

The Training of Statisticians for Cooperative Clinical Trials: a Working Statistician's Viewpoint¹

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SUMMARY

The methods of training statisticians for clinical trials can take diverse forms: attendance at courses and lectures, personal study, observing and doing, or working as an apprentice. Desirable qualifications for an effective working statistician are: adequate knowledge of biostatistics and the field of application for the clinical trial, an ability to communicate statistical ideas verbally at meetings and in the writing of reports and collaborative research papers, an awareness of potential sources of bias, an understanding of ethical issues, and an ability to set priorities for projects. These issues are discussed in the context of training, and personal comments are made from the viewpoint of a statistician with substantial experience of clinical trials in cancer.

1. Introduction

The training of statisticians to work in the field of clinical trials, like the training of individuals in any discipline, is probably best accomplished by various methods: by attending formal courses and lectures in biostatistics, statistical consulting and the particular field of application; by personal study of the literature; by working as an apprentice in a successful organization; and by working in the field. This paper will not recommend a best training method: I have always been impressed by the diversity of paths that individuals may take to achieve the same objective. Each individual must decide for himself or herself which methods of training work best.

The approach I will take is to outline the desirable qualifications for a successful statistician working in the field of clinical trials. If an individual is interested in entering this field, then it will be up to him or her to develop these qualifications by the most appropriate training method. I will also make some comments on training, mostly from the personal viewpoint of a statistician who has worked for more than 20 years in cancer clinical trials.

For other articles about training of statisticians, I suggest those by Hammond (1980) and Peterson and Fisher (1980) in this issue, and the excellent bibliography for statistical consulting by Woodward and Schucany (1977). Articles of particular interest in the biometric field are those of Finney (1968) and Zelen (1969).

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Key words: Training of statisticians; Clinical trials; Statistical consulting in clinical trials.

2. Qualifications for a Successful Statistician in Clinical Trials

Generally, an individual should have an adequate knowledge of statistics and of the field of application being studied, an ability to communicate ideas both in speaking and in writing, a sensitivity to possible biases in the design, analysis and interpretation of clinical studies, an appreciation of ethical issues, and an ability to set priorities for work to be accomplished.

2.1 Adequate Knowledge

A statistician beginning to work in clinical trials clearly must develop adequate knowledge of the theory and application of statistical ideas in clinical studies. Fields of study of special importance are: theory and analysis of survival time studies; theory and application of regression methods for relating patient characteristics to prognosis; methods of design, analysis and interpretation of clinical trials data; theory and analytic methods appropriate for categorical data; design and analysis of sequential studies; and, in general, the fields of hypothesis testing and estimation.

In addition, it is of nearly equal importance for the working statistician to have an in-depth understanding of the field of application. This is important because it enables the statistician to choose the design and method of analysis most appropriate for the clinical trial being conducted. Further, the statistician will not be accepted by the clinicians as an equal collaborator unless they have confidence that he knows what he is talking about.

It would certainly also be useful for a statistician to be acquainted with statistical packages (such as SPSS, BMDP, SASS, MINITAB, GLIM, etc.) for use in the analysis of clinical trials. For large clinical trials conducted over a period of time, knowledge of the capabilities of some data-base management systems, and of the advantages and disadvantages of each, would be desirable. Also, knowledge of a programming language, even one as simple as BASIC or APL, would be helpful for the development of statistical calculation procedures which might not be readily available elsewhere.

For statisticians working in cancer research, it would be important to know something about the following: the relevance of studies of agents in animals to studies in man; pharmacological considerations; the importance of cell-cycle kinetics in the choice of treatment for patients; the extent to which patient characteristics influence prognosis; and, in general, the relevance of other areas of medical research to the clinical trial in progress. Some knowledge in these areas will help to provide the breadth of perspective that the statistician will need in interpreting the results of the clinical study.

In other areas of clinical investigation, a general background of knowledge in a particular area may be useful, depending upon the clinical trial's application: for example, endocrinology (diabetes trials), circulatory physiology (cardiovascular trials), biochemistry (trials in metabolic disorders), microbiology (dental clinical trials), and so forth.

