GROUP SEQUENTIAL ANALYSES

In addition to the need for methods of monitoring multiple measures of therapeutic effect, more research is needed on methods of analyzing trials with three or more treatment arms. In a traditional two-arm trial, the determination that one arm is inferior to the other is tantamount to terminating the trial. Yet in a trial involving three or more treatment arms, the possible decisions to be made at each interim analysis are greater in number and in complexity, and will depend on the overall goals of the trial (e.g., to exclude clearly inferior treatments or to identify the single best treatment). Professor Michael Hughes, a colleague in my department, has made some important initial steps in this area, but additional approaches are needed.

SURROGATE MARKERS

In the field of HIV/AIDS, there is great interest in identification of "surrogate markers." Usually, this refers to a laboratory marker that can be used as a surrogate for a clinical outcome such as the development of an AIDS-defining opportunistic infection. The potential value of a valid marker is obvious, yet, as Professor Fleming notes, use of an invalid marker could lead to the widespread use of ineffective drugs and/or the non-use of effective drugs. Thus, the validation of markers becomes very critical. Some of the early investigations of surrogate markers in HIV/AIDS have attempted to determine whether a treatment's effect on a particular marker can fully explain its effect on clinical endpoints. And, in all cases, only part of the clinical effect could be explained by the effect on markers. In retrospect, this is not surprising because it is unrealistic to expect that any single laboratory marker could fully explain all of an AIDS drug's beneficial effect because of the complex nature of this disease and how it can be affected by intervention. Thus, it may be that a battery of several markers needs to be determined that collectively can explain most of a drug's beneficial clinical effect. Given the high cost of the assays that are needed to evaluate some of the virological and immunological markers in HIV/AIDS, the design of studies to assess the "surrogate marker" question becomes critical. More statistical research on this topic is urgently needed.

In closing, I would like to thank Professor Fleming for his excellent article.

Comment

Thomas A. Louis

INTRODUCTION

Professor Fleming has considerable experience in conducting clinical trials and serving on Data Monitoring Committees (DMCs). We are fortunate that he has prepared a debriefing. It reinforces the impact of statistical science potentiated by subject area expertise and of both technical and broad viewpoints. In complex applications, relevant disciplines must be represented, and statistics is central to the enterprise. As Fleming notes, we must provide strong and effective leadership. To do so, we must educate collaborators on the role of statistics and be educated on a study's scientific and clinical basis. Statistical philosophies, principles and methods (frequentist/Bayes, multiple comparisons, choice of tests and estimators) need to guide deliberations, but in the complex world of clinical trials absolute dictums are seldom appropriate.

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Statisticians and other DMC members are truly on the line. Stopped trials are very difficult to restart, and the decision to terminate can essentially freeze out other, similar trials. Continuing a trial beyond what many think is a reasonable stopping point puts study participants at unnecessary risk and delays dissemination of important information. Ware (1989) and related discussion show the heat generated by these issues. Contrast this situation to analysis of a stable data base: investigators can analyze, reanalyze, critique other analyses and sustain the give and take for years or decades. A DMC must make important decisions in an acute time frame.

GENERAL DISCUSSION

Data Quality

Building trust with patients and clinicians being recruited for a trial often is, and should be, a sensitive negotiation. Of course, all stake-holders need to be convinced that the question is clinically relevant. Of equal importance is assurance that everyone's interests