lambda, 2) = \infty, \qquad \lim_{N \to \infty} \frac{n(N, \pi, \lambda, 2)}{N} = 0.$$

The main purpose of the following development, Lemma 2.1 through Lemma 2.8, is to prove that

$$\begin{aligned} &W_2(N, n, \pi, \lambda) \\ &= \frac{n}{N} E(\theta) + \frac{N-n}{N} \Big[E(\theta \vee \lambda) - \frac{c(v+1)\pi_0(\lambda)}{n^{(v+2)/2}} + O\Big(\frac{1}{n^{(v+3)/2}}\Big) \Big] \end{aligned} \tag{2.3}$$

where prior density function $\pi(\theta) = |\lambda - \theta|^v \pi_0(\theta)$, $\pi_0(\theta)$ is assumed to satisfy a Lipschitz condition in a neighborhood of λ and $\pi_0(\lambda) > 0$. The constant $c(v+1)$ is defined by (2.15). Expression (2.3) will allow us to find the rate and the magnitude of the dominant term of the optimal first stage size.

The critical aspect of the following development is understanding the behavior of $E(E(\theta|S_n) \vee \lambda)$, the maximum worth per observation in the second stage, especially in comparison with $E(\theta \vee \lambda)$, the corresponding worth for perfect information. The next result is the initial step in this direction.

For any given n, define an integer $k(n)$ as the following:

$$\begin{aligned} &k(n) = 0, \quad \text{if } E(\theta|S_n = 0) > \lambda; \\ &k(n) = n, \quad \text{if } E(\theta|S_n = n) < \lambda; \\ &\text{otherwise,} \quad k(n) \text{ satisfies the inequalities:} \\ &\qquad\qquad E[\theta|S_n = k(n)] \leq \lambda < E[\theta|S_n = k(n) + 1]. \end{aligned} \tag{2.4}$$

For any given n, $\{E(\theta|S_n = k),\ k = 0, 1, ..., n.\}$ is a nondecreasing sequence in k. Therefore, such a $k(n)$ exists for every n.

Lemma 2.1. *Where $k(n)$ is defined by (2.4),*

$$\begin{aligned} &E(\theta \vee \lambda) - E[E(\theta|S_n) \vee \lambda] \\ &= \int_0^\lambda (\lambda - \theta) P_\theta[S_n > k(n)] \pi(\theta) d\theta + \int_\lambda^1 (\theta - \lambda) P_\theta[S_n \leq k(n)] \pi(\theta) d\theta. \end{aligned} \tag{2.5}$$

PROOF. The maximum worth per observation in the second stage is

$$\begin{aligned} E[E(\theta|S_n)\vee\lambda] &= \lambda P(S_n\le k(n)) + E[\theta\mathbf{1}_{\{i:\,i>k(n)\}}(S_n)] \\ &= \int_0^1 \lambda P_\theta[S_n\le k(n)]\pi(\theta)d\theta + \int_0^1 \theta P_\theta[S_n>k(n)]\pi(\theta)d\theta. \end{aligned} \tag{2.6}$$

(2.5) follows upon subtracting (2.6) from $E(\theta\vee\lambda)=\int_0^\lambda \lambda\pi(\theta)d\theta+\int_\lambda^1\theta\pi(\theta)d\theta$. □

LEMMA 2.2. *If the prior π satisfies a Lipschitz condition in a neighborhood of λ, then $k(n)=n\lambda+O(1)$, where $k(n)$ is defined by (2.4).*

PROOF. The difference between the posterior mean and the MLE S_n/n is $O(n^{-1})$ (Schervish, 1995. Ch. 7.4.). The result follows from definition (2.4). □

We will prove, using large deviation theory, that as n goes to infinity, the rate at which the right-hand side of (2.5) converges to zero is $O(n^{-1})$ if $\pi(\lambda)>0$.

We define $d(a,\theta)$ to be Kullback-Leibler distance:

$$d(a,\theta)=\ln\Big(\frac{a}{\theta}\Big)^a+\ln\Big(\frac{1-a}{1-\theta}\Big)^{1-a}. \tag{2.7}$$

LEMMA 2.3. *If the prior π satisfies a Lipschitz condition in a neighborhood of λ: $\{\theta:\,|\theta-\lambda|\le\delta\}$, $0<2\delta<\min\{\lambda,1-\lambda\}$, and constant $u\ge 0$, then*

$$\int_0^{\lambda-\delta}|\lambda-\theta|^u P_\theta[S_n>k(n)]\pi(\theta)d\theta$$

converges to zero exponentially and uniformly in prior π.

PROOF. According to Lemma 2.2, $k(n)/n=\lambda+O(1/n)$. When n is sufficiently large, $P_\theta[S_n\ge k(n)]\le P_\theta[S_n/n\ge\lambda-\delta/2]$. Let a be a constant, $0<a<1$. As a special case in R. R. Bahadur (1960), for any θ, $0<\theta<a$,

$$P_\theta\Big(\frac{S_n}{n}\ge a\Big)=\frac{e^{-nd(a,\theta)}}{\sqrt{2\pi n}}\frac{a(1-\theta)}{\sqrt{a(1-a)}(a-\theta)}\Big(\frac{(1-a)\theta}{a(1-\theta)}\Big)^{n(1-a)-[n(1-a)]}\Big(1+O(n^{-1/2})\Big),$$

where $[x]$ represents the integer part of x, and $a=\lambda-\delta/2$ in this case. Since $0<\theta<\lambda-\delta$,

$$\frac{a(1-\theta)}{\sqrt{a(1-a)}(a-\theta)}\Big(\frac{(1-a)\theta}{a(1-\theta)}\Big)^{n(1-a)-[n(1-a)]}$$

is bounded. Furthermore, $e^{-nd(a,\theta)}\le e^{-nd(\lambda-\delta/2,\lambda-\delta)}$, which converges to zero exponentially. Since

$$\int_0^{\lambda-\delta}|\lambda-\theta|^u\pi(\theta)d\theta\le 1$$

for any probability density function π on $(0,1)$, the result follows. $\square$

LEMMA 2.4. *For any δ defined in Lemma 2.3, any given positive constant $b > 0$ and $u \geq 0$,*

$$\int_{\lambda-\delta}^{\lambda+\delta} |\lambda-\theta|^u P_\theta\Big[\lambda - \frac{b}{n} \leq \frac{S_n}{n} \leq \lambda + \frac{b}{n}\Big]\pi(\theta)d\theta = O\Big(\frac{1}{n^{(u+2)/2}}\Big).$$

