

much is being asked of statisticians. New scientific approaches that accomplish rapid new drug development seem unlikely to exist. Although statisticians will make improvements, limited data sets only yield limited amounts of information. We cannot change that without making extensive unverifiable assumptions. Further, we often find ourselves in the position

of making decisions concerning study conduct that should involve more extensive input from clinicians and others. We must make sure that expectations of statisticians remain reasonable and balanced.

We welcome the opportunity to make these additions to an excellent discussion of the issues facing us in evaluating therapeutic interventions.

Comment

David L. DeMets

I appreciate the opportunity to comment on this paper by Professor Fleming and want to compliment him on a timely and very relevant discussion of current issues in clinical trials.

In general, I agree with Professor Fleming's key points, so my remarks are similar in spirit, based on my experience with cardiovascular clinical trials and, more recently, with cancer and AIDS trials. In particular, I will comment on two points: the data monitoring committee and surrogate outcomes.

Clinical trials play an important role in the long and complex process to develop and evaluate new drugs, devices or procedures. Because patients are involved, ethical issues as well as scientific and economic factors must be considered in the design, conduct and analyses. In order to establish a model for conducting such trials, the National Heart Institute in the 1960's formed a committee chaired by the late Professor Bernard Greenberg. This committee's report, typically referred to as the Greenberg Report (Heart Special Project Committee, 1988), became the framework for NIH-sponsored cardiovascular trials as well as many other disease areas. One of the first trials to implement this model was the Coronary Drug Project (Coronary Drug Project Research Group, 1981). A key component to this clinical trial model was the data monitoring committee (DMC), an independent body not directly participating in the conduct of the trial at the clinic level and charged with the responsibility of patient safety as well as monitoring accumulating data for early evidence of benefit. If either treatment safety or benefit becomes convincing, consideration should be given for early termination. The Coronary Drug Project foresaw that this decision process would be very complex and formed a committee with a diversity of

expertise. The complexity of this monitoring process and the need for this expertise is best illustrated by reading accounts of several examples of the data monitoring experience (Coronary Drug Project Research Group, 1981; DeMets et al., 1982, 1984; Cairns et al., 1991). This model has now been used in dozens of trials, especially in heart, lung, blood, eye and cancer. Recently, the NIH AIDS clinical trials groups also adopted a variation of this model.

Looking back on over 25 years of experience with this data monitoring committee, I would argue strongly that it has been very successful. Where it has not been used, problems have often occurred, as Professor Fleming points out. I would also argue that this clinical trial model should be used for any comparative (Phase III) trial that is pivotal and has either mortality or irreversible morbidity as a primary outcome.

One demand of this monitoring process not always appreciated is the need for a timely and reasonably clean data base, at least for the critical endpoint and safety variables. Not having current data could lead to incorrect or inappropriate decisions and inferences, a process almost experienced by the Nocturnal Oxygen Therapy Trial (DeMets et al., 1982). In addition, we cannot always anticipate the direction or rapidity in which convincing trends emerge. Such an example is provided by the Cardiac Arrhythmia Suppression Trial (Cardiac Arrhythmia Suppression Trial Research Group, 1989), a trial briefly discussed by Professor Fleming for which I served on the data monitoring committee. With less than 10% of the expected number of deaths, the results were already trending strongly in a negative direction. The DMC requested the statistical center to contact all clinical sites and obtain up-to-date mortality data before the critical meeting of the DMC. Fortunately, the statistical center was able to provide such analyses, even at this early stage. Results were even more convincing with the up-to-date data, and the trial was stopped, declaring the treatment to be harmful. It would have been much more difficult, perhaps impossi-

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