AN EXPOSITORY REVIEW OF SEQUENTIAL DESIGN AND ALLOCATION RULES

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Abstract

In this short and expository review we provide a history of the problems of sequential designs and early results. Then we discuss bandit problems and clinical trials. Finally, we briefly discuss some other works on sequential designs. An extensive bibliography of papers appearing in the major statistical journals in the last decade is given.

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An Expository Review of Sequential Designs and Allocation Rules

1. INTRODUCTION

Most of the recent work done in sequential designs can be broadly classified into one of the following two closely related areas — n-armed bandit problems and allocation rules in clinical trials. In addition to these, there has been some interesting theoretical studies of the general sequential design problems, for example by Lalley and Lorden (1986) as initiated in Chernoff (1959) and continued in Kiefer and Sacks (1963). Mention may also be made of the study of consistency of least squares estimates of regression coefficients in stochastic regression problems when the design levels are chosen adaptively as in the Robbins–Monroe stochastic approximation algorithm. Finally, some work on sequential designs has been done in problems of ranking and selection. However, the overwhelming majority of the papers has been in the first two areas mentioned above. Fortunately, two excellent books on bandit problems are now available — Berry and Fristedt (1985) and Gittins (1989). A comparable monograph on clinical trials is urgently needed.

To simplify our task of review and preparation of bibliography, without sacrificing much, we have adopted the following guidelines. Except for a few important papers retained for historical reasons, we have confined ourselves to the literature of the last ten years, i.e. from 1979 onwards. Since there are excellent bibliographies as well as reviews of recent work on bandit problems in the two books mentioned above, we have included only a few of the more important papers listed there and excluded the others. Consequently, to obtain a complete bibliography, the interested reader should consult their lists together with ours. Together, these three lists are fairly exhaustive, at least in respect of the papers that have appeared in statistical journals. Our list was prepared primarily by consulting Mathematical Reviews and Statistical Theory and Methods Abstracts. We have not tried to cover the vast related literature on dynamic control and learning, most of which appears in journals of control theory, computer science or mathematical psychology. The interested reader can get some idea of these topics as well as their relation to sequential design problems from Herkenrath (1983) and the references contained therein.

This short and expository review contains a section on the history of the problem of sequential designs and early results, a section each on bandit problems and clinical trials and a section on other works in sequential designs.

2. HISTORICAL BACKGROUND AND EARLY RESULTS

The subject goes back to Thompson (1933) who introduced the two-armed bandit problem and pointed out its many applications in biology and medicine. The next important paper is by Robbins (1952), who introduced certain strategies for the above problem, including the one that "stays on the winner." Bradt, Johnson and Karlin (1956) treat these problems in great technical depth, proposing general formulations and showing that many intuitive expectations are false. They introduce and completely solve the so called one-armed bandit problem. Their result is stated here briefly for later reference.

Suppose X_1 and X_2 are Bernoulli $B(1,p_1)$ and $B(1,p_2)$ respectively with p_2 known and p_1 a random variable with known distribution F. The object is to make n independent observations (n is often called the "horizon") which may be either on X_1 or on X_2 (the two "arms") such that the expectation of the sum of observations is a maximum. In Bradt et. al. (1956), it is shown that there exists a function $Q(n,F)$ with the following property. If $p_2 > Q(n,F)$, use X_2 for all n trials. If $p_2 \leq Q(n,F)$, use X_1 for the first trial and compute the posterior distribution F' of p_1 and compare p_2 with $Q(n-1,F')$, following the same rule at subsequent choices. An important property of the optimal rule is that once an X_2 is picked, all subsequent observations are from X_2.

In (1962) Feldman proved a long standing conjecture for a two-armed bandit problem. Consider the previous scenario but assume that (p_1,p_2) are dependent random variables of a special kind: $P(p_1 = p, p_2 = 1-p) = 1 - P(p_1 = 1-p, p_2 = p) = \xi$ where p and ξ are known. In this case the optimal strategy turns out to be as anticipated, namely, the "myopic" rule that chooses at each trial, the X_i having maximum conditional probability of being one, i.e. as if only one trial remained at each stage. Though very elegant, it remains an isolated result which has not had much impact on the general theory where the arms have been assumed independent. In Feldman's set-up, use of one arm gives information on

both. For extension of Feldman's result in different directions, the interested reader may consult the references given on page 419 of Berry (1985).

Chernoff (1968) proposed a continuous version of the two-armed bandit problem. His conjecture on this problem has not been settled yet. Another conjecture of Chernoff (1968) attempting to relate one- and two-armed bandit problems is also unresolved in the finite horizon setting.

By far the next most important result is Gittins' solution of the n-armed bandit problems, under geometric discounting through what are called dynamic allocation indices (DAI) or Gittins indices. This will be discussed in the next section.

As indicated in the introduction, Chernoff (1959) had shown how one can construct asymptotically optimal rules for choosing sequential designs. Chernoff's results were extended by Kiefer and Sacks (1963) who showed that the following simple idea of a two stage sample works. In the first stage sample one makes inference about the parameters and based on this, in the second stage only the best design (in terms of Fisher information) is chosen. For example, in the case of an n-armed bandit with $X_i \sim B(1, p_i), i = 1, \ldots, n$, one may allocate the first stage observations equally among the X_i's and then in the second stage stick to the X_i with largest estimated $\hat{p}_i$ from the first stage. The asymptotics works if the sample sizes for both the stages tend to infinity with the ratio of the first to the second going to zero. In the case of two-armed bandits, strategies similar to this go back to Robbins (1952), who allows possibility for learning about p_i's throughout but only on a relatively thin subset of the observations. See Keener (1984) and Tsitovich (1984) for sharper asymptotics in the context of Chernoff's problem.

It has been noted by Chernoff (1975) that the asymptotically optimal rules discussed above do not perform well even for moderately large samples. Alternative procedures were proposed by Lindley (1956), DeGroot (1962), and Box and Hill (1967). In particular, Lindley measured the value of experiments by their entropies and used it to sequentially select the experiment to be performed at the next step. Box and Hill modify this by basing the choice on an upper bound of the entropies, which simplifies the calculations.

Monte Carlo experimentations by Meeter, Piric and Blot (1970) show that Box and Hill's method, even though suboptimal, does better than Chernoff's methods for some problems. For more details see page 78–79 of Chernoff (1975).

In the field of clinical trials, Anscombe (1963) was the first to point out the need for optimizing allocation of patients to treatments in contrast to the traditional equal allocation using randomization. Anscombe suggested that one should try to minimize the number of patients allotted to the inferior treatment. This would be similar to a two-armed bandit problem in which the goal is to minimize the use of the inferior arm. Though much theoretical work has been done on the allocation problem, it appears that the traditional rules are still used in practice. Some discussion of the basic issues as well as the theoretical results and the limitations to their being practically used will be attempted in Section 4.

3. THE n-ARMED BANDIT PROBLEMS

We begin by describing Gittins' theorem. Suppose Z_m is the value of the variable (one of the X_i's) observed at stage m. The value of the payoff is $\sum_{m=1} \alpha_m Z_m$ where α_m are called *discount factors*. The objective is to find strategies (which variable to observe at any stage) so that the payoff is maximized. If $\alpha_m = 0$ for all $m \geq k$ for some k, then we say that we have a finite horizon. If $\alpha_m = \alpha^{m-1}$ for $m \geq 1$ and $0 < \alpha < 1$, we say that the discount is geometric. Suppose we have $X_i \sim B(1, p_i), i = 1, \ldots, n$ and p_i's are independent with (prior) distributions $F_1, \ldots, F_n$. Suppose also that we have geometric discounting and we wish to maximize the total reward.

Consider an auxiliary one-armed bandit problem as discussed earlier in Section 2 but with an infinite horizon and geometric discounting. In this case also, there exists a function $\wedge(F, \alpha)$ similar to the function $Q(n, F)$, such that arm 1 (i.e. X_1) is optimal initially if and only if $p_2 \leq \wedge(F, \alpha)$ and arm 2 (the known arm i.e. X_2 with known p_2) is optimal if and only if $p_2 \geq \wedge(F, \alpha)$. For the n-armed bandit, the DAI initially for the n arms are respectively the numbers $\wedge(F_i, \alpha)$. At subsequent trials, F_i is to be replaced by the posterior $\hat{F}_i$ of p_i at that trial. The optimal procedure is to choose the arm with the largest DAI at each trial. An elegant exposition of this result, based on Whittle (1980) can be

found in Chapter 6 of Berry and Fristedt (1985), who also show that the theorem would fail without geometric discounting. For an excellent motivation, extension and diverse applications, see Chapters 2 and 3 of Gittins (1989). In Chapter 9 of Gittins (1989), there is a brief review of the important recent theoretical papers on this subject, due mostly to Bather, Glazebrook and Whittle. Glazebrook and Whittle have extended the theorem in various ways, whereas Bather (1983) has obtained approximations using the Brownian motion, with tools of Bather (1962) along the lines initiated by Chernoff (1968). Glazebrook has also considered the effects of using various suboptimal policies.

One of the practical difficulties in implementing the optimal policy is that the DAI's are often difficult to compute. For some cases, tables have now been provided by Gittins (1989). There are two other serious difficulties in applying this optimal policy. The first is a philosophical one and relates to whether one believes in a Bayesian paradigm with a completely specified prior. It appears that the DAI's are sensitive to small deviations in the priors. The second difficulty relates to the sensitivity of DAI's to the choice of the discounting factor α, specially for α near 1. This is disturbing because, in practice, one may often want to use the discounted problem as an approximation to the undiscounted problem with a finite horizon.

In view of these difficulties and partly owing to the fact that the horizon though finite is often unknown, Bather (1980) has introduced stationary strategies using randomized allocation indices. Let $\{\lambda(n), n \geq 1\}$ be a sequence of strictly positive numbers such that $\lambda(n) \to 0$ as $n \to \infty$. Let $X_j(t), j = 1, \ldots, k, t \geq k$ be i.i.d. random variables which are positive and unbounded with common distribution function F. Initially each of the k treatments is used once initially and after t $(\geq k)$ trials, suppose $r_i(t)$ is the observed number of successes with treatment i being applied in $n_i(t)$ trials. Then the $(t+1)$th treatment is chosen to maximize $Q(t) = \max_{1 \leq i \leq k} Q_i(t)$ where $Q_i(t) = r_i(t)/n_i(t) + \lambda(n_i(t))X_i(t)$. Bather showed that these strategies are asymptotically optimal in a somewhat weak sense. Specifically, as $t \to \infty$, $\sum_{i=1}^{k} r_i(t) / \sum_{i=1}^{k} n_i(t) \xrightarrow{a.s.} \max(p_1, \ldots, p_k)$. The proof requires a martingale convergence theorem due to Chow (1965).

After considerable simulations and comparison with other allocation rules, Bather has

singled out the choices $\lambda(n) = (4+n)^{\frac{1}{2}}/15n$ and $X_i(t) = 2+Y_i(t)$ where $Y_i(t)$ are i.i.d. with density $e^{-x}, x > 0$. In Bather (1983) an approximate minimax property is proved with respect to a risk that measures the expected number of successes lost due to ignorance, i.e. the difference of $E\max(p_1, \ldots, p_k)$ and the expected number of successes for the strategy under consideration. Later Bather (1985) reports simulations with respect to this risk and makes out a strong case for use of his simple but effective strategy.

In this connection mention may be made of Simons (1986) who advocates sampling in pairs, until enough information is obtained on which treatment is better out of the two treatments under consideration and then allocate the remaining treatments to the better treatment. Here the stopping time of the first stage is determined as a solution to a Bayes problem.

Both Bather and Simons feel that their solutions are suitable for use in clinical trials. Simons has indicated that his method can take care of ethical costs introduced by Chernoff and Petkau (1985).

