SOME DEVELOPMENTS IN THE THEORY AND PRACTICE OF SEQUENTIAL MEDICAL TRIALS

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1. Introduction

It would have seemed unlikely fifteen years ago that the conduct of controlled medical trials should give rise to serious thought about the nature of statistical inference. These trials in preventive or clinical medicine seemed to provide a straightforward example of Fisherian experimentation, the mere application of which to as difficult a subject as medicine was more noteworthy than any subtleties of statistical design or analysis. Yet they have continued to stimulate theoretical study and controversy. Even the reader of our more recondite journals, deep in Radon-Nikodym territory, is apt to find himself without warning in a discussion starting "Consider now a trial of two drugs, A and B. . . ." Theoretical studies of this sort are often concerned particularly with the design and analysis of sequential experiments, which have been used in medicine from time to time over the last ten years or so. In this paper I shall try to review the development of sequential medical trials, consider the extent and propriety of their present use, and summarize some of the recent theoretical discussions on this topic.

The celebrated cooperative trials in preventive and clinical medicine of the 1940's and 1950's, accounts of many of which are contained in [1], set the standard in a number of respects. By the use of random allocation they provided information about the relative merits of different treatments which was not otherwise available and which, in its finer aspects, could not have been otherwise obtained. This information related both to the therapeutic or prophylactic value of the treatments and also to their potentially adverse effects. It was often possible to investigate interactions between treatment effects and particular characteristics of the subjects, such as age or severity of disease. Second, they provided valuable experience in the administrative problems of large scale trials, which have much in common with those of sample surveys. Third, they provided evidence on the nature of the ethical problems which are peculiar to this branch of experimentation and pervade almost all discussion upon it [2].

Since the case for sequential experimentation in medical trials is closely bound up with these ethical problems it is appropriate to discuss them a little further here. The basic point is that the physician will usually be unwilling to allocate