BIOMETRICS 36, 679–685
December 1980

The Training of Clinical Trials Statisticians: a Clinician's View[1]

Denman Hammond

The Childrens Cancer Study Group, University of Southern California Comprehensive Cancer Center, 1721 Griffin Avenue, Los Angeles, California 90031, U.S.A.

SUMMARY

Clinical investigation today involves not only multidisciplinary teamwork but also investigators at multiple institutions observing the same criteria and standards in order to make possible the valid pooling of data in collaborative studies. As a result, there has been increasing awareness of the biostatistician's role, not simply in interpreting the data at the end of the study, but in every step of clinical investigation. This involvement ranges from study design and feasibility testing to data analysis and reporting.

The problem is now a shortage of biostatisticians appropriately trained for clinical trials statistical methodology. As the statistician's role is of great importance, more graduate training programs in statistics should prepare statisticians for clinical trials work. This would pave the way to the many exciting and rewarding career opportunities which are available for statisticians in the area of clinical trials.

In the historical perspective, clinical investigation was conducted at the bedside and in the clinic by a physician who was, at one and the same time, a careful therapist and an astute observer. Such clinician–investigators developed valuable experience and insights during a lifetime of practice, and many of them became the great medical teachers of their time. It is unthinkable that clinical investigations would be done in this fashion today. Top-quality modern clinical therapeutic investigation is a matter of teamwork involving carefully disciplined investigators who represent many different areas of expertise; it is no longer the work of single observers, no matter how astute.

A few decades ago, the only biomedical investigators who, it was thought, were required to exercise strict scientific discipline were the basic scientists. It is still not widely recognized that first-rate clinical investigation requires the exercise of far more stringent discipline, and a far greater variety of quality control endeavors, than almost any nonclinical laboratory experimentation.

Today, not only does first-rate clinical investigation require a team approach involving multiple disciplines, but often the most productive and valid clinical investigation involves investigators at multiple institutions, each observing the same criteria and standards for the varieties of clinical decisions so that valid pooling of the data from multiple independent observations is possible in these collaborative studies.

The role of the biostatistician in clinical investigation has evolved significantly. There has been an increasing recognition not only of the need for biostatistical expertise in helping to fathom the meaning of data at the end of a study, but also of an increasing

[1] Based on an invited paper read at a meeting of the Biometric Society (WNAR), held in Los Angeles, June 1979.

Key words: Statisticians; Clinical trials; Graduate training; Clinical investigation; Multidisciplinary teamwork.

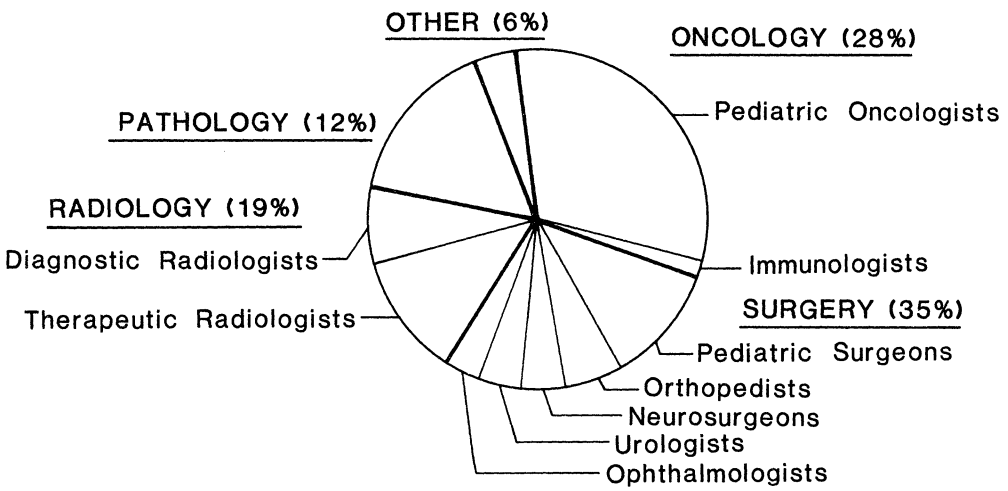

Figure 1. Distribution by discipline of the 830 physicians forming the membership of the Childrens Cancer Study Group.

dependence upon biostatistical methods for every step of clinical investigation, from clinical study design and feasibility testing to data analysis and reporting.