Finally we mention briefly some of the recent works that are not discussed in the two books on bandit problems. Mandelbaum (1988) provides an overview of his work on discrete and continuous time multiarmed bandit problems which is based on a multiparameter formulation. Among other things he explains the role played by simultaneous pulls of different arms and the Snell envelope martingale approach in optimal stopping. Some open problems are also mentioned. Eplett (1980) develops a convergence theory mainly to investigate whether approximating continuous-time problems by discrete time versions provides valid techniques. Lai (1988) provides a review and discussion on asymptotically optimal solution of some bandit problems. Ananthram et. al. (1987a) study the multiarmed bandit with multiple plays and obtains asymptotically optimal solution. This extends the work of Lai and Robbins (1985) who considered single plays. In Ananthram et. al. (1987b), this work is further extended to the situation where the reward sequence is necessarily i.i.d. but only Markovian. Agrawal et. al. (1988) extend the work of Lai and Robbins (1985) in a different direction by allowing a cost of switching between arms.

4. ALLOCATION AND ANALYSIS OF CLINICAL TRIALS

The basic problem of allocation in clinical trials is to allocate patients to one of two different treatments with goals of identifying the better treatment and/or minimizing the total number of patients receiving the inferior treatment (ITN).

In Anscombe's (1963) formulation for selecting the better of two treatments with a specified total number of N patients, there is a trial phase in which n (random) pairs are given both treatments and a decision is made regarding which is superior. The remaining $(N-2n)$ patients are then assigned to the (apparently) superior treatment. The problem then is to decide when to stop the trial phase because an early stopping may lead to a wrong decision about the efficacy of the treatments while a long trial phase will result in a large number of patients being allocated to the inferior treatment (known as the inferior treatment number (ITN)). Assuming that the difference in treatment response is normal with mean δ and known variance σ^2, and that δ has a prior G, Anscombe found the Bayes procedure which minimizes (with respect to n) the Bayes risk

$$\int_{-\infty}^{\infty} R(\delta, n) dG(\delta)$$

where

$$R(\delta, n) = \begin{cases} \delta E_\delta\{n + (N-2n)I(S_n < 0)\} & \text{if } \delta > 0 \\ (-\delta)E_\delta\{n + (N-2n)I(S_n > 0)\} & \text{if } \delta < 0. \end{cases}$$

with S_n denoting the sum of the observed treatment differences. He also suggested an ad hoc procedure when G is flat and it performs very well compared to the optimal procedure as shown later by Lai et. al. (1980). Lai et. al. (1980) also suggested another rule and made a thorough study of all the three rules, mathematically for large N and by Monte Carlo studies for small N. They also give a class of stopping rules which is asymptotically optimal, both from the Bayes and frequentist point of view as $N \to \infty$. The mathematical details of these results can be found in Lai and Siegmund (1983). Lai and Siegmund (1983) also study the rules proposed by Begg and Mehta (1979) and that of Colton (1963) and found that these rules perform poorly when compared to the optimal. A continuous version of this problem was taken up by Chernoff and Petkau (1981), who obtain similar results. The continuous version provides good approximation to the discrete problem even with

small horizon sizes. See Bather (1985) for comparison of different rules when the responses are Bernoulli.

Robbins and Siegmund (1974) point out that the inference and allocation problems can be separated for translation invariant procedures in the sense that the error probabilities or risk due to terminal decision is the same for a class of allocation rules. They formulate the problem of testing which of the two normally distributed treatment responses with a known common variance has the larger mean as follows. Let $X_1, X_2, \ldots, X_m, \ldots$ and $Y_1, Y_2, \ldots, Y_n, \ldots$ denote two independent normally distributed treatment responses with means μ_1 and μ_2, respectively, and a common variance 1, and let $\delta = \mu_2 - \mu_1$. To test H_0: $\delta = -\delta^*$ against H_1: $\delta = \delta^*$, the stopping rule used is

$$(M, N) = \inf\{(m, n): Z_{m,n} \notin (-b, a)\}$$

where $Z_{m,n} = \frac{mn}{m+n}(\overline{Y}_n - \overline{X}_m)$ and a and b are positive, and one accepts $H_0(H_1)$ if $Z_{M,N} < -b(> a)$.

The error probability functions of the procedure with the above stopping rule are independent of the allocation rule used. This fact can be used to consider various allocation rules aiming to minimize ITN. Robbins and Siegmund (1974) propose the following allocation rule. Choose $c \geq b$, Observe x_1 and y_1. For $m, n = 1, 2, \ldots$, having observed $x_1, x_2, \ldots, x_m$ and $y_1, y_2, \ldots, y_n$, the next observation should be y_{n+1} if $\frac{n-m}{m+n} \leq \frac{Z_{m,n}}{c}$, and x_{m+1} should be observed otherwise. Here c may be a constant or a function of b and $\frac{mn}{m+n}$. Monte Carlo studies on this allocation rule for different values of b and c show that for some parameter values ITN is one half of the sample size required by pairwise sampling, which is the minimum attainable ITN for any allocation rule. They also show that any departure from pairwise sampling increases the total expected sample size. See also Siegmund (1985, Chapter 6, Section 3) for a discussion of the above results. Flehinger et. al. (1972) discuss these results in brief. An excellent discussion of these issues is given in Siegmund (1983). He also describes a heuristic rule due to Hayre (1979) which is expected to be approximately optimum. A comparison of this rule with that of Bather (1985) and Simons (1986) would seem desirable. On the basis of a few simulations, Siegmund notes that in

the absence of stratification, the new allocation rule does substantially better than the equal allocation rule but this advantage disappears if stratification is introduced. These comparisons have been made in the context of a stopping and terminal decision rule due to Armitage but similar conclusions have been reached by Hayre (1979) in the context of a different stopping rule.

In the case of K treatments, all with unknown efficacies and with a long sequence of patients, Lai and Robbins (1985) study the problem of maximizing the total expected treatment response (i.e. as a k-armed bandit problem). Let $\pi_j, j = 1, 2, \ldots, k$ denote the K populations with treatment responses specified by univariate density functions $f(x, \theta_j), j = 1, 2, \ldots, K$ w.r.t. some measure ν with $f(.,.)$ known and θ_j's $\in \Theta$ unknown. Assume that

$$\int_{-\infty}^{\infty} |x| f(x, \theta) d\nu(x) < \infty \quad \forall\, \theta \in \Theta.$$

Define the regret as

$$R_n(\vec{\theta}) = n\mu^* - E(S_n) = \sum_{j:\mu(\theta_j)<\mu^*} (\mu^* - \mu(\theta_j)) E(T_n(j))$$

where $\vec{\theta} \equiv (\theta_1, \theta_2, \ldots, \theta_k), \mu(\theta) = \int_{-\infty}^{\infty} x f(x, \theta) d\nu(x)$, and $\mu^* = \max\{\mu(\theta_1), \ldots, \mu(\theta_K)\} = \mu(\theta^*)$ for some $\theta^* \in \{\theta_1, \ldots, \theta_K\}$. Here $T_n(j)$ is the number of times patients are allocated to π_j upto stage n and S_n is the partial sum of treatment responses upto stage n. Thus, maximizing $E(S_n)$ is equivalent to minimizing $R_n(\vec{\theta})$.

Lai and Robbins (1985) show that under certain conditions on these K density functions (involving Kullback-Leibler number) and the allocation rules satisfying $R_n(\vec{\theta}) = o(n^a) \quad \forall\, a > 0$,

$$\liminf_{n\to\infty} R_n(\vec{\theta}) / \log n \geq \sum_{j:\mu(\theta_j)<\mu^*} (\mu^* - \mu(\theta_j)) / I(\theta_j, \theta^*)$$

for all $\vec{\theta}$ s.t. $\mu(\theta_j)$'s are not all equal.

Here, $I(\theta_j, \theta^*) = \int_{-\infty}^{\infty} [\log(f(x, \theta_j)/f(x, \theta^*))] f(x, \theta_j) d\nu(x)$ is the Kullback-Leibler number involving $f(x, \theta_j)$ and $f(x, \theta^*)$. Lai and Siegmund (1985) construct adaptive allocation rules for which the above lower bound is attained as $n \to \infty$. Under certain

conditions, they give an asymptotic lower bound for the regret which is $0(\log n)$ and propose an adaptive allocation rule attaining it. With a knowledge about a separating value between the largest and the other means, one can achieve a bounded regret as shown by Lai and Robbins (1984b). The bounded regret can also be obtained for some configurations if the set of the possible values of the parameter is countable, see Lai and Robbins (1984a). Lai (1987) provides asymptotically optimal adaptive rules for a general exponential family.

Even though an allocation problem may be formulated as a bandit problem, there are factors dictating the choice of sequential designs which preclude the direct application of bandit problem techniques. For instance, while comparing two treatments, the objective may not be maximizing the total number of successes, but minimizing the number of applications on the inferior arm, together with an objective of inference about which arm is superior.

Randomization in various forms have been used to correct for imbalance and selection bias. See Blackwell and Hodges (1957) for one of the early works. Adaptive designs use some subset of the information available at any given time to determine how to allocate the next patient or whether to stop the trial. Consider a situation where subjects arriving sequentially have to be assigned to a treatment or to a control. Complete randomization is achieved by assigning each subject to one of these with equal probability, independently of the assignment of other subjects. This has three important advantages. First, if the experimenter knows for certain that the next assignment will be a treatment or control, he may consciously or unconsciously bias the experiment by such decisions as to who is, or is not a suitable experimental subject etc. This is known as selection bias and complete randomization guarantees freedom from such bias. Second, complete randomization tends to balance out factors which can cause accidental bias. Typically, this bias comes from nuisance factors such as time trends, sex-linked differences etc., systematically affecting the experimental units. Third, probability statements such as the significance level attained can be based entirely on this randomness. However in experiments which are limited to a small number of subjects, complete randomization may lead to a very imbalanced distribution of treatments and controls. To avoid this, Efron (1971) introduced the biased

coin design which can be described as follows. The subjects might be divided into categories depending on common factors. The assignment of treatments is done separately for each category. Suppose that at a certain stage in the experiment a new subject arrives and is noted to be in a category which has had D more treatments than the control previously assigned to it. If $D > 0$ the subject is assigned to the treatment with probabilty q and to control with probabilty p. If $D < 0$ the probabilities are switched and if $D = 0$, the probabilities are half each. Here $p \geq q$ and $p + q = 1$. When $p = \frac{1}{2}$ it reduces to complete randomization and when $p = 1$ it is a permuted block design with block size 2. (In a permuted block design of block size $2b$ the subjects are divided into blocks of length $2b$ and within each block b units are assigned to the treatment and b to the control and all combinations are equally likely.) Efron shows that the choice $p = \frac{2}{3}$ performs quite well in reducing the imbalance and studies the effect of his designs on accidental and selection bias. For small size experiments these designs often behave like permuted block designs. Efron's design does not distinguish between large and small nonzero absolute values of D. It does not also distinguish between large and small size experiments.

To take this into account, Wei (1978a) introduced adaptive biased coin designs for comparing two treatments. As in Efron (1971) the assignment of treatments is done separately in each stratum. The total number of patients is assumed to be known. The first assignment is done randomly. After n assignments let $D_n = N_A - N_B$ where N_A and N_B are the number of subjects assigned to treatments A and B respectively. Let p be a nonincreasing function of D_n/n with values between 0 and 1. The $(n+1)$th subject is assigned to treatments A and B respectively with probabilities $p = p(D_n/n)$ and $q = q(D_n/n)$. Here p is such that $p(x) = q(-x)$ for $x \in [-1, 1]$. Efron's (1971) design is a special case with $p(x) = p$ for $-1 \leq x \leq 0$, and $p(0) = \frac{1}{2}$. Wei shows this design almost eliminates selection and experimental biases as the size of the experiment increases. In particular if p is continuous at 0, then as $n \to \infty$ $Ep(-\frac{|D_n|}{n}) \to \frac{1}{2}$ and $E(T_n T_{n+k}) \to 0$ for $k = 1, 2, \ldots$ where $T_j = 1$ or -1 according as the jth subject is assigned to A or B. Further, if p is differentiable at 0, then $n^{-\frac{1}{2}} D_n$ converges to a normal distribution with mean 0 and variance $1/(1 - 4p'(0))$ thereby showing an asymptotic balancing property.