In my own work in consulting, it has often been evident that the clinician-collaborator knows what the general objectives of the clinical trial are, but has difficulty in translating these into a specific strategy for study. The successful statistician will be able to interpret the clinician's remarks and set up a design with provisions for the data to be collected and actions to be taken at appropriate time points for each patient. Clinicians are generally not quantitatively oriented and do not have adequate mathematical or statistical knowledge, yet medical research today must be objective and quantitative in order to be published and to persuade others, especially those making awards of financial support for clinical trials. It is the statistician's responsibility to be sure that the study will be designed, conducted and analyzed so that the results are relevant to the achievement of the major

objectives. Knowledge of statistics will be important in carrying out this task, but knowledge of the field of application will also be essential.

2.2 Ability to Communicate

Clinical trials are cooperative efforts involving clinicians, statisticians, nurses, data managers, computer programmers, and administrative and other personnel. The statistician's job is to suggest an appropriate design, to present reports concerning the progress of the study, and to collaborate in the writing of the research paper giving the results. Since decisions about the design of a trial are often made at committee meetings, it is important to have the ability to present in a simple and clear manner the set of options for the particular clinical study, with a specific recommendation about which designs might be best in various circumstances. Ideas concerning a study can flow and change rapidly at a committee meeting, so a statistician has to be quick at understanding how to deal with a new situation. The successful statistician will have a ready answer when, after 30–40 minutes of wide-ranging discussion concerning possible designs for the clinical study, the chairman of the committee asks: 'What do you think of this discussion, and what are *your* ideas as to how this study should be accomplished?'

The statistician should have the responsibility for writing the results section of the paper reporting the clinical study. Consequently, he or she must not only know statistics and the field of application, but also how to write simply and concisely the report to appear in the medical literature.

Under ability to communicate, I also include the problem of understanding what the clinicians expect to achieve in a particular clinical study. To have success in consulting with clinicians, I suggest asking yourself at regular intervals: 'What seems to be the real problem here? How are we going to answer the questions posed with the specific data being collected?' Having good answers to these questions involves mainly the ability to interpret a clinician's general statement of objectives in the particular context of the clinical trial. For example, in a recent consultation concerning a study of bone marrow transplantation and combination chemotherapy for lung cancer patients, the clinician did not understand the need to follow the patients 'unsuitable for bone marrow transplant' when comparisons were to be made with a historical control series of patients receiving combination chemotherapy alone.

The writing of collaborative papers has to be learned by doing, and by getting criticism from experienced colleagues. My policy has always been to write a report of each consultation. This should do the following: it should delineate the conclusions which could be demonstrated by conducting the study; it should give a well-defined statement of the population of patients; and it should give a statement about the general approaches to the analysis of the data. This will not only inform the clinician of what to expect from the study, but will also serve to remind the statistician of the details of the project when the report is referred to on a future occasion. Finally, it will be useful in the writing of the collaborative paper.

2.3 Sensitivity to Bias

An awareness of the possibility of bias is essential, especially since many clinicians seem unaware of how biases may influence the outcome of a study. The most damaging conclusion that can be drawn from a clinical study is that there exists (or does not exist) a real difference in outcome between treatments when, in fact, the difference (or lack of it) arose because of an unrecognized bias. Consequently, one should be aware of possible

biases in diagnosis, selection of patients, treatment of patients, reporting of data, evaluation of results and analysis of data.

Ambiguities may arise because of the number of possible denominators which can be used in the calculation of response rates: for example, the total number of patients considered for study, the number selected, the number eligible, and the number who were fully evaluated and included in the analysis. If the study is a comparison of two treatments, one must determine whether individuals excluded from the analysis will affect the reported differences. The approach should be to do multiple analyses, both including and excluding patients who are likely to cause biases in the estimation of the difference between treatments. If the conclusions regarding the difference differ according to the exclusion or not of a certain subgroup, for example those who did not receive an 'adequate course of treatment', then the study should be regarded as inconclusive until further patients can be studied.

