

The Statistician's Role in Developing a Protocol for a Clinical Trial

FRED EDERER*

As a member of a clinical investigative team developing a protocol for a clinical trial, the statistician has broad responsibilities for ensuring the scientific integrity of the product. To prepare for this role, the statistician must study and learn in detail the clinical subject matter and must be prepared, if necessary, to teach the statistical principles of clinical trials to collaborators. This article discusses various issues that arise in the design of a clinical trial and how the statistician can participate in their resolution.

KEY WORDS: Statistician; Clinical trials; Scientific collaboration.

1. INTRODUCTION

I shall limit discussion of the statistician's role in developing a protocol for a clinical trial to the kinds of studies I have had experience with, namely, randomized single-clinic and multiclinic trials that are intended to provide definitive information on the efficacy and safety of a treatment.

The statistician's role in developing a protocol for a clinical trial is much broader than might be supposed by a student completing a course in experimental design. That course merely provides the theoretical framework. The statistician in a clinical trial needs to be more than a consultant; he or she should be a full-fledged partner of the investigative team and must take responsibility for the scientific integrity of the product. As Bross (1974) put it, the statistician cannot be a shoe clerk in this enterprise, but must be a scientist.

The statistician should keep in mind that the protocol—some prefer to call it a manual of operations—must be written in excruciating detail, particularly in multiclinic studies, so that the various study procedures can be carried out uniformly by all persons who may be required to do so throughout the study. Bearman (1975, p. 775) said that the protocol bears the same relationship to a clinical trial as a road map does to an automobile trip:

1. Before the study starts, it should be a guide telling us where we are headed and how we are going to get there.

2. During the study, it should be a device that tells us where we are and how we got as far as we have come and a guide for the rest of the trip to point us in the proper direction.

3. After the study ends, it should be a document that tells us where we are and how we got there and the route over which we traveled.

The statistician assigned to work on a protocol for a clinical trial must be prepared to become both a student

and a teacher during the course of this work. This entails studying and learning in detail the clinical subject matter and, if necessary, teaching elementary statistical and research design concepts to collaborators.

2. LEARNING THE CLINICAL SUBJECT MATTER

The statistician cannot learn the necessary clinical subject matter in a few days or weeks. It is best to stretch this learning period out for several months. The collaborating clinicians can be helpful in providing a bibliography, which need not be confined to books and journals, but should include, if possible, audiovisual materials. Public-information offices at the National Institutes of Health and at voluntary health agencies may be able to furnish pamphlets, videotapes, or films. The statistician should become conversant with the terminology, the natural history, available forms of treatment, and epidemiology of the disease under study.

A visit to the clinic to observe patient examinations, diagnostic procedures, and treatment is helpful. Even more helpful, if feasible, is for the statistician personally to undergo the diagnostic procedures, at least those in which the patient may react subjectively, as in a blood-pressure test, an exercise electrocardiogram, or a visual function test. The statistician should also find out from the physician precisely how objective tests, such as biopsies or radiographs, are interpreted and whether anything is known about the reproducibility of the interpretations or measurements. The reason for these inquiries is that the biometrician, as an expert in problems of measurement, classification, and variability, may be able to suggest ways of improving these methods. For example, if the critical measurements are subjective or qualitative, the statistician should inquire into the possibility of developing objective or quantitative methods, and, if nothing is known about reproducibility, it may be appropriate to suggest obtaining sample estimates of intraobserver and interobserver error.

In addition to the clinical subject matter, the statistician, as a member of the investigative team, should become conversant with aspects of clinical trials other than the medical and statistical ones, in particular the ethical considerations and, in multiclinic trials, the administrative features.