In comparing K treatments, Wei (1978b) introduced an urn design which is an extension of a design due to Friedman (1949) and can be described as follows. An urn contains balls of K different colors. We start with w balls of color k, where $k = 1, \ldots, K$. A draw consists of the following operations: (i) select a ball at random from the urn; (ii) notice its color k' and return the ball to the urn; (iii) add to the urn α more balls of color k' and β more balls of each other color k, where $k \neq k'$. Each time a subject is waiting for an assignment, we draw a ball at random from the urn; if its color is k', then the treatment k' is assigned. The values of w, α, and β can be any reasonable nonnegative integers. If β is large with respect to α, then this design forces the trial to be balanced. The value of w determines the first few stages of the trial. If w is large, more randomness is introduced to the trial; otherwise more balance is enforced.

This design also forces small size experiments to be balanced but tends towards complete randomization as the experiment size increases. When the number of prognostic factors increases, the number of strata also increases and then very few patients may fall within each stratum. Wei also proposes a treatment assignment rule which achieves a degree of treatment balance simultaneously across all prognostic factors. For further theoretical investigations of these designs, see Smith (1984 a, b).

Another interesting adaptive design is the randomized play-the-winner rule of Wei and Durham (1978). Zelen (1969) introduced the play-the-winner rule (PW), which prescribes that a success with a given treatment generates a future trial with the same treatment, while a failure generates a trial with the alternative treatment. Wei and Durham (1978) propose a randomized play-the-winner rule, which keeps the spirit of the PW rule in that it assigns more patients to the better treatment. But this new rule has the advantages that it is not deterministic, is less vulnerable to experimental bias, allows delayed response by the patient, and is easily implemented in a real trial.

Suppose that the response of the patient to treatment is dichotomous, either a success or a failure, and the probability of a single trial success for treatment i is p_i, where $0 < p_i < 1$ and $i = A, B$. The randomized play-the-winner rule can be described as follows: A box has balls of two different types which are marked A and B. We start with

u balls of each type. When a patient is available for an assignment, a ball is drawn at random and replaced. If it is type i, then treatment i is assigned to this patient, where $i = A, B$. When the response of a previous patient to treatment i is available, we change the structure of the box based on the following rule: If this response is a success, then an addition β balls of type i and an additional α balls of type j are put in the box; if this response is a failure, then an additional α balls of type i and an additional β balls of type j are put in the box, where $\beta \geq \alpha \geq 0; i, j = A, B$; and $j \neq i$. Thus after each response, exactly $\alpha + \beta$ additional balls are added to the box. When the box is empty, a fair coin is tossed to decide which treatment is assigned in the next trial. We denoted this rule by RPW (u, α, β). In a small trial, the RPW (0, 0, 1) is better than the PW rule for some values of p_A and p_B with regard to expected numbers of patients assigned to the better treatment. The rule RPW (u, α, β) introduces more randomization when β/α is small, but tends to put more patients on the better treatment when β/α is large. For two of the few well documented cases of use of this design due to ethical considerations in actual clinical studies, see Bartlett et. al. (1985), Cornell et. al. (1986) and Ware (1989).

Among statistical tests applied to clinical trials repeated significance tests (RST) have received the most attention and have been both criticized and defended by researchers. When used for a two treatment comparison, an RST is a paired comparison test where at each stage, the two members of a pair of patients are subjected to the two alternative treatments under consideration and the responses are compared to decide whether to stop or continue the experiment. Let $X_i, i \geq 1$ be i.i.d. $N(\mu, 1)$ denoting the treatment difference of the i-th pair. To test $H_0 : \mu = 0$ against $H_A : \mu \neq 0$, an RST is defined by the stopping rule,

$$T = \inf\{n \geq m_0 : |S_n| > b\sqrt{n}\}, \tag{4.1}$$

where $m_0 \geq 1$ and $S_n = \Sigma_{i=1}^{n} X_i$. The test procedure stops sampling at min (T, m) and rejects H_0 if $T \leq m$. Here m and m_0 are the maximum and the minimum number of pairs under trial, respectively.

As in most other sequential tests, numerical analysis has been extensively used to study the properties of RST. Armitage et. al. (1969), and McPherson and Armitage (1971) evalu-

ated significance levels, powers and expected sample sizes of RST's by numerical methods. See also Armitage (1975). Woodroofe (1978) and Lalley (1983) obtained analytical approximation to significance levels of RST's for exponential families. See also Woodroofe (1982), and Woodroofe and Takahashi (1982).

Siegmund (1985) presents an extensive analytical study and review of the RST. Theories developed in Chapter 4 of Siegmund focus on RST for Brownian motion and on obtaining approximations for power function and expected sample size. These enable one to make similar approximations for a wide class of stopping boundaries. Siegmund (1985, Chapter 4, section 7) points out that exact results can be obtained for RST with a special set of nonlinear boundaries. RSTs for general one parameter families are also discussed in Chapter 4, section 8. See Chapter 9 for analytical studies of RSTs defined by equation 4.1 using nonlinear renewal theory. RSTs with more than two treatments (Chapter 5, section 3) and modified RSTs (Chapter 4, section 4) are also discussed. Modified RSTs have been developed to increase the power of RST. In the usual two-treatment, normal response set up, the stopping time of modified RST is the same as (4.1) with a larger value of b and the rejection region is given by $T \leq m$ or $T > m, |S_m| > c\sqrt{m}$ with $0 < c \leq b$. This procedure reduces to a fixed sample test if $b = \infty$ and to the usual RST if $b = c$. Thus it can be regarded as an intermediate form of these two tests. In a recent paper Hu (1988) reviews analytic techniques for working with modified RST's and extends results for normal families to general exponential families. See Hardwick (1989 a) for RST's which incorporate ethical costs.

In contrast to an RST which considers only a pair of patients at a time, group sequential designs apply significance tests to groups of patients (hence the name group) in order to avoid the difficulty of continuous assessment of data. In each group, patients are allocated to the alternative treatments according to some fixed scheme. For two-treatment normal response with known variance, Pocock (1977) points out the most attractive feature of group sequential designs – the early stopping of trials when the alternate hypothesis is true. Numerical studies in Pocock (1977) show that the use of two groups leads to substantial reduction of expected sample size under the alternate hypothesis over a one group

experiment, but the incremental benefit from an additional group is negligible if there are more than five groups. Pocock used equal group size and constant nominal significance level throughout the trial so that the overall significance level is the prespecified α. Extensive numerical studies help to determine the suitable values for the maximum number of groups and the size of the groups.

Often, studies on these designs have focused on the finding of Type I error i.e. on the determination of nominal significance levels at which tests are performed at different stages of the experiment so that the overall level of significance is the prespecified α. For two treatments and normal response with known variance, Pocock (1982) performed numerical studies to show that the use of varying nominal significance levels, more stringent at early stages and less so at the later stages, is more efficient than using a constant nominal significance level at all stages unless one has adequate overall size and power. See DeMets (1984) for an account of the experience of several clinical trials involving such interim analyses. Geller and Pocock (1987) mention several problems which need attention in group sequential schemes. In particular no group sequential work has been done in comparing more than two treatments.

Lan and DeMets (1983) propose a method to determine the boundary at arbitrary time intervals for a choice function $a(t)$ which characterizes the nominal significance levels in a group sequential trial. A major finding of this paper is that the boundary does not depend on the maximum number of groups as has been the case with Pocock (1977, 1982), O'Brien and Fleming (1979), DeMets and Ware (1980), DeMets (1984), Siegmund (1985), Slud and Wei (1982) and Whitehead (1990). For an overview of this topic, see DeMets and Lan (1984).

The studies discussed so far consider a single measurement of each patient. In a departure from that practice, Armitage et. al. (1985) present an interesting modification of the group sequential test where the number of patients for each treatment group is predetermined and repeated measurement is taken on each patient in each group.

Construction of confidence interval for the mean treatment difference following a sequential test has drawn the attention of many researchers. These studies have usually been motivated by the fact that tests alone are not sufficient for the final decision in comparing treatments, especially after rejecting the null hypothesis. Tsiatis et. al. (1984) suggested the construction of confidence intervals following group sequential tests based on numerical integration. Their procedure requires equal sample sizes at every stage. Kim and DeMets (1987a) modified the procedure of Tsiatis et. al. (1984) such that the requirement of equal sample size at each stage is relaxed, and it is possible to use the group sequential tests of Lan and DeMets (1983) which require no prior specification of the maximum number of groups. Other works in this area are by Jennison and Turnbull (1983, 1984, 1990), Siegmund (1985) and Rosner and Tsiatis (1988). Siegmund (1985) discussed interval estimation following sequential tests in Chapter 3 (sections 3 and 6), and confidence interval following an RST in Chapter 4, section 5.

Often it is desirable to allocate subjects as part of a group, for example, in multicenter trials. Multi-stage designs to handle this have been proposed as a variation on complete randomization, by Berry and Pearson (1985) and Witmer (1986), among others. However, these methods have seldom been used in practice. Adaptive multi-stage designs offer compromise between fully sequential and fixed proportion allocation rules. See Hall (1981), Siegmund (1985), Clayton and Witmer (1988), Woodroofe (1988) and Lorden (1988) for further discussion.

Recently researchers have tried to introduce ethical considerations into the designs. Tymchuck (1981, 1982) offers some discussion on how to structure decision processes, quantifying ethical considerations. See Woodroofe and Hardwick (1988) and Hardwick (1989 a) for decision theoretic formulations, in which ethical costs are explicitly expressed in the loss function. Lai (1984) introduces the concept of a confidence sequence incorporating ethical costs in situations where there are possibilities for early termination, unforeseen harmful effects and of no definite conclusions. Chernoff and Petkau (1985) formulate the following problem incorporating ethical cost. Suppose that a finite number N of patients are given one of two available treatments. During the experimental stage n patients are

paired and assigned to one of the two treatments at random. Let $X_1, X_2, \ldots$ denote the differences of the responses. Suppose they are i.i.d. $N(\mu, \sigma^2)$ where σ^2 is known. Suppose further that μ has a prior distribution $N(\mu_0, \sigma_0^2)$. The posterior distribution of μ is $N(Y_n, s_n^2)$ where $Y_n = (n\overline{X}_n + \sigma_0^{-2}\mu_0)/(n + \sigma_0^{-2})$ and $s_n^2 = n + \sigma_0^{-2}$ and $\overline{X}_n$ is the sample mean. The problem is to find a stopping time T which minimizes the expected value of

$$T|\mu| + (N - 2t)|\mu| I(\mu Y_n < 0) + \sum_{i=1}^{t} |Y_{i-1}|.$$

Here $T|\mu|$ denotes the cost of giving an inferior treatment to T patients (one from each pair), $(N - 2t)\mu I(\mu Y_n < 0)$ represents the danger of choosing the inferior treatment and $\sum_{i=1}^{T} |Y_{i-1}|$ represents the ethical cost. This stopping problem is analyzed by a continuous approximation. They provide extensive numerical analysis, tables and charts from which the optimal procedure may be approximated.