PROOF. According to Stirling's formula,

$$\frac{n!}{k!(n-k)!} = \frac{\sqrt{n}}{\sqrt{2\pi}\sqrt{k(n-k)}}\frac{n^n}{k^k(n-k)^{n-k}}\Big[1+O\Big(\frac{1}{n}\Big)\Big].$$

Furthermore, if $|k-n\lambda| \leq b$,

$$\frac{n!}{k!(n-k)!}\theta^k(1-\theta)^{n-k} = \frac{\exp\{-nd(k/n,\theta)\}}{\sqrt{2\pi n}\sqrt{\lambda(1-\lambda)}}\Big[1+O\Big(\frac{1}{n}\Big)\Big], \tag{2.8}$$

where $d(k/n,\theta)$ is defined by (2.7). Let $\pi_\delta = \max\{\pi(\theta) : |\theta-\lambda| \leq \delta\}$. We have

$$\begin{aligned}
&\int_{\lambda-\delta}^{\lambda+\delta} |\lambda-\theta|^u P_\theta\Big[\lambda - \frac{b}{n} \leq \frac{S_n}{n} \leq \lambda + \frac{b}{n}\Big]\pi(\theta)d\theta \\
&\quad = \sum_{|k-n\lambda|\leq b}\int_{\lambda-\delta}^{\lambda+\delta} |\lambda-\theta|^u \frac{n!}{k!(n-k)!}\theta^k(1-\theta)^{n-k}\pi(\theta)d\theta \qquad (2.9)\\
&\quad \leq \frac{\pi_\delta}{\sqrt{2\pi n}\sqrt{\lambda(1-\lambda)}}\Big[1+O\Big(\frac{1}{n}\Big)\Big]\sum_{|k-n\lambda|\leq b}\int_{\lambda-\delta}^{\lambda+\delta} |\lambda-\theta|^u \exp\Big\{-nd(k/n,\theta)\Big\}d\theta.
\end{aligned}$$

By Taylor expansion,

$$d(a,\theta) = \frac{(a-\theta)^2}{2\sigma^2(\theta)} + \Big[-\frac{2a}{\xi^3} + \frac{2(1-a)}{(1-\xi)^3}\Big]\frac{(a-\theta)^3}{6} \tag{2.10}$$

where $\sigma^2(\theta) = \theta(1-\theta)$, and ξ is between a the θ.

For $|\theta-\lambda| \leq \delta$ and $|k/n-\lambda| \leq b/n$, there exists $M > 0$, such that

$$d(k/n,\theta) \geq M(k/n-\theta)^2.$$

We obtain

$$\begin{aligned}
&\int_{\lambda-\delta}^{\lambda+\delta} |\lambda-\theta|^u \exp\Big\{-nd(k/n,\theta)\Big\}d\theta \\
&\qquad \leq \int_{\lambda-\delta}^{\lambda+\delta} |k/n-\theta+O(n^{-1})|^u \exp\Big\{-nM(k/n-\theta)^2\Big\}d\theta \qquad (2.11)\\
&\qquad \leq (Mn)^{-(u+1)/2}\int_{-\infty}^{+\infty} |t+O(n^{-1})|^u e^{-t^2}dt = O\Big(n^{-(u+1)/2}\Big).
\end{aligned}$$

In the last inequality, $t = (Mn)^{1/2}(k/n - \theta)$. Combining (2.9) and (2.11), the result follows. $\square$

The proof of the following Lemma 2.5 is analogous to that of Lemma 2.3 and is omitted.

LEMMA 2.5. *If the prior π satisfies a Lipschitz condition in a neighborhood of λ: $\{\theta : |\theta - \lambda| \le \delta\}$, $0 < 2\delta < \min\{\lambda, 1-\lambda\}$, and constant $u \ge 0$,*

$$\int_{\lambda-\delta}^{\lambda} |\lambda - \theta|^u P_\theta\Big[\frac{S_n}{n} > \lambda + \delta\Big]\pi(\theta)d\theta$$

converges to zero exponentially and uniformly in prior π. $\square$

In view of Lemmas 2.3, 2.4, and 2.5, we have

$$\begin{aligned}\int_0^{\lambda} &|\lambda - \theta|^u P_\theta[S_n > k(n)]\pi(\theta)d\theta \\ &= \int_{\lambda-\delta}^{\lambda} |\lambda - \theta|^u P_\theta\Big[\lambda \le \frac{S_n}{n} \le \lambda + \delta\Big]\pi(\theta)d\theta + O\Big(n^{-(u+1)/2}\Big).\end{aligned} \tag{2.12}$$

The following Lemmas 2.6 and 2.7 provide a double integral approximation to the right-hand side of (2.12).

LEMMA 2.6. *For $u \ge 0$, $w \ge 0$, $\sigma^2(\lambda) = \lambda(1-\lambda)$,*

$$\begin{aligned}\int_{\lambda-\delta}^{\lambda} d\theta &\int_{\lambda}^{\lambda+\delta} |\lambda - \theta|^u |x - \lambda|^w e^{-nd(x,\theta)} dx \\ &= \Big(\frac{\sigma(\lambda)}{\sqrt{n}}\Big)^{u+w+2} \int_0^\infty \int_0^\infty s^u t^w e^{-(s+t)^2/2} ds dt \Big[1 + O\Big(n^{-1/2}\Big)\Big].\end{aligned}$$

PROOF. By Taylor expansion,

$$d(x,\theta) = \frac{1}{2\sigma^2(\lambda)}\Big[(x-\lambda) - (\theta - \lambda)\Big]^2 + O\Big[(x-\lambda) - (\theta-\lambda)\Big]^3.$$