Although the statistician generally is not, and should not be, regarded as an expert in medical ethics, he or she should recognize that the basis for randomization in clinical trials is not only scientific but also ethical and that, unless the ethical issues are clearly resolved in the mind of the clinical investigator, there may be

* Fred Ederer is Chief, Office of Biometry and Epidemiology, National Eye Institute, National Institutes of Health, Bethesda, MD 20205.

difficulty in convincing patients to enter the study. Through reading on the subject of ethics in clinical trials, the statistician may be able to assist clinical colleagues in resolving ethical questions. Dr. Matthew D. Davis (1975), a physician, has said that a randomized clinical trial is ethical "when our best guess is that the chances of benefit and harm of the new therapy appear to be in balance." Another physician, Dr. Thomas C. Chalmers (1975, p. 753), believes that it is more ethical to randomize a patient into either a new or a standard therapy than to give the patient the new or standard therapy as if we knew that it was better when it might actually be more harmful. A third physician, Dr. Donald S. Fredrickson (1968), now the director of the National Institutes of Health, has said that a clinical trial is ethical when there is adequate collective doubt about the value of the new therapy.

3. TEACHING THE PRINCIPLES OF RESEARCH ON GROUPS OF PATIENTS TO COLLABORATORS

While acquiring clinical and related knowledge, the statistician should inquire about the degree of biostatistical preparation of co-investigators, either from course work or from practical experience in clinical trials or other research involving groups of patients. Why is it important for the clinical investigators to have adequate biostatistical preparation, and what should the statistician do if this preparation has been minimal, for example, no more than the usual biostatistics course given to medical students, a course for which they, as medical students, may have been poorly motivated?

Because the randomized clinical trial is an application of statistical methods, the statistician's clinical colleagues need to understand the principles of these methods. Many clinicians not only lack exposure to biostatistics and to systematic research on groups of patients, but certain aspects of their very clinical training are the antithesis of training for work in randomized clinical trials. As Mainland (1969, p. 17) said, ". . . the training of a doctor, as a doctor, is actually in some ways the reverse of an investigator's training." Clinical training emphasizes the uniqueness of patients, each patient having to get a thorough work-up so that his or her unique characteristics can be ascertained. The work-up, consisting of a medical history, physical examination, and laboratory tests, is in part routine and in part ad hoc; each new finding may suggest a new avenue of investigation. Usually the medical history is not recorded in a standardized fashion, and an item left blank may mean either that no attempt was made to obtain the information or that the patient did not know. Many clinicians inexperienced in clinical trials will instinctively resist procedures such as randomization, masking, and adherence to a prescribed, inflexible protocol as being incompatible with good clinical practice. The whole idea of the thorough work-up is to leave nothing to chance and to gain as

much information about the patient and the disease as possible. Randomization leaves the treatment to chance and masking obscures information. Moreover, following a prescribed, inflexible protocol leaves no room for the art of medicine. Ideally, the statistician's clinical collaborators, if without experience in clinical trials, will not merely learn to accept passively the principles of experimental design but will also become enthusiastic supporters. This can happen only if the collaborators understand that these principles are entirely compatible with the ethics of clinical medicine.

A good way to begin educating the statistician's collaborators, should they need it, is with a reading list. Two items I can suggest are the early chapters of E.B. Wilson's (1952) *Introduction to Scientific Research* and R.A. Fisher's (1935) tea-tasting experiment (Ch. II, *The Design of Experiments*). Both items are light reading and highly instructive. To these may be added selected chapters from elementary biostatistics texts, general material about clinical trials (Hill 1971 and Ederer 1975a), and specific materials about ethical aspects (Chalmers 1975), randomization (Ederer 1975b), and masking (Ederer 1975c). There is also a film illustrating the principles of clinical trials (National Eye Institute 1975). Last, but not least, a protocol from another clinical trial is valuable reading.

Clinicians must learn, if they do not already know, how clinical trials procedures differ from the thorough work-up. Clinicians must learn about the need for collecting information that is unbiased and reproducible and can be pooled. They need to be made aware of the various sources of bias, that is, failure to randomize or to adhere strictly to the randomization scheme (which clinicians have been prone to do), patient bias, investigator bias, and nonresponse bias. It is best to give examples of how these biases can cause trouble.