It appears that we have come full cycle from an almost total lack of awareness of the need for biostatistical input to the recognition that such expertise is mandatory in modern, sophisticated clinical investigation. The problem has become one of a deficiency in the number of biostatisticians appropriately trained in the statistical methodology of clinical trials.

It is appropriate that one considers the training and background required for biostatisticians to meet the needs of clinical trials and the expectations of clinicians engaged in investigation. Nowhere is there a greater need for biostatistical expertise than in clinical investigations done by multi-institutional cooperative groups, particularly those that conduct multiple protocols concurrently. For ten years I have been the Chairman of the Childrens Cancer Study Group, an organization of over 600 clinical investigators at 28 of the major pediatric medical centers in the United States and Canada. At the beginning of that period, although the Group had access to biostatistical consultation, it did not have a full-time statistician. It now has a statistical center with five statisticians and a staff of 20. It is with this background of experience that I would like to examine the training of biostatisticians for work in clinical investigations.

There are member institutions of the Childrens Cancer Study Group in 18 states and three Canadian provinces. These include many of the major pediatric referral institutions in North America. Figure 1 shows the multiple clinical disciplines represented among the membership of the Group. There are approximately 600 clinical investigators, including pediatric hematologists, pediatric oncologists, pediatric surgeons, radiation therapists, diagnostic radiologists and pathologists, and a variety of preclinical scientists. At each institution, the multidisciplinary team coordinates its activities with the therapeutic investigations of the whole Group.

The number of new patients registered annually by Group institutions is in excess of 2600. That is approximately one-third of the new cases of cancer among infants and children in the U.S. per annum. Over 70% of these are entered into the various therapeutic studies of the Group. The remainder are patients seen for consultation only,