Woodroofe (1979, 1982) introduced designs incorporating covariates. Consider a population of N subjects. Let X, Y^0, Y^1 denote respectively the covariate and potential responses of a typical subject to the control and the new treatment. Suppose that X has a known distribution F, the conditional distribution $G_0(\cdot|x)$ of Y^0 given $X = x$ is known and the conditional distribution $G_1(\cdot|x, \theta)$ of Y^1 given $X = x$ depends on an unknown parameter $\theta \in \Omega$ and θ has a known prior distribution π. Y^0, Y^1 are real valued with finite expectations but X and θ may be quite general. An allocation policy is a sequence $\delta = (\delta_1, \ldots, \delta_N)$ where each δ_k is 0 or 1 and δ_k is a measurable function of $X_1, \ldots, X_{k-1}$, $\delta_1, \ldots, \delta_{k-1}$ and (X_k, Y_k^0, Y_k^1) is the response of the kth subject. The value $V_N(\delta, \pi)$ is given by

$$V_N(\delta, \pi) = E^{\pi}\left(\sum_{k=1}^{N} (\delta_k Y_k^1 + (1 - \delta_k) Y_k^0)\right).$$

The optimal policy to maximize $V_N(\delta, \pi)$ has been obtained by backward induction. Several inequalities and limits (as $N \to \infty$) for the optimal policy and the resulting payoff have been given, along with a class of problems for which the limit of the optimal policy has a simpler form. Woodroofe (1979) studied a special case of this problem. Interestingly, in the presence of a covariate, an approximate solution is simpler to obtain, the discount factor is less important and the myopic strategy is asymptotically optimal. See also Clayton (1988)

and Sarkar (1989) for further recent work.

For work involving delayed response, see Wei and Durham (1978), who uses a randomized play-the-winner strategy with the possibility of delayed response. For other works, see Eick (1988a,b) and Flournoy (1989). Eick (1988a) introduces a two-armed bandit problem with delayed response. He shows that the delay introduces a new parameter and the bandit is no longer a stopping problem. In clinical trial applications, this delay parameter represents the number of patients previously treated with the unknown arm who are still living. Under regularity conditions on the discount sequence, there exists a manifold in the state space such that both arms are optimal on it, and arm 1 is optimal on one side and arm 2 on the other.

The use of control is important in clinical trials. Berry (1989c) in his discussion of Ware (1989) points out that there has not been much applied research on the use of historical controls, probably because it is not a problem of high priority. For a review on the use of controls, particularly when there are more than one control, see Rosenbaum (1987).

Nonsimultaneous (staggered) entries and possible drop outs cause complications in the statistical analysis. See Olschewski and Schumacher (1986) for a useful account of some of the implications of this on the classical parametric and nonparametric procedures.

To conclude this section, we like to mention the unfortunate fact that despite the vast literature on clinical trials, very few techniques are implemented in practice. Simon (1977) and more recently Armitage (1985) discuss these problems. Armitage (1985) pleads for a closer collaboration between the theoreticians and the statisticians who have to design and analyze clinical trials.

5. OTHER WORKS

In this section, we mention a few papers on other sequential design problems.

Lai (1983) reviews and clarifies the assumptions needed to obtain consistency of regression coefficient estimates in a stochastic regression problem when the design points

are chosen adaptively. He derives similar results for autoregressive time series and input-output models.

Lalley and Lorden (1986) refine the results of Chernoff on asymptotically optimal designs. Under strong assumptions, they provide rules whose asymptotic payoff differs from the optimum asymptotic payoff by a constant, and show it is possible to obtain a bound for this constant. While the result is interesting, its applicability is restricted by the rather strong assumptions.

Gebhardt and Heckendorff (1983) propose a sequential design for the regression problem based on heuristic considerations. From numerical simulations, they found that for linear models and for a small number of experiments there may be considerable improvement over non-sequential experiments in A- and D-criterion. Vuchkov (1982) shows how nearly D-optimal designs can be sequentially generated in some situations. Wu (1985a) shows that confidence regions for nonlinear parameters constructed by the repeated-sampling principle, are asymptotically valid for sequential designs in general linear models. Ford, Titterington and Wu (1985) show that to make inferences, the sequential nature of the design can be ignored asymptotically. They also provide some links to inference for stochastic processes and missing data problems.

For problems involving serial sacrifice experiments, see Bergman and Turnbull (1983). See also Hu and Wei (1989) who propose "irreversible adaptive allocation rules" motivated by the problem of scheduling such experiments. They obtain asymptotically efficient procedures and show that a lower bound for the regret is characterized by a linear programming problem.

Segreti et. al. (1981) discusses an interesting problem of finding an optimum combination of a new and standard treatment through sequential trials of different combiantions.

Shapiro (1983) discusses a problem of estimating two parameters simultaneously and finds asymptotically optimal rules.

Petruccelli (1982) and Chen et. al. (1984) discuss two different problems of sequentially observing variables subject to certain constraints and discuss their applications in clinical

trials.

Wu (1985b) discusses a sequential design for estimating the percentiles of a quantal response curve and derive its optimal properties.

References

Adelin, A. (1983). Discriminant analysis based on multivariate curve: A descriptive approach to dynamic allocation. *Stat. Med.*, **2**, 95–106.

Agrawal, R., Hegde, M.V. and Teneketzis, D. (1988). Asymptotically efficient adaptive allocation rules for the multiarmed bandit problem with switching cost. *IEEE Trans. Automat. Control*, **33**, 10, 899–906.

Aickin, M. (1982). A program for balancing the allocation of subjects to treatment in clinical trials. *Cmp. Bimd. R.*, **15**, 519–524.

Aickin, M. (1983). Some large trial properties of minimum likelihood allocation. *J. Stat. Plann. Inf.*, **1**, 11–20.

Ananthram, V., Varaiya, P. and Walrand, J. (1987b). Asymptotically efficient allocation rules for the multiarmed bandit problem with multiple plays. I. I.I.D. rewards. *IEEE Trans. Automat. Control*, **32**, 11, 968–976.

Ananthram, V., Varaiya, P. and Walrand, J. (1987b). Asymptotically efficient allocation rules for the multiarmed bandit problem with multiple plays. II. Markovian rewards. *IEEE Trans. Automat. Control*, **32**, 11, 977–982.

Angell, M. (1984). Patient's preferences in randomized clinical trials. *New England J. Med.*, **310**, 1385–1387.

Anscombe, F.J. (1963). Sequential medical trials. *J. Amer. Stat. Assoc.*, **58**, 365–383.

Arikawa, S. (1981). One-way sequential search systems and their powers. *Bull. Math. Statist.*, **19**, III/IV, 69–85.

Arkles, L. and Srinivasan, R. (1979). On the sequential selection of the better of two binomial populations. *Sankhyā B*, **41**, 15–30.

Armitage, P. (1975). *Sequential Medical Trials.* Second Edition. Blackwell Scientific Publications, Oxford, England.

Armitage, P. (1979a). The analysis of data from clinical trials. *Statistician*, **28**, 171–183.

Armitage, P. (1979b). The design of clinical trials. *Aus. J. Statist.*, **21**, 266–281.

Armitage, P. (1985). The search for optimality in clinical trials. *Int. Stat. Rev.*, **53**, 1, 15–24.

Armitage, P. and Hills, M. (1982). The two-period crossover trial. *Statistician*, **31**, 119–131.

Armitage, P., McPherson, C.K. and Rowe, B.C. (1969). Repeated significance tests on accumulating data. Jour. Roy. Stat. Soc. Ser. A, **132**, 235-244.

Armitage, P., Stratton, I.M., and Worthington, H.V. (1985). Repeated significance tests for clinical trials with a fixed number of patients and variable follow up. *Biometrics*, **41**, 353–359.

Atkinson, A.C. (1981). A comparison of two criteria for the design of experiments for discriminating between models. *Technometrics*, **23**, 301–305.

Atkinson, A.C. (1982). Optimum biased coin designs for sequential clinical trials with prognostic factors. *Biometrika*, **69**, 61–67.

Bartlett, R.H. (1984). Extracorporeal exygenation in neonates. *Hospital Practice*, April, 139–151.

Bartlett, R.H., Roloff, D.W., Cornell, R.G., Andrews, A.F., Dillon, P.W., and Zwischenberger, J.B. (1985). Extracorporeal circulation in neonatal respiratory failure: A prospective randomized study. *Pediatrics*, **76**, 479–487.

Bather, J. A. (1962). Bayes procedures for deciding the sign of a normal mean. *Proc. Cambridge Phil. Soc.* **58**, 599–620.

Bather, J. A. (1980). Randomized allocation of treatments in sequential trials. *Adv. Appl. Prob.* **12**, 174–182.

Bather, J.A. (1981). Randomized allocation of treatments in sequential experiments (with discussion) *J. R. Statist. Soc. B*, **43**, 265–292.

Bather, J.A. (1983). Optimal stopping of Brownian motion: a comparison technique. *Recent Adv. in Stat.: In honor of H. Chernoff* (eds. M.H. Rizvi, J.S. Rustagi and D. Siegmund). 19–49, Academic Press, New York.

Bather, J.A. (1985). On the allocation of treatments in sequential medical trials. *Int. Stat. Rev.*, **53**, 1–13.

Bather, J. A. (1986). Review of "*Bandit problems: Sequential allocation of experiments*" by D. A. Berry and B. Fristedt. *J. Roy. Stat. Soc. A*, **149**, 271.

Bather, J.A. (1988). Stopping rules and ordered families of distributions. *Seq. Anal.*, **7**, 2, 111–126.

Bather, J.A. and Simons, G. (1985). The minimax risk for two stage procedures in clinical trials. *J. R. Stat. Soc. B*, **47**, 3, 466–475.

Bauer, P. (1986). Two stage sampling for simultaneously testing main and side effects in clinical trials. *Biom. J.*, **28**, 871–879.

Bechhofer, R.E. (1985). An optimal sequential procedure for selecting the best Bernoulli process – a review. *Naval Res. Logist. Quart.*, **32**, 4, 665–674.

Bechhofer, R. et.al. (1983). Design of experiments for comparing treatments with a control: tables of optimal allocations of observations. *Technometrics*, **25**, 87–95.

Bechhofer, R.E., and Kulkarni, R.V. (1982/83). On the performance characteristics of a closed adaptive sequential procedure for selecting the best Bernoulli population. *Comm. Statist. Seq. Analysis*, **1**, 4, 315–354.

Begg, C.B., and Berlin, J.A. (1988). Publication bias: A problem in interpreting medical data (with discussion). *J. Roy. Statist. Soc. Ser. A*, **151**, 419–463.

Begg, C.B., and Iglewicz, B. (1980). A treatment allocation procedure for sequential clinical trials. *Biometrics*, **36**, 81–90.

Begg, C.B., and Kalish, L.A. (1982). Treatment allocation in sequential clinical trials : Non-linear model. *ASA Pro. St. Cp.*, 57–60.

Begg, C.B. and Kalish, L.A. (1984). Treatment allocation for non-linear models in clinical trials : The logistic model. *Biometrics*, **40**, 409–420.

Begg, C.B., and Mehta, C.R. (1979). Sequential analysis of comparative clinical trials. *Biometrika*, **66**, 1, 97–103.

Belekopytov, A. Ya. (1986). A lower bound in a problem of sequential design of screening experiments. (Russian). *Combinatorial analysis*, **7**, 38–41, 162–163.

Benkherouf, L. and Bather, J. A. (1988). Oil exploration: sequential decisions in the face of uncertainty. *Jour. Appl. Prob.*, **25**, 3, 529–543.

Benzing, H., Kalin, D., and Theodorescu, R. (1986). On the Bernoulli three armed bandit problem. *Optimization*, **17**, 6, 807–817.

Benzing, H., Kalin, D., and Theodorescu, R. (1987). Optimal policies for sequential Bernoulli experiments with switching costs. *J. Inform. Process Cybernet*, **23**, 12, 599–607.

Bergman, S.W. and Turnbull, B.W. (1983). Efficient sequential designs for destructive life testing with application to animal serial sacrifice experiments. *Biometrika*, **70**, 305–314.

