NIH WORKSHOP:
Research Needs for the Design and Analysis of Surrogate Endpoints in Clinical Trials

BACKGROUND

There is increasing interest in exploring ways to reduce the cost and time needed for drug development by using biomarkers as surrogate endpoints in clinical trials. The need for further development of methods to evaluate the potential uses of such surrogate endpoints has been a focus of Office of Science Policy (OSP) issue identification sessions, as well as in individual interviews with representatives from industry, academia, and the FDA. Often the process of evaluating a surrogate endpoint involves estimating the extent to which surrogate endpoints capture the effect of an intervention (drug, vaccine, surgery) on a true clinical endpoint.

Evaluating the usefulness of surrogate endpoints involves not only statistical considerations, but also understanding of biological mechanisms. Development of increasingly sophisticated drug discovery methods (combinatorial chemistry, high through-put screening, and recombinant DNA technologies) leads to a need for more sophistication in characterization of biological mechanisms. Because drugs have many different mechanisms of action, and because of the limitations of any on surrogates, future clinical trials based on such endpoints are likely to have multiple surrogate endpoints. Understanding of how a disease process is altered by treatment effects on these endpoints will likely come from information collected from many clinical trials.

Investigation by the OSP identified relatively few statistical and epidemiologic investigators who are dedicated to methodological analysis for evaluation of surrogate endpoints. In addition, statisticians report considerable difficulty in accessing data from large clinical trials to conduct the kinds of analyses needed to investigate the use of biomarkers as surrogate endpoints. The need for collaborative research based on data accumulated across all relevant clinical trials must be more broadly understood.

To address the anticipated analytical needs resulting from widespread interest in the use of surrogate endpoints in clinical trials, the OSP is organizing this workshop.

WORKSHOP PLANNING COMMITTEE

Victor DeGruttola, Harvard School of Public Health (Chair)
David DeMets, University of Wisconsin-Madison
Gregory Downing, Office of the Director, NIH
Susan Ellenberg, Center for Biologics Evaluation and Research, FDA
Lawrence Friedman, National Heart, Lung, and Blood Institute, NIH
Mitchell Gail, National Cancer Institute, NIH
Janet Wittes, Statistics Collaborative
Scott Zeger, Johns Hopkins University School of Public Health
Pamela Clax, Office of the Director, NIH

STRUCTURE OF THE WORKSHOP

The workshop will take place on December 1-2, 1998, at the William F. Bolger Center for Leadership Development in Potomac, MD. The workshop will be in a retreat format to encourage free discussion among all participants. Day 1 of the meeting will address disease-specific issues in four categories: cancer, cardiovascular disease, infectious disease, and mental health and alcoholism. Day 2 will be devoted to a case study, a modeling session, and summary of recommendations.

Each session of the workshop is being developed by members of the planning committee (see meeting agenda). Sessions will include one or two presentations followed by designated discussants who will review the presentations prior to the workshop. Organizers will take responsibility for assuring that their sessions address the workshop objectives. A series of questions will be prepared for each section of the workshop and presented to the participants before the workshop. It is the goal of the organizing committee to have each participant prepare remarks prior to coming to the workshop.

WORKSHOP PARTICIPANTS

Approximately 50 participants will be invited to the workshop. The speakers, discussants, and participants will represent prominent leaders in the fields of biostatistics and clinical trial methodology, representatives from FDA, key NIH Institutes and Centers, and the pharmaceutical and biotechnology industries. Participants and speakers are being selected by the planning committee.

WORKSHOP OBJECTIVES

The goal of the workshop is to develop a set of recommendations for the broad scientific and medical community to address research needs in the analysis of surrogate endpoints in clinical trials.

The recommendations will address:

- Development of a statistical and inferential framework for investigating surrogate endpoints
- Design and conduct of trials using and/or investigating surrogate endpoints (data collection)
- Assemblage of databases for evaluating surrogate endpoints
- Methods of analyses—adequacy of existing methods and needs for new techniques
- Usefulness of complex models for marker evaluation
- Educational needs for the medical and statistical communities.

The final recommendations of the workshop will reflect the consensus of the workshop, when possible, as well as any areas of controversy. The organizers expect to draft a document resulting from the workshop and prepare it for publication.

Prior to the workshop, the speakers will provide the OSP with materials describing their sessions, including abstracts, copies of slides, and any handout materials. During the first evening of the workshop, the organizers will meet to develop a session summary for presentation on the following day. After the workshop, a writing team will prepare a final report that will be circulated to all workshop participants for comment.