Let $t = \sqrt{n}(x - \lambda)/\sigma(\lambda)$ and $s = \sqrt{n}(\lambda - \theta)/\sigma(\lambda)$. We have

$$\begin{aligned}\int_{\lambda-\delta}^{\lambda} d\theta &\int_{\lambda}^{\lambda+\delta} |\lambda - \theta|^u |x-\lambda|^w e^{-nd(x,\theta)} dx \\ &= \int_{\lambda-\delta}^{\lambda} d\theta \int_{\lambda}^{\lambda+\delta} |\lambda - \theta|^u |x - \lambda|^w e^{-n[(x-\lambda)-(\theta-\lambda)]^2/2\sigma^2(\lambda)}\Big[1 + nO(x-\theta)^3\Big] dx \\ &= \Big(\frac{\sigma(\lambda)}{\sqrt{n}}\Big)^{u+w+2}\Big[1 + O\Big(\frac{1}{\sqrt{n}}\Big)\Big] \int_0^\infty \int_0^\infty s^u t^w e^{-(s+t)^2/2} ds dt. \qquad \square\end{aligned}$$

LEMMA 2.7. *If the prior π satisfies a Lipschitz condition in a neighborhood of λ: $\{\theta : |\theta - \lambda| \le \delta\}$, $0 < 2\delta < \min\{\lambda, 1-\lambda\}$, and constant $u \ge 0$,*

$$\begin{aligned} &\int_{\lambda-\delta}^{\lambda} |\lambda-\theta|^u P_\theta\Big[\lambda \le \frac{S_n}{n} \le \lambda+\delta\Big]\pi(\theta)d\theta \\ &\quad = \int_{\lambda-\delta}^{\lambda} d\theta \int_{\lambda}^{\lambda+\delta} |\lambda-\theta|^u \frac{\sqrt{n}}{\sqrt{2\pi}\sigma(x)} e^{-nd(x,\theta)}\pi(\theta)dx + O\Big(\frac{1}{n^{(u+2)/2}}\Big). \end{aligned} \tag{2.13}$$

PROOF. Let

$$f_n(x,\theta) = \frac{\exp\{-nd(x,\theta)\}}{\sigma(x)}.$$

Let $\lceil x \rceil$ be the smallest integer greater than or equal to x, and $\lfloor x \rfloor$ be the largest integer smaller than or equal to x. In view of Lemma 2.6, it is easy to see

$$\begin{aligned} &\int_{\lambda-\delta}^{\lambda} d\theta \int_{\lambda}^{\lambda+\delta} |\lambda-\theta|^u \frac{\sqrt{n}}{\sqrt{2\pi}\sigma(x)} e^{-nd(x,\theta)}\pi(\theta)dx \\ &\quad = \int_{\lambda-\delta}^{\lambda} d\theta \int_{\lceil n\lambda \rceil/n}^{\lfloor n(\lambda+\delta)\rfloor/n} |\lambda-\theta|^u \frac{\sqrt{n}}{\sqrt{2\pi}\sigma(x)} e^{-nd(x,\theta)}\pi(\theta)dx\Big[1+O\Big(\frac{1}{\sqrt{n}}\Big)\Big]. \end{aligned}$$

Similar to (2.8), we have

$$P_\theta\Big[\lambda \le \frac{S_n}{n} \le \lambda+\delta\Big] = \sum_{n\lambda \le k \le n(\lambda+\delta)} \frac{\sqrt{n}}{\sqrt{2\pi}}\frac{1}{n} f_n\Big(\frac{k}{n},\theta\Big)\Big[1+O\Big(\frac{1}{n}\Big)\Big].$$

Furthermore,

$$\begin{aligned} &\int_{\lceil n\lambda \rceil/n}^{\lfloor n(\lambda+\delta)\rfloor/n} f_n(x,\theta)dx - \sum_{n\lambda \le k \le n(\lambda+\delta)} f_n\Big(\frac{k}{n},\theta\Big)\frac{1}{n} \\ &\quad = \sum_{n\lambda \le k \le n(\lambda+\delta)} \int_{k/n}^{(k+1)/n} \frac{\partial f_n(\xi_k,\theta)}{\partial x}\Big(x-\frac{k}{n}\Big)dx = \sum_{n\lambda \le k \le n(\lambda+\delta)} \frac{\partial f_n(\xi_k,\theta)}{\partial x}\frac{1}{n^2}, \end{aligned}$$

where ξ_k is in $[k/n, (k+1)/n]$. Since

$$\frac{\partial f_n(x,\theta)}{\partial x} = \Big\{-\frac{1-2x}{2\sigma^3(x)} - \frac{n}{\sigma(x)}\Big[\ln\frac{x}{1-x} - \ln\frac{\theta}{1-\theta}\Big]\Big\}\exp\{-nd(x,\theta)\},$$

and by Taylor expansion,

$$\ln\frac{x}{1-x} - \ln\frac{\theta}{1-\theta} = \frac{(x-\theta)}{\sigma^2(\zeta)},$$

with ζ between x and θ, we obtain

$$\Big|\int_{\lambda-\delta}^{\lambda} |\lambda-\theta|^u P_\theta\Big[\lambda \le \frac{S_n}{n} \le \lambda+\delta\Big]\pi(\theta)d\theta$$

$$
\begin{aligned}
&- \int_{\lambda-\delta}^{\lambda} d\theta \int_{\lceil n\lambda\rceil/n}^{\lfloor n(\lambda+\delta)\rfloor/n} |\lambda-\theta|^u \frac{\sqrt{n}}{\sqrt{2\pi}\sigma(x)} e^{-nd(x,\theta)}\pi(\theta)dx \Bigg| \\
&= O\left(\frac{\sqrt{n}}{\sqrt{2\pi}} \int_{\lambda-\delta}^{\lambda} \sum_{n\lambda\le k\le n(\lambda+\delta)} \frac{|\lambda-\theta|^u|\xi_k-\theta|}{\sigma(\xi_k)\sigma^2(\zeta_k)} \exp\{-nd(\xi_k,\theta)\}\frac{1}{n}d\theta\right) \\
&= O\left(\sqrt{n}\int_{\lambda-\delta}^{\lambda} d\theta \int_{\lceil n\lambda\rceil/n}^{\lfloor n(\lambda+\delta)\rfloor/n} |\lambda-\theta|^u|x-\theta|\exp\{-nd(x,\theta)\}dx\right) \\
&= O\left(\sqrt{n}\int_{\lambda-\delta}^{\lambda} d\theta \int_{\lambda}^{\lambda+\delta} |\lambda-\theta|^u|x-\theta|\exp\{-nd(x,\theta)\}dx\right) = O\left(\frac{1}{n^{(u+2)/2}}\right).
\end{aligned}
$$

The last equality is a direct result of Lemma 2.6. ∎

Lemma 2.8 describes the asymptotic behavior of $E[E(\theta|S_n)\vee\lambda]$ in comparison with $E(\theta\vee\lambda)$.