Berry, D.A. (1985). One- and two- armed bandit problems. *Enc. Stat. Sci.*, **6**, 418–422.

Berry, D.A. (1987). Statistical inference, designing clinical trials, and pharmaceutical decisions. *Statistician*, **36**, 181–189.

Berry, D.A. (1988). Monitoring safety data in a clinical trial with the possibility of early stopping. Unpublished.

Berry, D.A. (1989a). Monitoring accumulating data in a clinical trial. *Biometrics*, to appear.

Berry, D.A. (1989b). Inferential aspects of adaptive allocation rules. Unpublished.

Berry, D. (1989c). Ethics and ECMO. (discussion of Ware (1989)). *Stat. Sci. 4*, **4**, 306–310.

Berry, D.A., and Eick, S. (1988). Decision analysis of randomized clinical trials: Comparison with adaptive procedures. Unpublished.

Berry, D.A. and Fristedt, B. (1985). *Bandit Problems: Sequential allocation of experiments.* Chapman and Hall, London.

Berry, D.A., and Hardwick, J. (1989). Using historical data in a Bayesian analysis of clinical trials. Unpublished.

Berry, D.A., and Pearson, I. (1985). Optimal designs for clinical trials with dichotomous responses. *Statist. in Medicine*, **4**, 497–508.

Blackwell, D., and Hodges, J.L., Jr. (1957). Design for the control of selection bias. *Ann. Math. Statist.*, **28**, 449–460.

Box, G.E.P., and Hill, W.J. (1967). Discrimination amoong mechanistic models. *Technometrics*, **9**, 57–71.

Bradt, R.N., Johnson, S.M., and Karlin, S. (1956). On sequential designs for maximizing the sum of n observations. *Ann. Math. Stat.*, **27**, 1060–1074.

Brown, B.W., Jr. (1980). Statistical controversies in the design of clinical trials – some personal views. *Controlled Clinical Trials*, **1**, 13–27.

Burkhardt, R., and Kienle, G. (1983). Basic problems in controlled trials. *J. Med. Ethics*, **9**, 80–84.

Burnasev, M.V. (1977). On the control of the observation process in the problem of sequential discrimination among N hypotheses. *Soviet Math.*, **18**, 1196–1199.

Buyse, M.E., Staquet, J., and Sylvester, R.J. (Ed.) (1983). *Cancer Clinical Trials: Methods and Practice.* Oxford University Press.

Canner, P.L. (1984). Monitoring long-term clinical trials for beneficial and adverse treatment effects. *Comm. Statist.-Theor. Meth.*, **13**, 2369–2394.

Case, L.D., Morgan, T.M., and Davis, C.E. (1987). Optimal restricted two-stage designs. *Controlled clinical Trials*, **8**, 146–156.

Chang, F., and Lai, T.L. (1987). Optimal stopping and dynamic allocation. *Adv. Appl. Prob.*, **19**, 4, 829–853.

Chen, R.W., Nair, V.N., Odlyzko, A.M., Shepp, L.A. and Vardi, Y. (1984). Optimal sequential selection of N random variables under a constraint. *J. Appl. Prob.*, **21**, 537–547.

Chernoff, H. (1959). Sequential design of experiments. *Ann. Math. Stat.*, **30**, 755–770.

Chernoff, H. (1968). Optimal stochastic control. *Sankhya A*, **30**, 221–252.

Chernoff, H. (1972). *Sequential Analysis and Optimal Design.* SIAM, J.W. Arrowsmith, Bristol, England.

Chernoff, H. (1975). Approaches in sequential design of experiments. In *A Survey of Statistical Design and Linear Models.* Ed. J.N. Srivastava, 67–90. North Holland, Amsterdam.

Chernoff, H., and Petkau, A.J. (1981). Sequential medical trials involving paired data. *Biometrika*, **68**, 119–132.

Chernoff, H., and Petkau, A.J. (1985). Sequential medical trials with ethical costs. *Proceedings of the Berkeley conference in honor of Neyman and Kiefer. Vol II.* Ed. Lucien M. LeCam and R.A. Olshen.

Chitke, S.D. (1980). Optimal sequential selection and resource allocation under uncertainty. *Adv. Appl. Prob.*, **12**, 942–957.

Chow, Y.S. (1965). Local convergence of martingales and the law of large numbers. *Ann. Math. Stat.*, **36**, 552–558.

Clayton, M. (1988). Bernoulli bandits with covariates. Tech. Rep., Dept. of Statistics, Univ. of Wisconsin, Madison.

Clayton, M.K., and Berry, D.A. (1985). Bayesian nonparametric bandits. *Ann. Statist.*, **13**, 4, 1523–1534.

Clayton, M.K., and Witmer, J.A. (1988). Two stage bandits. *Ann. Statist.*, **16**, 2, 887–894.

Colton, T. (1963). A model for selecting one of two medical treatments. *J. Amer. Statist. Assoc.*, **58**, 368–400.

Cornell, R.G. (1987). Play-the-winner in pediatrics: The ECMO trial. *ASA Proc. Biopharmaceutical Section*, 243–245.

Cornell, R.G., Landenberger, B.D., and Bartlett, R.H. (1986). Randomized play-the-winner clinical trials. *Comm. Statist. A Theory Methods*, **15**, 159–178.

Cox, D.R. (1982). A remark on randomization in clinical trials. *Utilitas Mathematica*, **21**, A, 245–252.

DeGroot, M.H. (1962). Uncertainty, information and sequential experiments. *Ann. Math. Stat.*, **33**, 404–419.

DeMets, D.L. (1984). Stopping guidelinews vs stopping rules: A practitioner's point of view. *Comm. Statist.-Theor. Meth.*, **13**, 2394–2417.

DeMets, D.L., and Gail, M.H. (1985). Use of logrank tests and group sequential methods at fixed calendar times. *Biometrics*, **41**, 1039–1044.

DeMets, D.L., and Kim, K. (1987a). Confidence intervals following group sequential tests in clinical trials. *Biometrics*, **43**, 857–864.

DeMets, D.L., and Kim, K. (1987b). Design and analysis of group sequential tests based on the type I error spending rate function. *Biometrika*, **74**, 149–154.

DeMets, D.L. and Lan, K.K.G. (1984). An overview of sequential methods and their application in clinical trials. *Comm. Statist.-Theor. Meth*, **13**, 2315–2338.

DeMets, D.L., and Ware, J. (1980). Group sequential methods in clinical trials with a one-sided hypothesis. *Biometrika*, **67**, 651–660.

DeMets, D.L. and Ware, J.H. (1982). Asymmetric group sequential boundaries for monitoring clinical trials. *Biometrika*, **69**, 661–663.

Diaconis, P., and Graham, R. (1981). The analysis of sequential experiments with feedback to subjects. *Ann. Statist.*, **9**, 3–23.

Doll, R., and Peto, R. (1980). Randomized control trials and retrospective controls. *Brit. Med. J.*, **280**, 44.

Donner, A. (1979). The design of a clinical trial with several patient categories. *Canad. J. Statist.*, **7**, 169–176.

Dunnett, C.W. (1984). Selection of the best treatment in comparison to a control with application to a medical trial. In *Design of Experiments: Ranking and Selection,* Ed. T.J. Santner and A.C. Tamhane, 47–66. New York: Dekker.

Dupac, V., and Herkenrath, U. (1983). Stochastic approximation on a discrete set and the multi armed bandit problem. *Seq. Anal.*, **1**, 1–25.

Dupac, V., and Herkenrath, U. (1983). Correction to "Stochastic approximation on a discrete set and the multi-armed bandit problem" *Metrika*, **30**, 109–115.

Edwards, D., and Hsu, J.C. (1983). Adaptive sequential procedures for comparing new treatments with a standard. *Comm. Statist. A, Theory Methods*, **12**, 10, 1135–1145.

Efron, B. (1971). Forcing a sequential experiment to be balanced. *Biometrika*, **58**, 403–417.

Efron, B. (1980). Randomizing and balancing a complicated sequential experiment. In *Biostatistics Casebook* (R.G. Miller ed.) Wiley, New York.

Eick, S.G. (1988a). The two armed bandit with delayed responses. *Ann. Statist.*, **16**, 1, 254–264.

Eick, S.G. (1988b). Gittins procedures for bandits with delayed response. *Jour. Roy. Stat. Soc. B*, **50**, 1, 125–132.

Eickhorn, B.H. (1986). Sequential allocation to two treatments that converges to an α superior treatment. *Metrika*, **33**, 189–195.

Eisle, J. (1989). An adaptive biased coin design for the Behrens-Fisgher problem. Tech. Rep., Dept. of Statistics, University of Michigan.

Elashoff, J.D., and Reedy, T.J. (1984). Two-stage clinical trial stopping rules. *Biometrics*, **40**, 791–795.

Eplett, W.J.R. (1986). Continuous time allocation indices and their discrete time approximation. *Adv. in Appl. Probab.*, **18**, 3, 724–746.

Feinstein, A.R. (1988). Scientific standards in epidemiologic studies of the menace of daily life. *Science*, **242**, 1257–1263.

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

Fidler, V. (1984). Change-over clinical trial with binary data: mixed-model-based comparison of tests. *Biometrics*, **40**, 1063–1070.

Flehinger, R. J., Louis, T. A., Robbins, H. A. and Singer, B. H. (1972). Reducing the number of inferior treatments in clinical trials. *Proc. Nat. Acad. Sci. USA 69*, **10**, 2993–2994.

Flournoy, N. (1989). Adaptive designs in clinical trials. *ASA Proc. Biopharmaceutical Section.* To appear.

Ford, I., and Silvey, S.D. (1980). A sequentially constructed design for estimating a nonlinear parametric function. *Biometrika*, **67**, 381–388.

Ford, I., Titterington, D.M., and Wu, C.F.J. (1985). Inference and sequential design. *Biometrika*, **72**, 3, 545–551.

Freedman, B. (1987). Equipoise and the ethics of clinical research. *New England J. Med*, **317**, 141–145.

Freedman, D., and Spiegelhalter, D. (1983). The assessment of subjective opinion and its use in relation to stopping rules for clinical trials. *The Statistician*, **32**, 153–160.

Freedman, L.S., Lowe, D., and Macaskill, P. (1984). Stopping rules for clinical trials incorporating clinical opinion. *Biometrics*, **40**, 575–586.

Friedman, B. (1949). A simple urn model. *Communications in Pure and Applied Mathematics*, **2**, 59–70.

Friedman, L.M., Furberg, C.D., and DeMets, D.L. (1981). *Fundamentals of Clinical Trials*, Boston, U.S.A. John Wright, PSG Inc.

Fushimi, M. (1983). Play-the-winner sampling procedure with nonsymmetric stopping boundaries for a binomial selection problem. *Rep. Stat. Appl. Res. Un. Japan Sci. Engre.*, **30**, 1, 18–25.

Garcia-Carrasco, P. (1985). Sequential design to discriminate models, based on the quadratic information. (Spanish). *Trab. Es.*, **36**, 153–164.

Geary, D.N., and Armitage, P. (1987). Sequential testing in clinical trials with serially correlated data. *Contributed paper presented to the 46 Session of the International Statistical Institute.*

Gebhardt, R., and Heckendorff, H. (1983). On Sequential design for regression problem. (German). *Math. Oper. Stat.*, **14**, 355–366.

Geertseema, J. C. and Reinecke, C. J. (1984). The application of a sequential procedure with elimination as a method for the screening for metabolic diseases. *Biometrics 40* **3**, 663–673.

Gehan, E. (1984). The evaluation of therapies: Historical control studies. *Statist. in Medicine*, **3**, 3315–3324.

Geller, N., and Pocock, S.J. (1987). Interim analysis in randomized clinical trials: ramifications and guidelines for practitioners. *Biometrics*, **43**, 213–223.