To some extent, individuals entering the field of statistics are inherently skeptical about analyses of data and will have a sensitivity to bias. This can be refined further by reading articles in the literature about clinical trials, by discussions with clinicians who plan and conduct clinical trials, by making direct observations of patients and by reviewing the individual patients' records.

2.4 *Ethical Issues*

The major difference between experiments generally, and clinical trials in particular, is that the patient is nearly always the experimental unit in the clinical trial whereas, in other fields, the unit may be the laboratory animal, a test tube filled with cells, a sample of blood, etc. The statistician should always consider the possibility of being a patient at some time in the future, and the question should be asked: 'If I were a patient, would I be willing to participate in the proposed clinical trial?' If the answer is 'No', then perhaps the design should be reconsidered. In a clinical trial comparing two treatments, there should be equal evidence favoring the two treatments before one should be willing to randomize patients.

Another area of concern is the accumulation of data during the conduct of a study. If, as the study proceeds, evidence accrues that Treatment A seems better than Treatment B, when should the study be stopped? When should all patients on Treatment B be transferred to Treatment A? The most ethical plan seems to be to conduct either a sequential clinical trial or a study of Treatment A in consecutive patients with comparison to B in a historical control series. It is surprising that more sequential studies have not been conducted to achieve ethical and statistical validity in clinical trials.

Statisticians can develop a greater appreciation of ethical issues by reading Levine and Lebacqz (1979). These authors state that when the words 'should' or 'ought' appear, an ethical question has been raised. Clearly, use of these words in a statement is an expression of the degree of belief of the author in the correctness of the statement. Consequently, one's ethics depend in large measure on one's knowledge of the particular clinical study and its relevance to the field of application.

2.5 *Setting Priorities*

If a reasonably successful statistical consultant comes to an institution, it does not take very long, say two to three years, before he is involved in a multiplicity of projects that can consume all of his time. Clinicians prepare abstracts for meetings, give talks requiring statistical analyses, write papers for medical journals, and prepare grant proposals for

support of projects. Demands may be continually made on the statistician for an up-to-date and comprehensive report of results. A statistician should realize that no one will be telephoning or knocking at his door pressing him to complete a current statistical research project. The outstanding problem raised by cooperative-group statisticians at a recent meeting was 'insufficient time for statistical research on problems arising in consulting.' If one wishes to be a well-rounded statistical consultant who makes contributions to collaborative clinical studies and does statistical research, then one must limit involvement in consulting projects and set realistic priorities for the completion of projects.

One suggestion I have heard is that a consulting statistician should change institutions about every three to four years since he can carry along with him his statistical research projects, but leave behind the collaborative clinical research projects that consume most of his time. An alternative is to set limits on the number of clinical studies in which one can be involved to a significant degree. The biometricians working on cancer clinical trials in the Southwest Oncology Group discussed this problem, and reached the consensus that a consulting statistician could be involved in 10–12 clinical research studies, three to five in the planning phase, four to six in the conduct and preparation of research papers.

A statistician may expect to be involved in activities such as design of forms, assistance in special studies, preparation of abstracts and reports for meetings, supervision of computer programming and data management staff, administrative and personnel responsibilities, and other activities such as attending meetings and planning workshops. Hence, it is essential that sufficient time be set aside for keeping up with the statistical literature and carrying out statistical research. Statisticians have adopted various means for achieving this end: refusing telephone calls or having appointment times for visitors only at specified times during the week, and visits to the library at regular intervals. But most statisticians doing research 'burn the midnight oil' and do it on their own time. One of the best techniques for giving priority to a particular statistical research project is to agree to give a lecture. As the time for the lecture draws near, one simply must give the project a high priority.

I do not have any real solution to the problem of setting priorities, but I would stress the importance of it for each individual. An awareness of the problem will help to limit the number of projects being worked on. In some cases, it will mean working on one investigator's project in preference to another's; this further stresses the importance of a broad perspective for evaluating research projects.

3. Comments on Consulting in Statistics

It may be helpful to neophyte statisticians to give some general comments about statistical consulting and, in particular, to issues arising in clinical trials. The following advice has been developed over the years by consulting at the National Cancer Institute and the University of Texas System Cancer Center.