LEMMA 2.8. *If prior $\pi(\theta)=|\theta-\lambda|^v\pi_0(\theta)$, $v\ge 0$, and $\pi_0(\theta)$ satisfies a Lipschitz condition in a neighborhood of λ, then*

$$E(\theta\vee\lambda)-E[E(\theta|S_n)\vee\lambda] = \frac{c(v+1)\pi_0(\theta)}{n^{(v+2)/2}} + O(n^{-(v+3)/2}), \tag{2.14}$$

where

$$c(u) = \frac{2^{(u+2)/2}\Gamma(\frac{u+2}{2})[\sigma(\lambda)]^{u+1}}{(u+1)\sqrt{2\pi}}. \tag{2.15}$$

PROOF. According to (2.12) and Lemma 2.7,

$$
\begin{aligned}
&\int_0^{\lambda} |\lambda-\theta| P_\theta[S_n>k(n)]\pi(\theta)d\theta \\
&\quad = \int_{\lambda-\delta}^{\lambda} d\theta \int_{\lambda}^{\lambda+\delta} |\lambda-\theta|^{v+1}\frac{\sqrt{n}}{\sqrt{2\pi}\sigma(x)}e^{-nd(x,\theta)}\pi_0(\theta)dx + O\Big(\frac{1}{n^{(v+3)/2}}\Big).
\end{aligned} \tag{2.16}
$$

Applying a Taylor expansion and a Lipschitz condition, respectively,

$$\frac{1}{\sigma(x)} = \frac{1}{\sigma(\lambda)} + O(|x-\lambda|), \quad \pi_0(\theta) = \pi_0(\lambda) + O(|\theta-\lambda|).$$

Apply Lemma 2.6 to the right-hand side of equation (2.16) to give

$$
\begin{aligned}
&\int_0^{\lambda} |\lambda-\theta|^{v+1} P_\theta[S_n>k(n)]\pi_0(\theta)d\theta \\
&\quad = \Big(\frac{\sigma(\lambda)}{\sqrt{n}}\Big)^{v+3}\frac{\sqrt{n}\pi_0(\lambda)}{\sqrt{2\pi}\sigma(\lambda)}\int_0^\infty\int_0^\infty s^{v+1}e^{-(s+t)^2/2}dsdt + O\Big(\frac{1}{n^{(v+3)/2}}\Big) \\
&\quad = \Big(\frac{\sigma(\lambda)}{\sqrt{n}}\Big)^{v+2}\frac{1}{\sqrt{2\pi}}\frac{2^{(v+1)/2}\Gamma(\frac{v+3}{2})\pi_0(\lambda)}{(v+2)} + O\Big(\frac{1}{n^{(v+3)/2}}\Big) \\
&\quad = \frac{c(v+1)\pi_0(\lambda)}{2n^{(v+2)/2}} + O\Big(\frac{1}{n^{(v+3)/2}}\Big).
\end{aligned} \tag{2.17}
$$

By analogy with the proof of (2.17), it can be shown that

$$\int_\lambda^1 |\theta-\lambda|^{v+1}P_\theta[S_n \le k(n)]\pi_0(\theta)d\theta = \frac{c(v+1)\pi_0(\lambda)}{2n^{(v+2)/2}} + O\Big(\frac{1}{n^{(v+3)/2}}\Big). \tag{2.18}$$

In view of Lemma 2.1, (2.17) and (2.18),

$$E[E(\theta|S_n)\vee\lambda] = E(\theta\vee\lambda) - \frac{c(v+1)\pi_0(\lambda)}{n^{(v+2)/2}} + O(n^{-(v+3)/2}). \qquad \square \tag{2.19}$$

We are ready to prove the main theorem of this section, which gives the dominant term of the optimal length of the first stage.

THEOREM 2.1. If $\pi(\theta) = |\lambda-\theta|^v\pi_0(\theta)$, $v \ge 0$, $\pi_0(\theta)$ satisfies a Lipschitz condition in a neighborhood of λ and $\pi_0(\lambda) > 0$, then

$$\lim_{N\to\infty}\frac{n(N,\pi,\lambda,2)}{N^{\frac{2}{v+4}}} = \Big[\frac{2^{(v+1)/2}\Gamma(\frac{v+3}{2})\pi_0(\lambda)[\sigma(\lambda)]^{v+2}}{\sqrt{2\pi}(E(\theta\vee\lambda)-E(\theta))}\Big]^{\frac{2}{v+4}}. \tag{2.20}$$

PROOF. According to (2.1) and (2.19),

$$\begin{aligned} &W_2(N,n,\pi,\lambda)\\ &= \frac{n}{N}E(\theta) + \frac{N-n}{N}\Big[E(\theta\vee\lambda) - \frac{c(v+1)\pi_0(\lambda)}{n^{(v+2)/2}} + O\Big(\frac{1}{n^{(v+3)/2}}\Big)\Big]\\ &= E(\theta\vee\lambda) - \frac{n}{N}\Big[E(\theta\vee\lambda)-E(\theta)\Big] - \frac{c(v+1)\pi_0(\lambda)}{n^{(v+2)/2}} + o\Big(\frac{1}{n^{(v+2)/2}}\Big). \end{aligned}$$

We assume $n/N = o(1)$ to get the last equality. The assumption has no effect on the dominant term of $n(N,\pi,\lambda,2)$ because

$$\lim_{N\to\infty}\frac{n(N,\pi,\lambda,2)}{N} = 0.$$

The terms $o(n^{-(v+2)/2})$ have no effect on the dominant term of $n(N,\pi,\lambda,2)$ either. The dominant term of $n(N,\pi,\lambda,2)$ defined by (2.20) maximizes the first three dominant terms of $W_2(N,n,\pi,\lambda)$, which can be proved by differentiation. The theorem follows.