Geller, N., and Pocock, S. (1988). Design and analysis of clinical trials with group sequential stopping rules. In *Biopharmaceutical Statistics for Drug Development*, (K.E. Peace, Ed.), 489–508. Dekker: New York.

Gittins, J.C. (1979). Bandit processes and dynamic allocation indices (with discussion). *J. Royal Statist. Soc. B*, **41**, 148–177.

Gittins, J.C. (1989). *Multi-armed Bandit Allocation Indices.* Wiley: Chichester.

Gittins, J.C., and Jones, D.M. (1979). On the index for the discounted multi-armed bandit problem. *Biometrika*, **66**, 561–566.

Glazebrook, K.D. (1980). On randomized dynamic allocation indices for the sequential design of experiments. *J. R. Statist. Soc. B*, **42**, 342–346.

Glazebrook, K.D. (1983). Some reward penalty rules for the multi-armed bandit problem which are asymptotically optimal. *Ma. Opt. Sto.*, **12**, 307–316.

Goldman, A. (1987). Issues in designing sequential stopping for monitoring side effects in clinical trials. *Controlled Clinical Trials*, **8**, 324–337.

Gould, A.L., and Pecore, V.J. (1982). Group sequential methods for clinical trials allowing early acceptance of H_0 and incorporating costs. *Biometrika*, **69**, 75–80.

Govindarajulu, Z. (1985). A survey of sequential statistical analysis. *Sequential methods in statistics*, 133–179 *Banach center Publ.*, **16**, PWN, Warsaw.

Greenhouse, S.W. (1989). Some historical and methodological developments in early clinical trials at the National Institutes of Health. *Statist. in Medicine.* To appear.

Grieve, A.P. (1985). A Bayesian analysis of the two-period crossover design for clinical trials. *Biometrics*, **41**, 979–990.

Grizzle, J.E. (1987). Completely random assignment versus stratification in clinical trials. *New Perspect. Theor. Appl. Statist.*, 13–20.

Hall, P. (1981). Asymptotic theory of triple sampling for sequential estimation of the mean. *Ann. Statist.* **9**, 1229–1238.

Halpern, J., and Brown, B.W. (1986). Sequential treatment allocation procedures in clinical trials with particular attention to the analysis of results for the biased coin design. *Statist. Med.*, **5**, 219–229.

Hamada, T. (1984). On a uniform two-armed bandit. *J. Japan Statist. Soc.*, **14**, 2, 179–187.

Hamada, T. (1985). Further results on a uniform two-armed bandit problem with one arm known. *J. Jour. Stat.*, **15**, 193–208.

Hardwick, J. (1986a). Adaptive allocation in clinical trials, the ECMO controversy. Tech. Rep., Dept. of Stat., University of Michigan.

Hardwick, J. (1986b). The modified bandit: An approach to ethical allocation in clinical trials. Tech. Rep., Dept. of Stat., University of Michigan.

Hardwick, J. (1989a). Randomized repeated significance tests with unbalanced sampling. *ASA Proc. Biopharmaceutical Section.* To appear.

Hardwick, J. (1989b). Practical adaptive allocation rules with loss functions that incorporate ethical costs. *Cotemp. Math. Proc. of the Conference on Statistical Multiple Integration.* (N. Flournoy and R. Tsutakawa, eds). To appear.

Hardwick, J., and Woodroofe, M. (1989). Bias corrections for randomly censored survival data. Tech. Rep., Dept. of Stat., University of Michigan.

Hayre, L.S. (1979). Two population sequential tests with three hypotheses. *Biometrika*, **66**, 465–474.

Hayre, L.S., and Turnbull, B.W. (1981). A class of simple approximate sequential tests for adaptive comparison of two treatments. *Comm. Statist. A*, **10**, 2339–2360.

Hearron, A.E., Elfring, G.L., and Schultz, J.R. (1984). Biopharmaceutical applications of group sequential designs. *Comm. Statist.-Theor. Meth.*, **13**, 2419–2450.

Heckendorff, H. (1981). On the comparison of sequential statistical experiments. *Wiss. Z. Tech. Hochsch. Karl Marx-Stadt.*, **23**, 4, 383–386.

Heckmann, N.E. (1985). A sequential probability ratio test using a biased coin design. *Ann. Statist.*, **13**, 789–794.

Heckmann, N.E. (1985). A local limit theorem for a biased coin design for sequential tests. *Ann. Statist.*, **13**, 2, 785–788.

Heckmann, N.E. (1986). Repeated significance tests with biased coin allocation schemes. *Probab. Theory and Related Fields*, **73**, 4, 627–637.

Hellman, S. (1979). Randomized clinical trials and the doctor-patient relationship: An ethical dilemma. *Cancer Clin. Trials*, **2**, 189–193.

Hengartner, W., Kalin, D., and Theodorescu, R. (1983). On the Bernoulli two-armed problem. *Seq. Anal.*, **2**, 175–185.

Herkenrath, U., Kalin, D. and Vogel W. (Eds.) (1983). *Mathematical Learning Models — Theory and Algorithms.* Lecture Notes in Statistics 20. Springer–Verlag.

Hu, I. (1988). Repeated significance tests for exponential families. *Ann. Statist.*, **16**, 1643–1666.

Hu, I., and Wei, C.Z. (1989). Irreversible adaptive allocation rules. *Ann. Statist.*, **17**, 2, 801–823.

Huang Wen Tao, and Wu Chin Chuan (1987). Sequential selection of a best coin. *Tamkung J. Management Sci.*, **8**, 2, 15–23.

Huh, Myung-Hoe (1985). A comparative study of restricted randomization methods in clinical trials. *J. Korean Statist. Soc.*, **14**, 48–55.

Hummel, T.J., and Johnston, C.B. (1979). Comparing techniques for selecting successive values of the treatment valuable in sequential experimentation. *Jour. Ed. Stat.*, **4**, 139–160.

Iglewicz, B. (1983). Alternative designs: sequential multi-stage decision theory and adaptive designs. In *Cancer Clinical Trials: Methods and Practice* ed. M.E. Buyse, J. Staquet and R.J. Sylvester, 312–334. Oxford University Press.

Jamart, J. (1985). Combining the pragmatic attitude and the play-the- winner in controlled clinical trials. *Biom. J.*, **27**, 199–203.

Jennison, C. (1983). Equal probability of correct selection for Bernoulli selection procedures. *Comm. Statist. A Theory Methods*, **12**, 24, 2887–2896.

Jennison, C. (1987). Efficient group sequential tests with unpredictable group sizes. *Biometrika*, **74**, 155–165.

Jennison, C., and Turnbull, B.W. (1983). Confidence intervals for a binomial parameter following a multistage test with application to MIL-STD 105D and medical trials. *Technometrics*, **25**, 49–58.

Jennison, C., and Turnbull, B.W. (1984). Repeated confidence intervals for group sequential trials. *Controlled Clinical Trials*, **5**, 33–45.

Jennison, C., and Turnbull, B.W. (1990).

Jones, P.W., and Kandeel, H.A. (1984). A comparison of sampling rules for a Bernoulli two armed bandit. *Seq. Anal.*, **3**, 1, 85–92.

Jones, P.W., and Madhi, S.A. (1986). Bayesian sequential methods for choosing the better of two binomial populations. *Seq. Anal.*, **5**, 2, 127–138.

Jones, P.W., and Madhi, S.A. (1988). Bayesian minimum sample size designs for the Bernoulli selection problem. *Seq. Anal.*, **7**, 1, 1–10.

Kadane, J. (1980). Predictive and structural methods for eliciting prior distributions. In *Bayesian Analysis in Econometrics and Statistics: Essays in Honor of Sir Harold Jeffreys* (A. Zellner, ed.). North-Holland, Amsterdam.

Kadane, J.B. (1986). Progress toward a more ethical method for clinical trials. *J. Med. Philos.*, **11**, 385–404.

Kakigi, R. (1983). A note on discounted future two-armed bandits. *Adv. Appl. Prob.*, **15**, 221–222.

Kalin, D., and Theodorescu, R. (1984). A learning approach to sequential design: infinite horizon. *Statistics and Decision*, **2**, 23–38.

Kalish, L.A., and Begg, C.B. (1987). The impact of treatment allocation procedures on nominal significance levels and bias. *Controlled Clinical Trials*, **8**, 121–135.

Kallenberg, L.L.M. (1986). A note on M.N. Ketahakis' and Y.R. Chen's computation of Gittins index. *Math. Oper. Res.*, **11**, 1, 184–186.

Karunamuni, R.J. (1988). An empirical Bayes testing with sequential components. *Ann. Statist.*, **3**, 1270–1282.

Keener, R.W. (1980). Renewal theory and the sequential design of experiments with two states of nature. *Special issue on sequential analysis. Comm. Stat. Theory Methods*, **16**, 1699–1726.

Keener, R.W. (1984). Second order efficiency in the sequential design of experiments. *Ann. Statist.*, **12**, 510–532.

Keifer, J., and Sacks, J. (1963). Asymptotically optimal sequential inference and design. *Ann. Math. Statist.*, **34**, 705–750.

Kim, K., and DeMets, D.L. (1987). Design and analysis of group sequential tests based on the type II error spending rate function. *Biometrika*, **74**, 149–154.

Kleijnen, J.P.C. (1986). A scenario for sequential experimentation. *Comm. Statist.-Theor. Meth.*, **15**, 3067–3078.

Kourouklis, S. (1984). Bahadur optimality of sequential experiments for exponential families. *Ann. Statist.*, **12**, 1522–1527.

Kroeber, D.W. (1980). A graphical approach to the design of sequential attribute sampling plans. *J. Qual. Tek.*, **12**, 36–39.

Kulkarni, R. (1988). Adaptive statistical procedures. *Enc. Statist. Sci.*, **8**, 399–404.

Lachin, J.M. (1981). Sequential clinical trials for normal variates using interval composite hypotheses. *Biometrics*, **37**, 87–101.

Lagakos, S.W., and Pocock, S.J. (1984). Randomization and stratification in cancer clinical trials: an international survey. In *Cancer Clinical Trials: Methods and Practice* (M.E. Buyse, M.J. Staquet and R.J. Sylvester eds.) Oxford University Press.

Lai, T. L. (1983). Stochastic regression models and consistency of the least squares identification scheme. In *Mathematical Learning Models — Theory and Algorithms.* (Eds. V. Herkenrath, D. Kalin and W. Vogel). Lecture Notes in Statistics 20. Springer–Verlag.

Lai, T.L. (1984). Incorporating scientific, ethical and economic consideration into the design of clinical trials in pharmaceutical industry. *Comm. Statist. A*, **13**, 2355–2368.

Lai, T.L. (1986). Asymptotic solutions of bandit problems. *Stochastic differential systems, stochastic control theory and applications.* 275–292. *IMA vol. Math. Appl.*, **10**, Springer, New York-Berlin, 1988.

Lai, T.L. (1987). Adaptive treatment allocation and the multi-armed bandit problem. *Ann. Statist.*, **15**, 3, 1091–1114.

Lai, T.L. (1988). Nearly optimal seuential tests of composite hypotheses. *Ann. Statist.*, **16**, 2, 856–886.

Lai, T.L., Levin, B., Robbins, H., and Seigmund, D. (1980). Sequential medical trials. *Proc. Natl. Acad. Sci. U.S.A.*, **77**, 3135–3138.

Lai, T.L., and Robbins, H. (1984a). Optimal sequential sampling from two population. *Proc. Nat. Acad. Sci. Phys. Sci.*, **4**, 81, 1284–1286.

Lai, T.L., and Robbins, H. (1984b). Asymptotically optimal allocation of treatments in sequential experiments. *Design Exp. Ranking and Selection*, 127–142, Statistics 56. Ed. T.J. Santner and A.C. Tamhane. Dekker, New York.