Avoid investigators bearing large quantities of data that they refer to as a 'gold mine' of information concerning a particular project. Usually, these data have been gathered over a long period of time by the investigator, and he would like to put on record his accomplishments in treating a particular condition and determine patient characteristics related to prognosis. Unfortunately, the data have usually been collected with no particular hypotheses to be tested or general plans for study, so that the data are usually incomplete and inconsistent with respect to prognostic characteristics, the follow-up of patients, and reports of response. Consequently, the consulting statistician may spend a

large amount of time in the 'mining' of information that has very limited usefulness. These investigators may be recognized because they ordinarily carry large numbers of forms and wish to transfer them to the desk of the consulting statistician with very little guidance about what is to be achieved through the analytic effort. Such investigators are best avoided.

Secondly, be wary of investigators who telephone with a request for only five minutes of your time to solve a small problem. If an appointment is accepted with such an investigator, you will usually find that the investigator has spent a very long time trying to solve the problem that he expects you to solve in a few minutes. I have found that one of the following is true in this type of situation: the investigator does not really understand his problem and he expects you to figure out what the problem is and to provide the solution; there are some basic difficulties and possible biases in the data, which the investigator recognizes but does not know what to do about; or the investigator does not have a very good understanding of what a statistician does and is unlikely to give you very much credit even if you do solve his problem— because he told you at the outset 'it would only take five minutes.'

Learn some shortcut methods and be able to give 'ball-park' estimates for numbers of patients in clinical studies. This advice was learned from Mr Nathan Mantel at the National Cancer Institute. Invariably, he would return from a consulting visit having satisfied the investigator completely, having advised him how to analyze his own data, and carrying no data with him. On my consultation visits, I would leave the investigator without having answered his questions fully, but with a promise to get back with him in a few days with the answers to his problems, and would carry large amounts of data back to the office. The latter condition can be avoided by learning shortcut methods. For example, a useful shortcut method is that the standard error of a mean is approximately the range of the observations divided by the number and this is roughly true for sample sizes up to 15 (Mantel, 1951). This rule is useful in the analysis of small studies where the data are listed. Advising an investigator about simple graphical methods for presentation can start him happily analyzing his own data. Finally, a useful number to recall is 75. If one wishes to do a clinical trial comparing two treatments and to test for 20% differences in response rate (at a 5% significance level and 80% power), then roughly 75 patients should be included in each treatment group (for a one-sided test). Consequently, if an investigator should ask how many patients are needed for a clinical trial comparing two treatments when it is desired to test whether one treatment is better than another, one can answer 150 with a reasonable degree of confidence.

One often hears the phrase at committee meetings or at meetings of a group of cooperative investigators, 'Does anyone object to that?', when 'that' may refer to a protocol that the investigators seem to be agreeing upon, or to some course of action that the investigators propose to take over the next several months. The experienced consulting statistician rises immediately and asks the chairman to rephrase the question to: 'Which investigators will give their solid support to this protocol (or course of action) and contribute their patients (or time and effort) to assure the success of the project?' For the first question, no one may object, but then later they fail to give the project any support. It is quite a different matter to ask which investigators give the proposal their solid backing.

A statistician should be an equal collaborator with the clinicians in clinical trials. Avoid situations where the clinicians believe that the statistician is working 'for' rather than 'with' them. In the former situations, the statistician will never be given full credit for his efforts. Authorship of papers may depend on whether a statistician is accepted as an equal

collaborator. When reporting the therapeutic results of a study, it is logical and proper for a clinician to be the first author even when the statistician may expend major efforts during the conduct of the study and in the write-up of the conclusions. However, in a related clinical paper, on topics such as the determination of patient characteristics related to prognosis or the development of a statistical model for prediction of prognosis, in which the major effort is analytical, the statistician should properly be the first author.