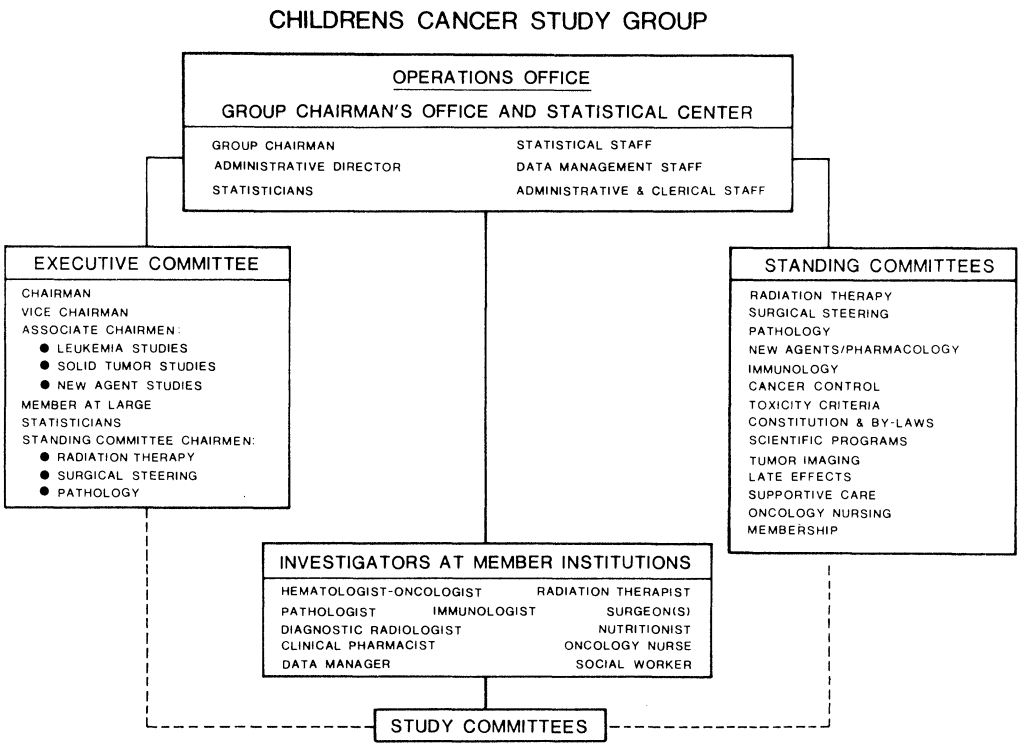

Figure 2. Organizational chart of the Childrens Cancer Study Group.

or are ineligible for entry to the studies by reason of previous treatment, or they have cancers of rare occurrence for which the Group has no active studies. The active studies include protocols for various types and stages of leukemia, studies of the various solid tumors of children, trials of new anticancer agents that may be useful for treatment of the cancers of children, and special studies that deal with clinical pharmacology, immunology, the natural history of pediatric cancers, complications of treatment, complications of the disease, etc.

Figure 2 is an organizational chart. Group activities are coordinated and directed from a central operations office which includes the Group chairman's office, the centralized data management center, and the statistical center. In addition to the Group chairman and the Group administrator, there are two full-time and one part-time doctoral-level statisticians, two master's level statisticians, and a staff of 20 including data managers, clinical analysts, programmers, and the required secretarial and clerical staff.

The Group is directed by the Group chairman, assisted by an executive committee that includes associate chairmen for the major areas of Group activity: leukemia, solid tumors and new agents. It includes the Group statistician and the chairmen of the specialty discipline committees: surgery, radiation therapy and pathology.

Perhaps the most challenging role for a biostatistician involved in clinical trials is to work in a multidisciplinary, multi-institutional, multiprotocol cooperative clinical investigations group. I would like to propose what might be considered as the ideal training and background experience for a biostatistician who wishes to enter this important, exciting and challenging career. It will be recognized that these considerations require modification when applied to the realities of the doctoral training curriculum in statistics.

Consider first the basic ingredients of formal graduate training in statistics. Most formal training programs leading to a doctoral degree in statistics will certainly include training in statistical theory, mathematical statistics and various forms of applied statistics. It is becoming increasingly necessary for the applied statistician also to understand computer science, and have some knowledge of programming, programming languages and database management. Certainly in the clinical trials setting, most statisticians will be responsible for supervising some aspects of computer operation and the activities of programmers. I would like to assume that these basic skills can be obtained in any good graduate biostatistics program.

Certain additional training and skills are needed by clinical trials statisticians. These should be emphasized more in good graduate programs intended to prepare biostatisticians for clinical trials. In many graduate courses, training in clinical trials methodology and the techniques of survival analysis will be available. Additional training in some biological science, such as physiology, biology or pharmacology, would be enormously helpful. One needs to know something about how diseases occur, what effects they have on the body, and some of the clinical terminology. In addition to a knowledge of appropriate statistical literature and reference sources, it would be useful if the statistician had some knowledge of medical literature sources in order to become familiar with the manifestations of the diseases under study and to acquire some understanding of the clinical problems which the disease creates in patients, and with which physician colleagues must deal. It is essential that the statistician acquires some practical experience in the clinical applications of statistical skills. It is recognized that experience in all of these areas will not necessarily be available, even in some excellent graduate training programs in statistics. Many of these skills will have to be learned on the job.

The statistician's various roles in clinical investigations include the planning of clinical studies, the establishment of systems to permit the initiation of such studies, the monitoring of various aspects of the study during its conduct, and, finally, a responsibility of overriding importance in the analysis and reporting of the clinical trial.

