Comment

Stephen Lagakos

As Professor Fleming notes, leadership from statistical scientists is crucial in the design, conduct and interpretation of therapeutic intervention trials in major diseases such as AIDS, cancer and cardiovascular disease. For a disease such as AIDS, where many of the natural history and pathogenesis issues are still not well understood, yet where there is extreme pressure to develop effective therapies, this leadership is especially important. The statistical scientist must on one hand be familiar with the practical issues surrounding the conduct of a therapeutic trial, yet also have the technical skills to develop creative designs and methods of analysis that can address the variety of challenges present in these studies. The number of statisticians who are currently filling this dual role is very limited. Fortunately, Professor Fleming is one such individual and hence is ideally suited to relate some of the key issues in this area to his statistical colleagues.

I will focus on three of the issues raised in Professor Fleming's paper—data monitoring committees, group sequential analyses and surrogate markers—and attempt to raise additional points related to their roles in therapeutic trials, especially in AIDS, where I have had the most experience.

DATA MONITORING COMMITTEES

In the AIDS Clinical Trials Group (ACTG), which has conducted the largest number of federally sponsored trials in persons infected with HIV, a data monitoring committee is used in virtually all of the comparative (Phase III) trials. This committee is composed of clinicians, ethicists and statisticians. The only other individuals present at meetings (and with access to the interim results of a trial) are statisticians from the ACTG Statistical Center who conducted the analysis and representatives from the National Institutes of Health. Representatives from the pharmaceutical companies whose drugs are being tested, as well as the clinical investigators who are heading the trial, do not have access to the interim efficacy results.

When I first became involved with AIDS clinical trials, I was unconvinced about the need for and value of data monitoring committees. Furthermore, the restriction of information to a very small group that excluded the medical head of the study struck me as unnecessary and rather silly. However, over the years my attitude on the value and composition of a data monitoring committee has changed dramatically, and I now strongly support both the concept and current ACTG model because I believe that these help to ensure the scientific success of studies.

In my view, the value of a data monitoring committee is that it can provide an independent and unbiased "second opinion" about whether and how a study should be modified. In the ACTG, this advice is taken very seriously and has on many occasions led to improvements in studies that had either not occurred to those conducting the study or were a result of the data monitoring committee's support of a change recommended made by the investigators conducting the study.

The issue of who should have access to the interim results of a study is more complicated and can depend on many factors, including the disease area being studied. One rationale for excluding the medical head of a clinical trial from the interim results is that if this individual is treating patients in the trial, knowledge of the interim results may compromise his or her ability to unbiasedly evaluate the patient's response or may cause an ethical dilemma if the interim results show a possible "trend" favoring one of the treatments. Another reason is that this individual may be involved as a consultant with the pharmaceutical company that produces the drug used in the trial; clearly, this could make it difficult for him/her to effectively advise the company and at the same time not compromise the ongoing study.

Similar arguments about access to interim results apply to representatives from the pharmaceutical companies who produce the drugs being evaluated in the trial. Here, however, the company's desire for access to interim results may be due to their larger plans for development of this and other drugs. Because our ability to ultimately benefit individuals who are afflicted with the diseases being studied in these trials depends heavily on the licensure of drugs shown to be effective in trials, it becomes critical to explore ways of possibly modifying the current use of data monitoring committees that might be more responsive to the needs of sponsors, yet do not compromise our ability to successfully complete these trials. I note, however, that what might work best in one disease area, such as HIV/AIDS, may not be best in another, such as cancer.

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