

ON CERTAIN ASPECTS OF SEQUENTIAL CLINICAL TRIALS

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1. Introduction

A clinical trial can become considerably more complicated than elementary accounts would lead one to expect. Often, despite simple initial objectives, unforeseen complications develop and the questions that one started out to answer become modified. We shall give an example to illustrate this in the next section, but merely emphasize here that, because of the possibility of unforeseen complications, one needs a good deal of *flexibility* to engage in and learn from a clinical trial. Yet much of the theory that biostatisticians are accustomed to use as guides in the planning and analysis of such trials makes for inflexibility. One must specify an exact hypothesis, an exact alternative, a criterion or end point for choosing between them, numerical values for type I and type II errors, probability models, and stopping rules. If the trial is sequential and uses binomial responses patients must be paired. If it is a fixed sample size trial, some biostatisticians will not release preliminary results, even to the participating clinicians, for fear of upsetting the significance level.

The conflicting pressures towards and away from flexibility create a problem that each biostatistician actively involved in such trials tends to resolve in his own way. A solution favored by clinicians is to consider each problem on its own scientific merits and without reliance upon theoretical rules as guides. Alternatively, one can accept the inflexibility that theory seems to impose, and resist any compromise with experimental pressures for flexibility. As statisticians interested in the probabilistic basis of methodology used in practice, we clearly cannot be happy with the first solution. At the same time if biostatisticians are to be of help to biomedical scientists, we feel that a relaxation of current restrictive attitudes is essential. In what follows we describe our own efforts to resolve this conflict.

2. An example of unforeseen complications

To illustrate the effect of unforeseen complications we shall consider the results of a recently published trial concerned with the effectiveness of an estrogen, premarin, in the secondary prevention of coronary disease [1]. The trial included 275 men, each with a diagnosis of definite clinical coronary disease. All patients entering the study were assigned either to the treatment or the