SEQUENTIAL MODELS FOR CLINICAL TRIALS

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1. Introduction

This paper presents a model, variations of which have been considered by Anscombe [1] and Colton [4] and others, which is relevant to the problem of sequential testing in clinical trials. This model is the same as one discussed by Chernoff and Ray [3] and by Wurtele [7] in a sampling inspection problem and is naturally related to a *one armed bandit* problem. The object of this paper is to demonstrate that techniques exist for dealing with some of the technical problems raised by these and similar models. A few of the insights derived from the results on the one armed bandit problem will be described in terms of nominal significance levels corresponding to the rejection of a new drug.

The model is oversimplified for many practical applications. Alternative models, including a two armed bandit problem are described. An important element in most of these models is the *horizon* consisting of the total number of anticipated patients to be treated.

2. The model

Suppose that a new drug is produced to treat an illness for which the treatment in the past has been a standard drug with known properties. We shall assume here that the result of the use of the drug can be classified simply as a success or failure in the treatment, and once one drug is applied, treatment cannot shift to the other. Then the known drug is characterized by a known probability p_0 of success while the new drug has unknown probability p of success. If it is anticipated that a horizon of N patients will have to be treated by one drug or another, the expected number of successes given that the new drug is used n times, is $np + (N - n)p_0 = Np_0 + n(p - p_0)$.

Clearly, the expected number of successes attains a maximum of Np_0 if $p < p_0$ (with $n = 0$) and Np if $p > p_0$ (with $n = N$). In view of the ignorance of p, it is desired to select a sequential procedure to maximize the expected number of successes which is equal to

$$Np_0 + E[n(p - p_0)], \tag{2.1}$$

where n is possibly a random quantity determined by the procedure. Since p_0 is known, it is apparent that a reasonable procedure ought to consist of sampling