$\square$

COROLLARY 2.1. *If $\pi(\theta)$ is positive at λ and it satisfies a Lipschitz condition in a neighborhood of λ, then*

$$n(N,\pi,\lambda,2) \sim \left\{\frac{\sigma^2(\lambda)\pi(\lambda)}{2[E(\theta\vee\lambda)-E(\theta)]}\right\}^{1/2}\sqrt{N}; \tag{2.21}$$

$$V_2(N,\pi,\lambda) = E(\theta\vee\lambda) - \Big\{\frac{\sigma^2(\lambda)\pi(\lambda)}{2}[E(\theta\vee\lambda)-E(\theta)]\Big\}^{1/2}\frac{2}{\sqrt{N}} + O\Big(\frac{1}{N^{3/4}}\Big). \tag{2.22}$$

PROOF. Equation (2.21) is a special case of (2.20) with $v = 0$, $\pi_0(\lambda) = \pi(\lambda)$, $\Gamma(3/2) = \sqrt{\pi}/2$ and $c(1) = \sigma^2(\lambda)/2$. (2.22) follows when we substitute (2.20) into the right-hand side of (2.3). □

Table 2.1 shows the magnitude of the dominant terms of the optimal sizes, for the combinations of five different prior distributions and two different values of λ. The magnitude in (2.21) is $m_2(\pi, \lambda) = \{0.5\sigma^2(\lambda)\pi(\lambda)/[E(\theta \vee \lambda) - E(\theta)]\}^{1/2}$.

Table 2.1

Prior π	λ	Magnitude $m_2(\pi, \lambda)$
Beta(1, 1)	0.5	1.00000
	0.8	0.50000
Beta(3, 1)	0.5	2.44949
	0.8	1.22474
Beta(1, 5)	0.5	0.34100
	0.8	0.03179
Beta(1.5, 0.5)	0.5	1.52639
	0.8	0.90499
Beta(0.5, 0.5)	0.5	0.70712
	0.8	0.43350

3. BOTH ARMS UNKNOWN, TWO STAGES

A more general setting is where the success rates of both arms, denoted by θ_1 and θ_2, are unknown. Colton (1963) and Canner (1970) have studied this case assuming that the numbers of patients assigned to the two arms are equal. Cornfield, Halperin and Greenhouse (1969) considered unbalanced designs, however they supposed that the sample sizes for both arms were linear in N. Cheng (1996) found an upper bound of rate $N^{1/2}$ for the optimal sample size for each arm in the first stage. We will find the dominant terms of the optimal allocations of both arms in the first stage in this section.

Denote $\vec{\theta} = (\theta_1, \theta_2)$. Let $\pi(\vec{\theta}) = \pi(\theta_1, \theta_2)$ be the joint prior probability density. The expected worth of assigning n_1 observations to arm 1 and n_2 observations to arm

2 in the first stage is

$$
\begin{aligned}
&W_2(N,(n_1,n_2),\pi) \\
&= \frac{1}{N}\Big\{n_1 E(\theta_1) + n_2 E(\theta_2) + (N-n_1-n_2)E\left[E(\theta_1|S_{n_1},T_{n_2}) \vee E(\theta_2|S_{n_1},T_{n_2})\right]\Big\}
\end{aligned}
$$

where $E(\theta_i|S_{n_1},T_{n_2})$ is the posterior mean of θ_i given S_{n_1} successes on arm 1 and T_{n_2} successes on arm 2, $i=1,2$.

The main purpose of Lemmas 3.1 through 3.5 is to prove that

$$
E\Big[E(\theta_1|S_{n_1},T_{n_2}) \vee E(\theta_2|S_{n_1},T_{n_2})\Big] = E(\theta_1 \vee \theta_2|\pi) - c\Big(\frac{1}{n_1}+\frac{1}{n_2}\Big) + o\Big(\frac{1}{n_1}+\frac{1}{n_2}\Big)
$$

where c is defined in (3.9).

LEMMA 3.1. *Let* $A_{n_1,n_2} = \{(k,j):\ E(\theta_1-\theta_2|S_{n_1}=k, T_{n_2}=j) \le 0\}$. *Then*

$$
\begin{aligned}
&E(\theta_1 \vee \theta_2) - E\Big\{E(\theta_1|S_{n_1},T_{n_2}) \vee E(\theta_2|S_{n_1},T_{n_2})\Big\} \\
&\quad = \iint_{\theta_1<\theta_2} (\theta_2-\theta_1) P_{\vec\theta}(A^c_{n_1,n_2})\pi(\vec\theta)d\vec\theta + \iint_{\theta_1\ge\theta_2} (\theta_1-\theta_2) P_{\vec\theta}(A_{n_1,n_2})\pi(\vec\theta)d\vec\theta.
\end{aligned} \tag{3.1}
$$

PROOF. The term subtracted on the left-hand side of (3.1) is

$$
\begin{aligned}
&E\left[E(\theta_1|S_{n_1},T_{n_2}) \vee E(\theta_2|S_{n_1},T_{n_2})\right] \\
&\quad = \sum_{(k,j)\in A^c_{n_1,n_2}} \Big[\int_0^1\int_0^1 \theta_1 P_{\vec\theta}(S_{n_1}=k,T_{n_2}=j)\pi(\vec\theta)d\vec\theta\Big] \\
&\qquad + \sum\sum_{(k,j)\in A_{n_1,n_2}} \Big[\int_0^1\int_0^1 \theta_2 P_{\vec\theta}(S_{n_1}=k,T_{n_2}=j)\pi(\vec\theta)d\vec\theta\Big] \\
&\quad = \int_0^1\int_0^1 \theta_1 P_{\vec\theta}(A^c_{n_1,n_2})\pi(\vec\theta)d\vec\theta + \int_0^1\int_0^1 \theta_2 P_{\vec\theta}(A_{n_1,n_2})\pi(\vec\theta)d\vec\theta.
\end{aligned} \tag{3.2}
$$