Lai, T.L., and Robbins, H. (1985). Asymptotically efficient adaptive allocation rules. *Adv. Appl. Math.*, **6**, 1, 4–22.

Lai, T.L., Robbins, H., and Siegmund, D. (1983). Sequential design of comparative clinical trials. *Recent Advancement in Statistics, In Honor of H. Chernoff*, Ed. M.H. Rizvi, J.S. Rustagi and D. Siegmund), 51–68.

Lalley, S.P. (1986). Repeated likelihood ratio tests for curved exponential families. *Zeit. Wahr. ver. Gebiete*, **62**, 293-321.

Lalley, S.P., and Lorden, G. (1986). A control problem arising in the sequential design of experiments. *Ann. Prob.*, **14**, 136–172.

Lan, K.K.G., and DeMets, D.L. (1983). Discrete sequential boundaries for clinical trials. *Biometrika*, **70**, 3, 659–663.

Lan, K.K.G., and DeMets, D.L. (1984). More flexible sequential and non-sequential designs in long term clinical trials. *Comm. Statist.-Theor. Meth.*, **13**, 2339–2353.

Lan, K.K.G., Simon, R., and Halperin, M. (1982). Stochastic curtailed tests in long term clinical trials. *Comm. Statist.-Seq. Anal.*, **1**, 3, 207–214.

LeCam, L. (1979). A reduction theory for certain sequential experiments. *Ann. Statist.*, **7**, 1034–1039.

Lewis, J.A. (1983). Clinical trials: Statistical developments of practical benefit to the pharmaceutical industry (with discussion). *J. Roy. Statist. Soc. A*, **146**, 362–393.

Lindley, D.V. (1956). On the measure of the information provided by an experiment. *Ann. Math. Stat.*, **27**, 986–1005.

Lorden, G. (1988). Testing in stages. Abstract 206–66. *Inst. Math. Statist. Bull.* **17**, 234.

Louis, T. (1984). Efficient time-ordered sequential design. Tech. Rep., Dept. of Biostatistics, Harvard School of Public Health.

Louis, T.A., Mosteller, F., and McPeek, B. (1982). Timely topics in statistcal methods for clinical trials. *Ann. Rev. Biophys. Bioeng.*, **11**, 81–104.

Louis, T.A., and Orav, E.J. (1985). Adaptive sacrifice plans for the carcinogen bioassay. *Proc. Long-Term Animal Carcinogenicity Studies: A Statistical Perspective*, 36–41. Amer. Statist. Assoc., Washington.

Mandelbaum, A. (1987). Continuous multi-armed bandits and multiparameter processes. *Ann. Probab.*, **15**, 4, 1527–1556.

Mandelbaum, A. (1988). Navigating and stopping multiparameter bandit processes. *Stochastic differential systems, stochastic control theory and applications* (Minneapolis, MN, 1986), 339-372, *IMA Vol. Math. Appl.*, **10**, Springer, New York-Berlin.

McPherson, C.K., and Armitage, P. (1971). Repeated significance tests on accumulating data when the null hypothesis is not true.*Jour. Roy. Stat. Soc. Ser. A*, **134**, 15-25.

McPherson, K. (1982). On choosing the number of interim analyses in clinical trials. *Biometrika*, **67**, 247-249.

Meeker, W.Q., Jr. (1981). A conditional sequential test for the equality of two binimial populations. *J. Roy. Statist. Soc. C*, **30**, 2, 109–115

Meeter, D., Pirie, W., and Blot, W. (1970). A comparison of the two model-discrimination criteria. *Technometrics*, **12**, 457–470.

Morris, M.D. (1987). A sequential experimental design for estimating a scale parameter from quantal life testing data. *Technometrics*, **29**, 173–181.

Moussa, M.A.A. (1986). Clinical trial size: Fixed versus group sequential designs. *Mln. fo. Med.*, **25**, 233–236.

Namakata, T., Tabata, Y., and Nishida, T. (1979). A sequential allocation problem with two kinds of targets. *J. P. Rs. Jpn.*, **22**, 16–18.

Namakata, T., Tabata, Y., and Nishida, T. (1980). A sequential unit allocation for parallel redundant sysytem. *J. P. Rs. Jpn.*, **23**, 353–366.

Namakata, T., Tabata, Y., and Nishida, T. (1981a). A sequential allocation problem with perishable goods. *J. P. Rs. P.*, **24**, 202–211.

Namakata, T., Tabata, Y., and Nishida, T. (1981b). Some remarks on sequential allocation problem over unknown number of periods. *Jo. P. Rs. Jpn.*, **24**, 339–349.

O'Brien, P.C., and Fleming, T.R. (1979). A multiple testing procedure for clinical trials. *Biometrics*, **35**, 549–556.

Olschewski, M., and Schumacher, M. (1986). Sequential analysis of survival times in clinical trials. *Biometrical Journal*, **28**, 3, 273–293.

Paneth, N., and Wallenstein, S. (1985). Extracorporeal membrane exygenation and the play-the-winner rule. *Pediatrics*, **76**, 622–623.

Percus, O.E., and Percus, J.K. (1984). On the Bechhofer-Kulkarni stopping rule for sequential clinical trials. *SIAM J. Appl. Math.*, **44**, 6, 1164–1175.

Petkau, A.J. (1980). Frequentist properties of three stopping rules for comparative clinical trials. *Biometrika*, **67**, 690–692.

Petkau, A.J. (1987). Truncated sequential medical trials involving paired data. *Canad. J. Statist.*, **15**, 4, 363–374.

Petruccelli, J.D. (1980). On a best choice problem with partial information. *Ann. Statist.*, **8**, 1171–1174.

Petruccelli, J.D. (1982). Full-information best-choice problems with recall of observations and uncertainty of selection depending on the observation. *Adv. Appl. Prob.*, **14**, 340–358.

Pocock, S.J. (1977). Group sequential methods in the design and analysis of clinical trials. *Biometrika*, **64**, 191-199.

Pocock, S.J. (1979). Allocation of patients to treatments in clinical trials. *Biometrics*, **35**, 183–197.

Pocock, S.J. (1982). Interim analysis for randomized clinical trials: The group sequential approach. *Biometrics*, **38**, 153–162.

Pocock, S.J. (1983). *Clinical Trials*, Chichester; Wiley.

Pocock, S.J., Geller, N.L., and Tsiatis, A.A. (1987). The analysis of multiple endpoints in clinical trials. *Biometrics*, **43**, 3, 487-498.

Raghavarao, D. (1980). Use of distance function in sequential treatment assignment for prognostic factors in the controlled clinical trial. *Cal. Statist. Assoc. Bull.*, **29**, 99–102.

Reimnitz, P. (1982). Asymptotic near admissibility and asymptotic near optimality by the two armed bandit problem. *Ma. Opt. Sts.*, **13**, 245–263.

Reimnitz, P. (1986). Minimax and Bayes strategies for the discounted infinite horizon one-armed bandit. Explicit formulae and structural properties. *Statistics*, **17**, 2, 249–260.

Risko, K.J. (1985). Selecting the better binomial population under a budget constraint. *Jour. Stat. Plan. and Inf.*, **11**, 341–353.

Robbins, H. (1952). Some aspects of the sequential design of experiments. *Bull. Amer. Math. Soc.* **58**, 527–535.

Robbins, H. (1974). A sequential test for two binomial populations. *Proc. Nat. Acad. Sci. U.S.A.*, **71**, 4435–4436.

Robbins, H., and Siegmund, D. (1974). Sequential tests involving two populations. *J. Amer. Stat. Assoc.*, **69**, 132–139.

Robinson, D. (1983). A comparison of sequential treatment allocation rules. *Biometrika*, **70**, 492–495.

Rosenbaum, P. R. (1987). The role of a second control group in an observational study — with comments. *Statist. Sci.* **2**, 292–316.

Rosner, G., and Tsiatis, A. (1988). Exact confidence intervals following a group sequential trial: A comparison of methods. *Biometrika*, **75**, 311–318.

Sakaguchi, M. (1978). A sequential allocation problem for randomly appearing targets. *Ma. Japan*, **21**, 89–103.

Samuel-Cahn, E., and Wax, Y. (1984). A sequential "gambler's ruin" test for $p_1 = p_2$ with a medical applicaiton and incorporation of data after stopping. Tech. Rep., Hebrew University.

Sanchez, S.M. (1987). A modified least failures sampling procedure for Bernoulli subset selection. *Comm. Statist. Theory Methods*, **16**, 12, 3609–3629.

Sario, V. (1983). Limiting properties of a sequential allocation problem. *AU Tmpr. A*, **153**, 130–136.

Sarkar, J. (1989). A one-armed bandit problem with a concomitant variable. Tech. Rep., Dept. of Statistics, University of Michigan.

Sato, M., Abe, K., and Tekeda, H. (1984). A learning algorithm for the finite-time two-armed bandit problem. *IEE Trans. Systems Man. Cybernet*, **14**, 3, 528–534.

Schwarz, D., Flamant, R., and Lallouch, J. (1980). *Clinical Trials*, Trans, M.J.R. Healy. London, Academic Press.

Segreti, A.C., Carter, W.H., Jr., and Wampler, G.L. (1981). A Monte Carlo evaluation of the robustness of several sequential optimization techniques when the response is time to an event. *J. Statist. Comp. Simul.*, **12**, 209–216.

Shapiro, C.P. (1982). Myopic sequential allocation procedures for Bayesian simultaneous estimation. *Seq. Anal.*, **1**, 145–158.

Shapiro, C.P. (1983). Sequential allocation and optimal stopping in Bayesian simultaneous estimation. *J. Amer. Statist. Assoc.*, **78**, 382, 396–402.

Shapiro, S., and Louis, T.A. (Ed) (1983). *Clinical Trials: Issues and Approaches.* New York: Dekker.

Siegmund, D. (1983). Allocation rules for sequential clinical trials. *Mathematical learning models – theory and algorithms*, 203–212, *Lecture Notes in Statist.*, **20**, Springer, New York-Berlin.

Siegmund, D. (1985). *Sequential analysis: Tests and confidence intervals.* Springer series in Statistics, Springer Verlag, New York.

Simons, G. (1985). A comparison of seven allocation rules for a clinical trial model. *Seq. Anal.*, **3**, 193–221.

Simons, G. (1986). Bayes rules for a clinical trials model with dichotomous responses. *Ann. Statist.*, **14**, 3, 954–970.

Simons, G. (1987). Easily determining which urns are favourable. *Stat. Prob. Letters*, **5**, 43–48.

Simons, G., and Wu, X. (1985). On Bayes tests for $p \leq 1/2$ versus $p > 1/2$. *Adaptive statistical procedures an Related Topics.* J. van Ryzin ed. IMS Lecture notes. Monograph series no. 8, 79–95.

Simon, R. (1977). Adaptive treatment assignment methods and clinical trials. *Biometrics*, **33**, 743–749.

Simon, R. (1979). Restricted randomization designs in clinical trials. *Biometrics*, **35**, 503–512.

Slud, E.V., and Wei, L.J. (1982). Two-sample repeated significance tests based on the modified Wilcoxon statistic. *Journ. Amer. Stat. Assoc.*, **77**, 862–868.

Smith, R.L. (1984a). Sequential treatment allocation using biased coin designs. *J. Roy. Statist. Soc. B*, **46**, 519–543.

Smith, R.L. (1984b). Properties of biased coin designs in sequential clinical trials. *Ann. Statist.*, **12**, 3, 1018–1034.

Soares, J.F., and Wu, Chien-Fu (1981). Extended truncated binomial in sequential experiments. *Bull. Int. Statist. Inst.*, **49**, 566–579.

Soares, J.F., and Wu, C.F.J. (1983). Some restricted randomization rules in sequential designs. *Comm. Statist.-Theory Methods*, **12**, 17, 2017–2034.