4. PROTOCOL DEVELOPMENT

Not until the statistician has acquired background knowledge is he or she prepared to think about the major design problems of the trial. How many different groups will be randomized? Will the control group be untreated, treated with placebo, or treated with a standard treatment? What are the major and minor response variables? What is the minimum required sample size? Are there any available data to help estimate this quantity? What precautions need to be taken to prevent various forms of bias? How long and how often will patients be followed, and what are the prospects for keeping dropouts to an acceptable minimum so as to prevent serious nonresponse bias? To prevent investigator or patient bias, is it desirable or necessary to do the study double-masked or at least single-masked? (Incidentally, I believe that these terms are more descriptive than double-blind and single-blind and, particularly in vision research, less awkward.) If so, are such procedures feasible? If not, can the main response variables be measured by a masked

observer? What problems must be solved to make masking successful? Can procedures be instituted to evaluate the success of the masking?

Are the criteria for patient eligibility and patient exclusion well defined, and, if not, what can be done to sharpen these? Can the diagnostic and treatment procedures be described in such detail that other investigative groups could reproduce the experiment from the descriptions?

If a multiclinic trial, should any of the specimens, such as blood or biopsy, or medical documents, such as radiographs or electrical tracings, be analyzed centrally in order to reduce interlaboratory error? What other measures should be instituted to help assure data quality? Need all the tests and measurements be performed by physicians, or can greater consistency be obtained by training technicians or secretaries? Some tests that are routinely done by physicians in everyday clinical practice, such as measurements of blood pressure, electrocardiograms, and visual function, have in some clinical trials been successfully taken over by technicians, and it is generally believed that technicians can be taught to carry tests out more consistently. Whether the tests are administered by technicians or physicians, the question should be raised, particularly in multiclinic trials, about the possible need to train personnel and, if the need exists, whether the training programs can be started while the research protocol is being developed.

The statistician, although not necessarily an expert in the administration of multiclinic studies, has the responsibility as a member of the investigative team to participate in designing the organization and formulating the special procedures needed for multiclinic studies (Ederer 1975d). The following issues need to be addressed in multiclinic studies, and all investigators, whether clinical or statistical, would do well to study existing protocols to learn how others have dealt with these problems. How should the study be organized and managed so as to assure that all the work that needs to get done gets done efficiently? What are the functions and responsibilities of various subgroups of the organization, such as the steering committee, principal investigators, coordinating center, and various committees? What is the process for getting study papers published? Whose responsibility is it to get papers published? Under whose authorship will papers be published? Will individual clinics be permitted to do ancillary studies that could interfere with the main course of the study? What will be the policy governing ancillary studies?

The answers to the foregoing questions may not be simple. The attempt to answer any one of them may raise a host of problems the solutions to which require collaboration between clinician and statistician. To illustrate the potential complexities, I will consider two questions, which in one particular study, a multiclinic pulmonary-embolism trial, happened to be intertwined. It is interesting to note that statisticians first

became involved in this study when clinical investigators requested help in constructing a method for randomizing the patients. The statisticians succeeded in prevailing on the clinicians to delay randomizing until a detailed protocol was written. One of the questions raised by the statisticians during the course of protocol development was "What are the major response variables?" The answer provided by the clinicians was "Resolution of pulmonary thromboemboli as demonstrated by pulmonary angiogram (major response variable) and pulmonary photoscan (minor response variable)." These are two photographic techniques, each requiring the injection of a contrast medium into the blood stream, for detecting circulatory defects caused by pulmonary emboli. The second question, which, as I said, was interrelated with the first, was "Will the angiograms and photoscans be read at the clinic of origin, or will they be read centrally?" The decision on the second question was made quickly: The angiograms and scans would be read centrally, each type by a panel of experts. This decision also answered a third question affirmatively, namely, whether the evaluation of response variables would be performed masked. It was far from clear, however, how the circulatory defects noted on the radiographs would be classified or quantified. No methods had been developed. It was then decided to have each of the two expert panels meet with a statistician to develop a system for grading the radiographs. It turned out that the systems could not be developed in single meetings. Each group held a series of meetings over a number of months to prepare and revise drafts of grading forms. Between meetings there was communication by mail and phone. Eventually the panels developed both subjective and semiobjective methods for grading the radiographs. These methods then had to be pretested. The pretest was followed by another meeting of the panel, at which time a final version was agreed on.