The result follows from subtracting (3.2) from

$$
E(\theta_1 \vee \theta_2) = \iint_{\theta_1<\theta_2} \theta_2 \pi(\vec\theta)d\vec\theta + \iint_{\theta_1\ge\theta_2} \theta_1\pi(\vec\theta)d\vec\theta. \qquad \Box \tag{3.3}
$$

LEMMA 3.2. *If* π *satisfies a Lipschitz condition on the set* $\{(\theta_1,\theta_2):\ |\theta_1-\theta_2|\le\delta\}$ *for some* $\delta>0$, *then*

$$
E(\theta_1|S_{n_1},T_{n_2}) = S_{n_1}/n_1 + O(n_1^{-1}); \quad E(\theta_2|S_{n_1},T_{n_2}) = T_{n_2}/n_2 + O(n_2^{-1}).
$$

PROOF. Use Lemma 2.2. $\square$

LEMMA 3.3. *Under the condition of Lemma 3.2,*

$$\iint_{\theta_1<\theta_2-\delta}(\theta_2-\theta_1)\pi(\vec{\theta})P_{\vec{\theta}}(A^c_{n_1,n_2})d\vec{\theta} \tag{3.4}$$

and

$$\iint_{\theta_1>\theta_2+\delta}(\theta_1-\theta_2)\pi(\vec{\theta})P_{\vec{\theta}}(A_{n_1,n_2})d\vec{\theta} \tag{3.5}$$

converge to 0 *exponentially as* $n_1^{-1}+n_2^{-1}$ *goes to zero.*

PROOF. We prove (3.4) only. (3.5) can be proved by a similar argument. As a direct result of Lemma 3.2,

$$P_{\vec{\theta}}(A^c_{n_1,n_2}) = P_{\vec{\theta}}\Big(\frac{S_{n_1}}{n_1}-\frac{T_{n_2}}{n_2}+O(n_1^{-1}+n_2^{-1})\geq 0\Big) < P_{\vec{\theta}}\Big(\frac{S_{n_1}}{n_1}-\frac{T_{n_2}}{n_2}\geq -\delta/3\Big)$$

when $n_1^{-1}+n_2^{-1}$ is sufficiently small. According to the Central Limit Theorem,

$$\begin{aligned} P_{\vec{\theta}}\Big(\frac{S_{n_1}}{n_1}-\frac{T_{n_2}}{n_2}\geq -\delta/3\Big) &< 1-\Phi\left(\frac{-\delta/2-(\theta_1-\theta_2)}{\sqrt{n_1^{-1}\sigma^2(\theta_1)+n_2^{-1}\sigma^2(\theta_2)}}\right)\\ &< 1-\Phi\left(\frac{\delta/2}{\sqrt{n_1^{-1}\sigma^2(\theta_1)+n_2^{-1}\sigma^2(\theta_2)}}\right), \end{aligned} \tag{3.6}$$

where Φ is the standard normal cumulative distribution function and $n_1^{-1}+n_2^{-1}$ is sufficiently small. The last inequality in (3.6) holds because $\theta_1-\theta_2<-\delta$.

The lemma is proved since the right-hand side of (3.6) converges to zero exponentially and uniformly in $\vec{\theta}$, and

$$\iint_{\theta_1<\theta_2-\delta}(\theta_1-\theta_2)\pi(\vec{\theta})d\vec{\theta}\leq 1. \qquad \square$$

LEMMA 3.4. *Assume that* π *satisfies a Lipschitz condition in the region* $\{(\theta_1,\theta_2): |\theta_1-\theta_2|<\delta\}$ *for some* $\delta>0$. *Then*

$$I_1=\iint_{\theta_2-\delta<\theta_1<\theta_2}(\theta_2-\theta_1)\pi(\vec{\theta})P_{\vec{\theta}}(A^c_{n_1,n_2})d\vec{\theta}=\frac{c}{4}\Big(\frac{1}{n_1}+\frac{1}{n_2}\Big)+o\Big(\frac{1}{n_1}+\frac{1}{n_2}\Big), \tag{3.7}$$

$$I_2=\iint_{\theta_2+\delta\geq\theta_1\geq\theta_2}(\theta_1-\theta_2)\pi(\vec{\theta})P_{\vec{\theta}}(A_{n_1,n_2})d\vec{\theta}d\vec{\theta}=\frac{c}{4}\Big(\frac{1}{n_1}+\frac{1}{n_2}\Big)+o\Big(\frac{1}{n_1}+\frac{1}{n_2}\Big), \tag{3.8}$$

where

$$c=\int_0^1\sigma^2(x)\pi(x,x)dx=\int_0^1 x(1-x)\pi(x,x)dx, \tag{3.9}$$

and A_{n_1,n_2} is defined in Lemma 3.1.

PROOF. We prove (3.7); (3.8) follows by symmetry. According to Lemma 3.2 and the Central Limit Theorem,

$$
\begin{aligned}
P_{\vec\theta}(A^c_{n_1,n_2}) &= P_{\vec\theta}\Big(\frac{S_{n_1}}{n_1} - \frac{T_{n_2}}{n_2} + O(n_1^{-1}+n_2^{-1}) \geq 0\Big) \\
&= \Big[1-\Phi\big(\frac{\theta_2-\theta_1}{\sqrt{n_1^{-1}\sigma^2(\theta_1)+n_2^{-1}\sigma^2(\theta_2)}}\big)\Big][1+o(1)].
\end{aligned}
$$

Applying a Lipschitz condition, we have

$$
\pi(\theta_1,\theta_2) = \pi(\theta_1,\theta_1) + O(|\theta_2-\theta_1|).
$$

Therefore,

$$
\begin{aligned}
I_1 = \iint_{\theta_2-\delta<\theta_1<\theta_2} &\pi(\theta_1,\theta_1)\Big[(\theta_2-\theta_1)+O(\theta_2-\theta_1)^2\Big] \\
&\cdot\Big[1-\Phi\big(\frac{\theta_2-\theta_1}{\sqrt{n_1^{-1}\sigma^2(\theta_1)+n_2^{-1}\sigma^2(\theta_1+\xi)}}\big)\Big][1+o(1)]d\vec\theta,
\end{aligned}
$$

where ξ is between 0 and δ. Letting $u=\theta_2-\theta_1$,

$$
\begin{aligned}
I_1 = \Big(\int_0^{1-\delta}\int_0^{\delta} + \int_{1-\delta}^{1}\int_0^{1-\theta_1}\Big)\, &\pi(\theta_1,\theta_1)\Big[u+o(u^2)\Big] \\
&\cdot\Big[1-\Phi\big(\frac{u}{\sqrt{n_1^{-1}\sigma^2(\theta_1)+n_2^{-1}\sigma^2(\theta_1+\xi)}}\big)\Big][1+o(1)]dud\theta_1.
\end{aligned}
$$