Soares, J.F., and Wu, C.F.J. (1985). Optimality of random allocation design for the control of accidental bias in sequential experiments. *J. Statist. Planning Inf.*, **11**, 81–87.

Sobel, M., and Weiss, G.H. (1970/71). Recent results on using the play-the-winner sampling rule with binomial selection problem. *Proc. sixth Berkeley Sym. Math. Stat. and Prob. Vol. 1. Theory of Statistics*, 717–736. Univ. of Calif. Press, Berkeley, Californa.

Solarin, A., and Roland, T. (1982). On play-the-winner rule in clinical trials. *Bull. Math. Soc. Sci. Math. R. S. Roumanie*, **26 (74)**, 4, 373–375.

Steele, J.M. (1980). Efron's conjecture on vulnerability to bias in a method for balancing

Siegmund, D. (1983). Allocation rules for sequential clinical trials. *Mathematical learning models – theory and algorithms*, 203–212, *Lecture Notes in Statist.*, **20**, Springer, New York-Berlin.

Siegmund, D. (1985). *Sequential analysis: Tests and confidence intervals.* Springer series in Statistics, Springer Verlag, New York.

Simons, G. (1985). A comparison of seven allocation rules for a clinical trial model. *Seq. Anal.*, **3**, 193–221.

Simons, G. (1986). Bayes rules for a clinical trials model with dichotomous responses. *Ann. Statist.*, **14**, 3, 954–970.

Simons, G. (1987). Easily determining which urns are favourable. *Stat. Prob. Letters*, **5**, 43–48.

Simons, G., and Wu, X. (1985). On Bayes tests for $p \leq 1/2$ versus $p > 1/2$. *Adaptive statistical procedures an Related Topics.* J. van Ryzin ed. IMS Lecture notes. Monograph series no. 8, 79–95.

Simon, R. (1977). Adaptive treatment assignment methods and clinical trials. *Biometrics*, **33**, 743–749.

Simon, R. (1979). Restricted randomization designs in clinical trials. *Biometrics*, **35**, 503–512.

Slud, E.V., and Wei, L.J. (1982). Two-sample repeated significance tests based on the modified Wilcoxon statistic. *Journ. Amer. Stat. Assoc.*, **77**, 862–868.

Smith, R.L. (1984a). Sequential treatment allocation using biased coin designs. *J. Roy. Statist. Soc. B*, **46**, 519–543.

Smith, R.L. (1984b). Properties of biased coin designs in sequential clinical trials. *Ann. Statist.*, **12**, 3, 1018–1034.

Soares, J.F., and Wu, Chien-Fu (1981). Extended truncated binomial in sequential experiments. *Bull. Int. Statist. Inst.*, **49**, 566–579.

Soares, J.F., and Wu, C.F.J. (1983). Some restricted randomization rules in sequential designs. *Comm. Statist.-Theory Methods*, **12**, 17, 2017–2034.

Soares, J.F., and Wu, C.F.J. (1985). Optimality of random allocation design for the control of accidental bias in sequential experiments. *J. Statist. Planning Inf.*, **11**, 81–87.

Sobel, M., and Weiss, G.H. (1970/71). Recent results on using the play-the-winner sampling rule with binomial selection problem. *Proc. sixth Berkeley Sym. Math. Stat. and Prob. Vol. 1. Theory of Statistics*, 717–736. Univ. of Calif. Press, Berkeley, Californa.

Solarin, A., and Roland, T. (1982). On play-the-winner rule in clinical trials. *Bull. Math. Soc. Sci. Math. R. S. Roumanie*, **26 (74)**, 4, 373–375.

Steele, J.M. (1980). Efron's conjecture on vulnerability to bias in a method for balancing sequential trials. *Biometrika*, **67**, 503–504.

Stewart, T.J. (1981). Optimal selection from a random sequence with observation errors. *Naval Res. Logist. Quart.*, **28**, 393–406.

Sun, Jia Yang (1986). On a multi-armed bandit problem with nuisance parameter. *Sci. Sinica, Ser. A*, **29**, 5, 464–475.

Surgailis, D. (1972). Certain properties of the optimal risk in the generalized two-armed bandit problem. (Russian). *Litovsk. Mat. Sb.*, **12**, 3, 181–184.

Sylvester, R.J. (1983). *A decision theoretic approach to the design of Phase II Clinical trials in cancer.* D. Sc. Thesis, Universite Libre de Bruxelles.

Sylvester, R.J., and Staquet, M.J. (1980). Design of Phase II clinical trials in cancer using decision theory. *Cancer Treat. Rep.*, **64**, 519–524.

Takahashi, H. (1987). Asymptotic expansions in Anscombe's theorem for repeated significance tests and estimation after sequential testing. *Ann. Statist.*, **15**, 278–295.

Tamhane, A.C. (1985). Some sequential procedures for selecting the better Bernoulli treatment by using a matched sample design. *Jour. Amer. Stat. Assoc.*, **80**, 390, 455–460.

Thompson, E.I. (1980). Application of restricted sequential design in a clinical protocol. *Cancer Trt. Res.*, **64**, 399–403.

Thompson, W.R. (1933). On the likelihood that one unknown probability exceeds another in view of the evidence of two samples. *Biometrika*, **25**, 275–294.

Titterington, D.M. (1983). On constrained balance randomization for clinical trials. *Biometrics*, **39**, 1083–1086.

Tong, Y.L., and Wetzel, D.E. (1984). Allocation of observations for selecting the best normal population. *Design of experiments - Selection and Ranking*, 213–224.

Tsiatis, A.A., Rosner, G.L., and Mehta, C.R. (1984). Exact confidence intervals following group sequential tests. *Biometrics*, **40**, 797–803.

Tsitovich, I.I. (1985). Sequential design of experiment for hypothesis testing. *Th. Prob. Appl.*, **29**, 814–817.

Turnbull, B.W., and Hayter, A.J. (1985). A forward stochastic approximation for scheduling sacrifices in tumorigenicity studies. *Proc. Biopharmaceutical Sec.*, 131–136. Amer. Statist. Assoc., Washington.

Tymchuck, A. (1981). Ethical decision making and psychological treatment. *J. Psychiatric treatment Evaluation*, **3**, 507–513.

Tymchuck, A. (1982). Strategies for resolving value dilemmas. *Amer. Behav. Scientist*, **26**, 159–175.

Vere, D.W. (1983). Problems in controlled clinical trials – a critical response. *J. Med. Ethics*, **9**, 85–89.

Vuchkov, I.N. (1982). Sequentially generated designs. *Biom. J.*, **24**, 751–763.

Vuchkov, I.N., Damgaliev, D.L., and Yontchev, Ch.A. (1981). Sequential generated econd order quasi D-optimal designs for experiments with mixure and process variable. *Technometrics*, **23**, 233–238.

Wald, N.J., and Polani, P.E. (1984). Neural-tube defects and vitaminds: The need for a randomized clinical trial. *Brit. J. Obstetr. Gynaecol.*, **91**, 516–523.

Wang, S.K., and Tsiatis, A.A. (1987). Approximately optimal one-parameter boundaries for group sequential trials. *Biometrics*, **43**, 1, 193–200.

Ware, J.H. (1989). Investigating therapies of potentially great benefit: ECMO (with discussion). *Statistical Science*, **4**, 4, 298–340.

Wei, L.J. (1978a). The adaptive biased coin design for sequential experiments. *Ann. Stat.*, **6**, 92–100.

Wei, L.J. (1978b). An application of an urn model to the design of sequentially controlled clinical trials. *J. Amer. Statist. Assoc.*, **73**, 559–563.

Wei, L.J. (1979). The generalized Polya's urn design for sequential medical trials. *Ann. Statist.*, **7**, 291–296..

Wei, L.J. (1988). Exact two-sample permutation tests based on the randomized play-the-winner rule. *Biometrika*, **75**, 3, 603–606.

Wei, L.J., and Durham, S. (1978). The randomized play the winner rule in medical trials. *J. Amer. Statist. Assoc.*, **73**, 840–843.

Wei, L.J., and Lachin, J. (1988). Properties of the urn randomization in clinical trials. *Controlled clinical Trials*, **9**, 345–364.

Wei, L.J., Smythe, R.T., Lin, D.Y., and Park, T.S. (1990). Statistical inference with data-dependent treatment allocation rules. *J. Amer. Statist. Assoc.*, **85**. To appear.

Wei, L.J., Smythe, R.J., and Smith, R.J. (1986). K-treatment comparisons in clinical trials. *Ann. Statist.*, **14**, 265–274.

Wetherill, G.B., and Glazebrook, K.D. (1986) *Sequential methods in statistics.* Third edition. Monographs on statistics and applied probability. Chapman and Hall, London-New York.

Whitehead, J. (1983). *The design and Analysis of Sequential clinical Trials.* Chichester: Horwood.

Whitehead, J. (1986). Sample sizes for phase II and phase III clinical trials: an integrated approach. *Statist. Med.*, **5**, 459–464.

Whitehead, J. (1990).

Whitehead, J., and Jones, D. (1979). The analysis of sequential clinical trials. *Biometrika*, **66**, 443–452.

Whitehead, J., and Stratton, I. (1983a). Group sequential clinical trials with triangular continuation regions. *Biometrics*, **39**, 1, 227–236.

Whitehead, J., and Stratton, I. (1983b). Correction to "Group sequential clinical trials with triangular continuation regions". *Biometrics*, **39**, 4, 1137.

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

Whittle, P. (1988). Restless bandits: activity allocation in a changing world. *Jour. Appl. Prob. Special Vol.* 25A, 287–298.

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

Woodroofe, M. (1978a). On the random allocation designs for the control of selection bias in sequential experiments. *Biometrika*, **65**, 79–84.

Woodroofe, M. (1978b). Large deviations of the likelihood ratio statistic with applications to sequential testing. *Ann. Statist.*, **6**, 72–84.

Woodroofe, M. (1979). A one armed bandit problem with a concomitant variable. *J. Amer. Statist. Assoc.*, **74**, 799–806.

Woodroofe, M. (1982a). Sequential allocation with covariates. *Sankhyā*, 403–414.

Woodroofe, M. (1982b). *Nonlinear Renewal Theory in Sequential Analysis.* Society for Industrial and Applied Mathematics. Philadelphia.

Woodroofe, M. (1986). Very weak expansions for sequential confidence levels. *Ann. Statist.*, **14**, 1049–1067.

Woodroofe, M. (1988). Fixed proportional accuracy in three stages. In *Statistical Theory and related topics IV*, (S.S. Gupta and J.O. Berger, eds.) **2**, 209–221.

Woodroofe, M. (1989). Very weak expansions for sequentially designed experiments: Linear Models. *Ann. Statist.*, **17**, 1087–1102.

Woodroofe, M., and Hardwick, J. (1988). Sequential allocation for an estimation problem with ethical costs. *Ann. Statist.*. To appear.

Woodroofe, M., and Takahashi, M. (1982). Asymptotic expansions for the error probabilities of some repeated significance tests. *Ann. Statist.*, **10**, 895–908. Correction (1985) 13.

Wu. C.F.J. (1985a). Asymptotic inference from sequential design in a nonlinear situation. *Biometrika*, **72**, 553–558.

Wu, C.F.J. (1985b). Efficient sequential designs with binary data. *J. Amer. Stat. Assoc.*, **80**, 974–984.

Yahav, J.A. (1979). On a screening problem. *Ann. Statist.*, **7**, 1140–1143.

Zaborskis, A., and Zmotiza, A. (1976). Sequential Bayesian plan for choosing the best method of medical treatment. (Russian). *Avtomat. i. telemech*, **11**, 144–153. Translated as *Remote Control* **37**, 1976, 1, 2, 1750–1757 (1977).

Zelen, M. (1979). A new design for randomized clinical trials. *New England J. Med.*, **300**, 1242–1245.

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