In discussing the various protocol questions with co-investigators, the statistician should be a good listener, open-minded and flexible, and, when necessary, firm. On many of the routine statistical issues, the clinical investigators will generally rely on the statistician's recommendations. Other issues may be controversial, and if they are not critical, the statistician can afford to be flexible. But if the statistician runs into resistance on the major design features (such as randomization and masking) because they increase logistical complexities (they usually do), he or she will have to be firm.

5. CONCLUSION

Collaborating on the preparation of a protocol for a clinical trial can be a rewarding and exciting experience for a statistician. It is an opportunity for the statistician to apply skills and ingenuity and learn from and teach other scientists. It is the start of a new venture—an exploration into the unknown. If the study

is planned in accordance with the best scientific principles, then, no matter what the findings, the statistician can look forward not only to helping to increase knowledge about the treatment or prevention of disease but also to deriving the rich personal satisfaction of knowing that the job was well done.

[Received October 1977. Revised November 1978.]

REFERENCES

- Bearman, Jacob E. (1975), "Writing the Protocol for a Clinical Trial," *American Journal of Ophthalmology*, 79, 775-778.
- Bross, Irwin D.J. (1974), "The Role of the Statistician: Scientist or Shoe Clerk," *The American Statistician*, 28, 126-127.
- Chalmers, Thomas C. (1975), "Ethical Aspects of Clinical Trials," *American Journal of Ophthalmology*, 79, 753-758.
- Davis, Matthew D. (1975), "Applications of the Principles of Clinical Trials," *American Journal of Ophthalmology*, 79, 779-785.
- Ederer, Fred (1975a), "The Randomized Controlled Clinical Trial," *American Journal of Ophthalmology*, 79, 752-789.
- (1975b), "Why Do We Need Controls? Why Do We Need to Randomize?" *American Journal of Ophthalmology*, 79, 758-762.
- (1975c), "Patient Bias, Investigator Bias, and the Double-masked Procedure in Clinical Trials," *American Journal of Medicine*, 58, 295-299.
- (1975d), "Practical Problems in Collaborative Clinical Trials," *American Journal of Epidemiology*, 102, 111-118.
- Fisher, R.A. (1935), *The Design of Experiments*, New York: Hafner Press.
- Fredrickson, Donald S. (1968), "The Field Trial: Some Thoughts on the Indispensable Ordeal," *Bulletin of the New York Academy of Medicine*, 44, 985-993.
- Hill, A. Bradford (1971), *Principles of Medical Statistics*, London: Oxford University Press.
- Mainland, D. (1969), "Clinical Trials and Health Care Administrators," Note 42, Notes on Biometry in Medical Research, Washington, D.C.: Veterans Administration Monograph 10-1 (Suppl. 6).
- National Eye Institute (1975), "The Diabetic Retinopathy Study—A Nationwide Clinical Trial" (35-mm film), Bethesda, Md.: National Eye Institute, Public Health Service, Dept. of Health, Education and Welfare.
- Wilson, E.B. (1952), *An Introduction to Scientific Research*, New York: McGraw-Hill Book Co.



The Statistician's Role in Developing a Protocol for a Clinical Trial

Author(s): Fred Ederer

Source: *The American Statistician*, Vol. 33, No. 3 (Aug., 1979), pp. 116-119

Published by: Taylor & Francis, Ltd. on behalf of the American Statistical Association

Stable URL: <https://www.jstor.org/stable/2683811>

Accessed: 15-03-2019 21:48 UTC

JSTOR is a not-for-profit service that helps scholars, researchers, and students discover, use, and build upon a wide range of content in a trusted digital archive. We use information technology and tools to increase productivity and facilitate new forms of scholarship. For more information about JSTOR, please contact support@jstor.org.

Your use of the JSTOR archive indicates your acceptance of the Terms & Conditions of Use, available at <https://about.jstor.org/terms>



JSTOR

American Statistical Association, Taylor & Francis, Ltd. are collaborating with JSTOR to digitize, preserve and extend access to *The American Statistician*