Now let

$$
t = \frac{u}{\sqrt{n_1^{-1}\sigma^2(\theta_1)+n_2^{-1}\sigma^2(\theta_1+\xi)}}.
$$

Then

$$
\begin{aligned}
&\int_{1-\delta}^{1}\int_0^{1-\theta_1} \pi(\theta_1,\theta_1)\Big[u+o(u^2)\Big]\Big[1-\Phi\big(\frac{u}{\sqrt{n_1^{-1}\sigma^2(\theta_1)+n_2^{-1}\sigma^2(\theta_1+\xi)}}\big)\Big]dud\theta_1 \\
&\qquad = O\Big(\int_{1-\delta}^{1}\pi(\theta_1,\theta_1)\big(\frac{\sigma^2(\theta_1)}{n_1}+\frac{\sigma^2(\theta_1+\xi)}{n_2}\big)\Big[\int_0^\infty t(1-\Phi(t))dt\Big]d\theta_1\Big) \\
&\qquad = O\Big(\delta\big(\frac{1}{n_1}+\frac{1}{n_2}\big)\Big).
\end{aligned}
$$

Since

$$
\int_0^\infty t(1-\Phi(t))dt = 1/4,
$$

we have

$$\begin{aligned} I_1 &= \int_0^{1-\delta} \frac{1}{4}\pi(\theta_1,\theta_1)\Big(\frac{\sigma^2(\theta_1)}{n_1} + \frac{\sigma^2(\theta_1+\xi)}{n_2}\Big)d\theta_1 + O\left(\delta\Big(\frac{1}{n_1}+\frac{1}{n_2}\Big)\right) \\ &= \frac{1}{4}\int_0^1 \pi(\theta_1,\theta_1)\sigma^2(\theta_1)\Big(\frac{1}{n_1}+\frac{1}{n_2}\Big)d\theta_1 + O\left(\delta\Big(\frac{1}{n_1}+\frac{1}{n_2}\Big)\right). \end{aligned}$$

Letting δ go to 0, we obtain

$$I_1 = \frac{c}{4}\Big(\frac{1}{n_1}+\frac{1}{n_2}\Big) + o\Big(\frac{1}{n_1}+\frac{1}{n_2}\Big). \qquad \square$$

The following theorem gives the dominant terms of the optimal allocation in the first stage. Asymptotically, the arm with larger expectation with respect to the prior should be allocated to more patients in the first stage.

Theorem 3.1. *Assume that π satisfies a Lipschitz condition and is positive in the region $\{(\theta_1,\theta_2) : |\theta_1-\theta_2| < \delta\}$ for some $\delta > 0$. If n_1^* and n_2^* are optimal allocations, then*

$$n_1^* \sim \Big[\frac{0.5cN}{E(\theta_1\vee\theta_2|\pi) - E(\theta_1|\pi)}\Big]^{1/2}, \quad n_2^* \sim \Big[\frac{0.5cN}{E(\theta_1\vee\theta_2|\pi) - E(\theta_2|\pi)}\Big]^{1/2}, \tag{3.10}$$

where c is defined in (3.9).

Proof. According to Lemmas 3.1, 3.3, and 3.4,

$$E\Big[E(\theta_1|S_{n_1},T_{n_2}) \vee E(\theta_2|S_{n_1},T_{n_2})\Big] = E(\theta_1\vee\theta_2) - \frac{c}{2}\Big(\frac{1}{n_1}+\frac{1}{n_2}\Big) + o\Big(\frac{1}{n_1}+\frac{1}{n_2}\Big),$$

where c is defined in (3.9), and

$$\begin{aligned} W_2(N,(n_1,n_2),\pi) &= E(\theta_1\vee\theta_2) - \frac{n_1}{N}\Big[E(\theta_1\vee\theta_2) - E(\theta_1)\Big] \\ &\quad -\frac{n_2}{N}\Big[E(\theta_1\vee\theta_2) - E(\theta_2)\Big] - \frac{c}{2}\Big(\frac{1}{n_1}+\frac{1}{n_2}\Big) + o\Big(\frac{1}{n_1}+\frac{1}{n_2}\Big). \end{aligned}$$

Thus, the dominant terms of the optimal solutions of n_1 and n_2 must minimize

$$\frac{n_1}{N}\Big[E(\theta_1\vee\theta_2) - E(\theta_1)\Big] + \frac{n_2}{N}\Big[E(\theta_1\vee\theta_2) - E(\theta_2)\Big] + \frac{c}{2}\Big(\frac{1}{n_1}+\frac{1}{n_2}\Big).$$

(3.10) follows by differentiation. $\square$

If θ_2 is degenerate at λ and θ_1 has a prior π_1, then $c = \sigma^2(\lambda)\pi_1(\lambda)$. n_1^* is the same as the answer given by Corollary 2.1. However, n_2^* is not equal to 0. Therefore, Section 2 is not exactly a special case of Section 3, and should be addressed separately.

The order in which patients are assigned in the first stage is irrelevant. Since randomization minimizes the potential for bias in treatment assignment, first-stage patients should be randomized to the two arms, with proportions implied by (3.10). In the special case where θ_1 and θ_2 are exchangeable (that is, π is symmetric in its arguments), Theorem 3.1 indicates that the proportions allocated to the two arms should be equal (asymptotically). Therefore, in settings in which treatment arms are regarded as exchangeable a priori, Theorem 3.1 is a decision-theoretic justification of balanced randomized clinical trials. A discrepancy between the theorem and standard practice in medical research is that the theorem implies that overall trial size—order of magnitude $\sqrt{N}$—should depend on the prevalence of the disease or condition being treated and not on considerations of statistical power.