The statistician's roles in the planning of a clinical study will include the testing of the appropriateness of the study design for answering the clinical questions posed, the development of randomization and stratification schemes for controlling the study, the determination of sample size requirements and establishing the number of patients available for the study in order to determine the feasibility of the design and of the very study itself. To translate a clinical study plan to a detailed written protocol to insure identical criteria and performance at each participating institution will require that the critical data needed for analysis, the endpoints for various phases of the study, and the stopping rules all be written into an appropriate statistical section. Thus, the statistician has a responsibility to specify the standards for quality control to insure the proper performance of the study, including compliance with protocol provisions to insure the proper performance of the study, including compliance with protocol provisions to insure the generation of the data needed to answer the study questions posed. The statistician thus has the crucial role of determining whether the study can be done, and how it should be done in order to obtain a valid answer. In a well-disciplined clinical investigations group, the statistician is in a position to determine whether or not the study should be carried out at all.

Once a study has been designed and has met quality control and feasibility requirements, the statistician has several tasks to perform in setting up the study. Various clinical data forms, adequate to identify and insure capture of the detailed data needed from each patient, need to be designed. Sometimes the data capture forms must be tailored to the

diagnosis under study, and occasionally the forms may need to be specific for a single protocol. The requirements expected of each participating investigator and institution for submission, quality and scope of data must be determined and specified in the protocol in sufficient detail to assure uniform compliance. Also, at this stage, the clinical trials group statistician will need to convey to the programmers the general design and purpose of the study, and also an understanding of the data which the study will generate and how these data will be analyzed, so that the data management system can be programmed appropriately.

Major clinical trials may require several years of patient entry and several more years of study conduct and patient follow-up. There are several important features of the statistician's role while the study is in progress. In a well-run study, certain persons are responsible for monitoring study compliance, the efficacy of data capture and the quality of the data being reported, not only at each institution, where multiple investigators are involved, but also at the statistical center to which all institutions submit data during the study. This system requires the training and supervision of data managers who receive, review, monitor and process the data reported from each institution during the study. At intervals, the statistician will wish to know from the study data managers and from interim study analyses how carefully the protocol is being followed. What problems might need correction? Are more detailed specifications needed in the protocol? Once the initial group of patients has been entered on the study and their data has been submitted, the statistician has the opportunity to determine whether the design will be satisfactory, whether the data forms have been designed adequately, and whether the protocol conveys adequately to all investigators the requirements with which they must comply. Finally, throughout the several years during which the study is active, the statistician will have the important job of doing interim study analyses in order to determine what the study is showing in terms of the experimental questions for which it was designed.

The statistician has important responsibilities in the final study analysis and in the reporting of results. Various tests of the adequacy of the study design, and of how successfully the patients actually were randomized and stratified according to protocol requirements, can be performed. The statistician can confirm the comparability of patient groups among the treatment regimens which are to be compared, and he has the excitement of doing a variety of analyses to describe the outcome, determine the results of the study and propose the important conclusions that may be based upon the data. The statistician also plays important roles in writing up major sections of the results for publication, explaining the design, the quality control procedures and the statistical analyses performed, and illustrating their validity.

Many multi-institutional clinical trial groups require the establishment of a central statistical center. In such situations the scope and variety of roles and responsibilities, which the group statistician may carry out, are even greater. In a cooperative clinical trials group involving many investigators at many institutions and multiple studies of various clinical diagnoses, the group statistician has major responsibilities for determining the quality of group performance as it relates to the sophisticated data requirements of each study. Also, in this setting, the statistician needs to have close communication with the study chairman, and often with the members of several study committees. The statistician also carries out the important task of providing informational feedback to investigators at multiple institutions, as required for appropriate interpretation of protocol requirements, data requirements, missing data, questionable data, etc., which may have been called to his attention by the data managers assigned to various studies.