A further point concerning the interrelationship between statisticians and clinicians is the responsibility that each should bear for management of the data in the study. Some clinicians believe that the statistician should accept full responsibility; however, these are usually the same clinicians who believe that the statisticians are working 'for' the clinicians. Ultimately, it should be the responsibility of the clinicians to collect and report appropriate data for each patient, but the statistician should be willing to assist in this process by training a staff of data managers who assume a day-to-day responsibility for editing and assuring the completeness and accuracy of data. Responsibilities of the statistician may differ depending on whether the clinical study is being carried out at one institution or more than one. When the study is done at a single institution, data-management staff should be employees of the clinician. In a cooperative cancer study group, there should be data managers employed at the statistical center supporting the project and at the separate institutions.

In deciding a strategy for a particular clinical study, I have sometimes found myself in substantial disagreement with some or all of the clinician-investigators about how to proceed. It is naturally depressing when one's carefully-considered ideas are rejected. I have found it psychologically beneficial to consider the conduct of cancer clinical trials over a period of time as a 'war against cancer' in which one might be willing to lose a few battles. In some cases, clinician-investigators with whom I have argued have come closer to my viewpoint in subsequent studies. In others, I have become more aware of issues to which the clinicians are sensitive. It is inherently extremely difficult (or sometimes impossible) to persuade people to change their minds about an approach to a subject in which they are professionally and emotionally involved, such as a cancer clinical trial. The more a statistician can argue an objective viewpoint from current or previous data, the more he can be persuasive.

During the conduct of a clinical study, there are often discussions about whether to change the design or to stop. I believe the statistician's responsibility should be to give the statistical evidence in support of various options, but that it should be the responsibility of the clinicians to decide the final course of action based on an integration of the statistical and medical evidence. For example, a statistician might make a report which gives the evidence that the toxicity of a particular treatment changes with age, say under one year of age *vs* one or more years of age. It should be for the clinicians to determine whether the dosage of treatment should be changed according to the age of the patient.

I have heard it argued by an eminent clinician that the statistical and medical evidence for deciding on a particular course of action should not be separated. I think a statistician should base an analysis on objective evidence, such as response rate, length of response, or survival. The strength of the evidence that two treatments differ can be evaluated statistically and this should form the basis of the statistician's report. If medical considerations suggest a different course of action from that suggested by the statistical evidence, then the action taken should depend on the clinician's weighing of the medical and statistical evidence.

The question sometimes arises about the responsibility for a particular design of a clinical trial or method of approach to a problem. Sometimes, I have heard it argued that

the statistician should accept full responsibility for the design and analysis of the study, even when he may have proposed a different design. A cooperative clinical trial is a cooperative venture involving clinicians and statisticians. No one individual should accept full responsibility for the study; however, the statistician should be prepared to defend the design and analysis chosen or to indicate the nature of his disagreement with what the clinicians chose to do.

4. Final Remarks

The job of the consulting statistician in clinical trials can be a rewarding one. One has the opportunity actually to participate in the design, conduct and analysis of clinical experiments, whereas an academic statistician may only have the opportunity to teach courses in design and analysis. When one's work results in advances being made in the treatment and prognosis of patients, then it is gratifying to have contributed to the total effort. Finally, if the statistical research that one accomplishes is derived from real problems, then one can be assured that the research methodology developed will have direct application in future studies.

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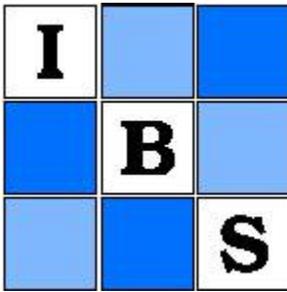
RÉSUMÉ

Les méthodes de formation des statisticiens aux essais cliniques peuvent prendre différentes formes: assistance à des cours ou à des conférences, étude personnelle, observation et réalisation, ou travail comme débutant. Les qualifications pour un travail effectif de statisticien sont: connaissance suffisante en biostatistique et dans le champ d'application pour l'essai clinique, aptitude à communiquer oralement les idées statistiques, aptitude dans la rédaction de rapports et d'articles de recherche écrits en commun, une aptitude à déceler les sources potentielles de biais, une compréhension des conséquences éthiques, et une capacité à voir les priorités des projets. On discute de ces conséquences pour le problème de formation, et on évoque le point de vue d'un statisticien ayant une bonne expérience dans les essais cliniques en cancérologie.

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