Table 3.1 shows the magnitude of the dominant terms of the optimal sizes.

$$m(1,\pi) = \Big[\frac{0.5c}{E(\theta_1 \vee \theta_2|\pi) - E(\theta_1|\pi)}\Big]^{1/2}, \quad m(2,\pi) = \Big[\frac{0.5c}{E(\theta_1 \vee \theta_2|\pi) - E(\theta_2|\pi)}\Big]^{1/2}.$$

Table 3.1

Prior π	$m(1,\pi))$	$m(2,\pi)$
$\theta_1 \sim$ Beta(1, 1) $\theta_2 \sim$ Beta(1, 1)	0.70711	0.70711
$\theta_1 \sim$ Beta(3, 1) $\theta_2 \sim$ Beta(3, 1)	1.00000	1.00000
$\theta_1 \sim$ Beta(1, 2) $\theta_2 \sim$ Beta(2, 1)	0.42640	2.0000
$\theta_1 \sim$ Beta(5, 1) $\theta_2 \sim$ Beta(1, 1)	1.58114	0.40825
$\theta_1 \sim$ Beta(1.5, 0.5) $\theta_2 \sim$ Beta(2, 2)	1.17670	0.48349

4. DISCUSSION

Section 2 addresses the case in which one treatment has known effectiveness. Because patient populations and diseases themselves change over time, and because physicians change their attitudes about which patients should be treated, this case has limited applicability in modern clinical trials. The main applications of Section 2 is to settings in which there is a well known standard therapy and a clinical trial will consist of an experimental therapy that will be compared to historical controls treated with the standard. The order of magnitude of the first stage is $\sqrt{N}$. The experimental therapy should be used exclusively in this first of two stages.

The second stage of a three-stage trial is the first stage of a 2-stage trial. Therefore, its length has order of magnitude $\sqrt{N}$. However, the length of the second stage will be different from the length of the first of a two-stage trial, and for two reasons. Firstly, N will have been decreased by the length of the first stage. Secondly, the length of the second stage will depend on the current distribution of θ which will have been updated from the initial distribution π based on the observations from the first stage.

In Section 3 neither arm has known effectiveness. As indicated in the Introduction, the case $r = 2$ applies both to a clinical trial conducted in two stages and to choosing a sample size for a single-stage clinical trial where N is the patient horizon. For a large class of prior distributions π, the optimal length of the first stage (or the clinical trial, in the second interpretation) is $\sqrt{N}$. Theorem 3.1 gives the proportional allocation to the two arms. If $\pi(\theta_1, \theta_2)$ is symmetric in its arguments then the numbers of patients allocated to the two arms should be (approximately) equal. Whether balanced or not, the order of patients allocated to the two arms is irrelevant. Therefore, allocation can (and should) be made randomly during this first stage.

Whether one or both arms have unknown characteristics, the order of magnitude of the length of the first stage of a 2-stage trial is $\sqrt{N}$. We conjecture that the length of the first stage of an $r-$stage trial is $\sqrt[r]{n}$ for arbitrary r. Moreover, we conjecture that this result holds for an arbitrary (but finite) number of arms, known or not.

An important message in our article is that the size of a clinical trial should depend on the prevalence of the disease or condition being treated. It should also depend on the possibility of future treatments being developed (because this affects the size of the patient horizon). A trial addressing overall effective treatment of a common ailment such as coronary artery disease should be larger than a trial to evaluate treatment of a rare form of cancer. In both cases the order of magnitude of the trial length should be $\sqrt{N}$, but N is much smaller in the second case.

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REFERENCES

Anscombe, F. J. (1963). Sequential medical trials. *Journal of the American Statistical Association.* **58** 365-383.

Bahadur, R. R. (1960). On deviations of the sample mean. *Ann. Math. Stat.,.* **31** 1015-1027.

Bather, J.A. (1981). Randomized allocations of treatments in sequential experiments (with discussion). *J Roy. Statist. Soc. Ser. B.* **43** 265-292.

Berk, R.H. (1966). Limiting behavior of posterior distributions when the model is incorrect. *Ann. Math. Statist..* **37** 51-58.

Berry, D.A. & Eick, S.G. (1995). Adaptive assignment versus balanced randomization in clinical trials: A decision analysis. *Statistics in Medicine.* **14** 231-246.

Berry, D.A. & Fristedt, B. (1985). *Bandit Problems, Sequential Allocation of Experiments.* Chapman and Hall.

Berry, D.A. & Pearson, L. (1985). Optimal designs for clinical trials with dichotomous responses. *Statistics in Medicine.* **4** 497-508.

Canner, P.L. (1970). Selecting one of two treatments when the responses are dichotomous. *J. Amer. Statist. Assoc..* **65** 293-306.

Cheng, Y (1996). Multistage Bandit Problems. *Journal of Statistical Planning and Inference.* **53** 153-170.

Cheng, Y (1994). Multistage Decision Problems. *Sequential Analysis.* **13** 329-350.

Colton, T. (1963). A model for selecting one of two medical treatments. *J. Amer. Statist. Assoc.* **58** 388-400.

Cornfield, J., Halperin M & Greenhouse S. W. (1969). An adaptive procedure for sequential clinical trials. *J. Amer. Statist. Assoc.* **64** 759-770.

Feldman, D. (1962). Contribution to the "two-armed bandit" problem. *Ann. Math. Statist..* **33** 847-856.

Gittins, J.C. (1979). Bandit processes and dynamic allocation indices. *J. Roy. Statist. Soc. Ser. B.* **41** 148-177.

Pearson, L. (1980). Treatment allocation for clinical trials in stages. Ph.D. Dissertation, School of Statistics, University of Minnesota.

Rodman, H. (1978). On the many-armed bandit problem. *Ann. Probab.*. **6** 491-498.

Schervish, M.J. (1995). *Theory of Statistics*. Springer-Verlag.

Su, F. (1996). Limit theorems on deviation probabilities with applications in two-armed clinical trials. Ph.D. Dissertation, Institute of Statistics and Decision Sciences, Duke University.

Whittle, P. (1980). Multi-armed bandits and the Gittins index. *J Roy. Statist. Soc. Ser. B.* **42** 143-149.

Witmer, J.A. (1986). Bayesian multistage decision problems. *Ann. Statist.* **14** 283-297.