In the setting of a statistical center for a major multi-institutional clinical trials group,

the statistician has the enjoyment of communicating about current methodology and statistical center operational procedures with statisticians in other statistical centers, who share statistical and data management know-how and also share important clinical findings from studies which can be compared between different investigative groups. In this setting, the group statistician also becomes involved in the recruitment and training of the statistical center staff, including junior statisticians, study data managers, clinical analysts and programmers. The statistician may help to conduct workshops for the data managers from member institutions, concerning performance requirements at the institutional level. The statistical center statistician also develops skills in personnel and resources management, since there seems always more to do than can be accomplished. This requires the setting of priorities, communications to the staff, changes in priorities as appropriate, the assignment of specific tasks, etc.

One of the most important roles of a cooperative group statistician is to assist in the evaluation of overall group performance. Here, the statistician shares major responsibilities with the group chairman and the administrative personnel that determine the course and performance of the group.

In the statistical center of a large clinical trials group, there are many opportunities for the professional and scientific development of the statistician, which stem from statistical center responsibilities. There are opportunities to develop and promote improvements in data management systems and in data forms, and to develop new techniques in analytic capability and improvements in computational methods. Since most statistical centers will be situated in major educational institutions, there are opportunities for formal undergraduate and graduate teaching, and for presentation and publication of the results of methodological research or statistical theory that have been stimulated by the statistician's work.

A successful clinical trials group statistician has the opportunity to develop and combine a variety of important skills. The successful group statistician combines the skills of an investigator, a communicator, a collaborator, a student, an educator, an administrator, an economist and an innovator. The successful statistician learns to speak a statistical language that his clinical colleagues can understand, and that increases their understanding of his methods.

Compared to test-tube research or to laboratory investigations employing biological and animal systems, clinical investigation demands much more sophisticated statistical expertise and far greater investigator discipline. Much clinical research continues to be poor in concept, design, compliance and quality, has limited statistical input, and contributes to misinformation. The improvement in scientific discipline required by clinical research demands the participation of a statistician adequately trained to carry out the statistical responsibilities of clinical trials.

In summary, the statistician's role in clinical trials is of enormous importance. Much more first-quality clinical investigation is needed, and many more well-trained statisticians are needed. Furthermore, there are many attractive and rewarding career opportunities for statisticians working with clinical colleagues in clinical trials. Surely, this is an exciting role professionally and in humanitarian terms, and offers the opportunity for considerable career satisfaction.

It appears obvious that more graduate training programs in statistics should provide opportunities for excellent statisticians to learn the requirements of clinical trials work, and should prepare a larger number of statisticians for the many exciting academic career opportunities which are available.

ACKNOWLEDGEMENTS

I would like to express my appreciation to Dr Harland Sather, Dr James Anderson, Dr John Weiner and Dr Richard Honour, my colleagues in the operations office and statistical center of the Childrens Cancer Study Group, who have made many personal contributions to the concepts expressed in this article. This investigation was supported by CCSG Grant CA-13539 from the National Cancer Institute.

RÉSUMÉ

De nos jours, l'investigation clinique ne relève pas seulement du travail d'équipes pluridisciplinaires, mais encore de chercheurs, dans des institutions multiples, observant les mêmes critères et les mêmes standards pour rassembler les données de façon valide dans les études en collaboration. De ce fait, le rôle du statisticien est de mieux en mieux perçu, non seulement à l'interprétation des données à la fin de l'étude, mais à chaque étape de la recherche clinique. Cette implication va de la planification de l'étude et des essais de faisabilité à l'analyse des données et aux conclusions.

Le problème est maintenant la pénurie de statisticiens proprement formés à la méthodologie statistique des essais cliniques. Compte tenu de la grande importance du rôle du statisticien, des programmes de formation de licenciés en statistiques plus nombreux devraient préparer les statisticiens au travail d'essais cliniques. Ceci préparerait le terrain pour les nombreuses, intéressantes et rémunératrices opportunités de carrière qui s'ouvrent au travail des statisticiens dans les essais cliniques.

Received February 1980