STATISTICAL PRACTICE

This department publishes articles of interest to statistical practitioners. Innovative applications of known methodology may be suitable, but sizable case studies should be submitted to other journals. Brief descriptions and illustrations of new developments that are potentially useful in statistical practice are appropriate. Acceptable articles should appeal to a substantial number of practitioners.

The Multicenter Clinical Trials Coordinating Center Statistician: "More Than a Consultant"

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Over the past several decades the employment of statisticians in the area of medical clinical trials in private industry, academic centers, and the federal government has increased significantly. This trend does not appear to be slowing, particularly in those organizations that have come to be termed coordinating centers. In this article we will describe the expanded role that statisticians employed in these centers are expected to be able to fill.

KEY WORDS: Consulting statistician; Coordinating center; Multicenter randomized clinical trial.

1. INTRODUCTION

The evolution and acceptance of the randomized clinical trial has been one of the most significant medical research developments over the past 60 years. The superiority of the randomized clinical trial versus other nonrandomized outcome-oriented clinical research is generally accepted (Anderson 1994a; Byar et al. 1976; Chalmers, Block, and Lee 1972; Cutler, Greenhouse, Cornfield, and Schneiderman 1966; Ederer 1975; Gehan and Freireich 1974). However, it is also recognized that the cost and management of such trials are respectively expensive and complex. With the advent of the multicenter randomized clinical trial (MRCT) the cost and complexity have both escalated. The complexity aspect of the MRCT has given rise to the need for a coordinating center (CC), that is, a unit dedicated to managing all aspects, statistical and otherwise, of the MRCT. The CC is generally staffed with individuals with backgrounds in statistics, statistical computing, data processing, and management, as well as the appropriate types of clerical staff. The overall management and coordination of such centers and their MRCT's is usually the responsibility of statisticians (Weiss, Williford, Collins, and Bingham 1983a).

The practice (Boen and Zahn 1982; Hand and Everitt 1987), ethics (Boen and Smith 1975; Court 1952; Gibbons 1973; Morton 1952), and education (Baskerville 1981; Boen 1972; Cox 1968; Zelen 1969) of the consulting statistician have received considerable attention in the literature in general and in *The American Statistician* in particular. A third (23 of 67) of the articles cited in a bibliography on statistical consulting prepared by D. J. Hand were published in *The American Statistician* (Hand and Everitt 1987). The industrial (Cameron 1969; the Committee on Training of Statisticians for Industry 1980; Greenfield 1979; Marquardt 1979, 1981) and academic (Boen 1982; Carter, Scheaffer, and Marks 1986; Joiner 1982; Mead 1976) milieus have been extensively reviewed, surveyed, and discussed. However, the role of the coordinating center (CC) consulting statistician seems to have been relatively overlooked (Weiss, Williford, Collins, and Bingham 1983b). These CC's are in large part located in the pharmaceutical industry (those involved in developing both drugs and devices), academic institutions (public health and medical schools), and government agencies [National Institutes of Health (NIH) and the Department of Veterans Affairs (VA)], and offer increasing employment opportunities (review any recent *Amstat News*). A further indication of the increasing opportunities for statisticians in the general area of clinical trials was the founding in 1980 of the Society for Clinical Trials and its associated journal, *Controlled Clinical Trials*.

The MRCT is always a complicated endeavor that requires the CC statistician to engage in a variety of roles, both statistical and otherwise, in the design and planning, implementation, and final analysis of the clinical trial. Some aspects of the CC statistician's role such as those involving the design and/or statistical analysis of clinical trials have been discussed in journal (Feigl 1980; Gehan 1980; Hammond 1980; Peterson and Fisher 1980; Schoolman 1979) and text (Feinstein 1977; Friedman, Furberg, and DeMets 1985; Hill 1960; Mainland 1963; Pocock 1983; Tygstrup, Lachin, and Juhl 1982) literature. However, the overall role of the CC statistician has not, to our knowledge, been discussed except for Meinert's (1986, chap. 5, "Coordinating and Other Resource Centers in Multicenter Trials") discussion of the CC in general. This text probably comprises as complete a review of the randomized clinical trial itself as exists in the literature at this time. In this article we will describe the expanded role that the statistician in the coordinating center is expected to fill during the various phases of the MRCT, in particular, that role as it exists in the VA Cooperative Studies Program Coordinating Center (CSPCC) at the VA Medical Center, Perry Point, MD. This role is, in fact, not fundamentally different from that of the statistician employed at the NIH, in the pharmaceutical industry, or in academic CC's.

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Prior to delineating the role of the CC consulting statistician, it will be useful to briefly outline the organizational structure of the VA CSP and the CC personnel. Then the role of the CC statistician will be described through the three phases of the MRCT—namely: planning, implementation, and final analysis (including manuscript preparation).

2. THE DEPARTMENT OF VETERANS AFFAIRS (VA) COOPERATIVE STUDIES PROGRAM COORDINATING CENTER (CSPCC)

The Cooperative Studies Program Coordinating Center (CSPCC) at the Perry Point, MD VAMC is one of four such VA CC's (other CC's are located at VAMC's at Hines, IL; West Haven, CT; and Palo Alto, CA), as well as a pharmacy coordinating center (VAMC, Albuquerque, NM). All are responsible to the Chief, CSP at the VAMC, Boston, MA and funded by the VA Medical Research Service in Washington, DC.

The personnel (approximately 40) at the Perry Point CC are divided into three groups: administrative support (including clerical, budget, forms design, and travel specialists, as well as printers and project managers—13 people), data processing and management (data entry computer assistants and programmers—18 people), and statistical (statisticians and programmers—9 people). There are currently 27 (MRCT's) studies in various phases: three in planning, one approved and awaiting funding, two (approved and funded) in an organizational prepatient intake phase, seven in patient accrual, and ten in final or continuing analytic activity. The 5 statisticians at Perry Point have in total over 100 years of MRCT experience in over 50 trials, and on average each is involved with between 5 and 7 MRCT's.

Each trial is assigned a study team consisting of a statistician (who coordinates the activities of the team as it relates to the specific MRCT), a statistical programmer, a data management programmer, and two or three computer assistants. Particularly large MRCT's are also assigned project managers who coordinate a portion of the nonstatistical and data management activities ordinarily performed by the statistician. Team members are usually members of several nonidentical study teams.

3. PLANNING THE MRCT AND PROTOCOL DEVELOPMENT

The CC statistician becomes involved in a VA CSP projected MRCT when the scientific (medical) hypothesis has been judged to be both relevant to the VA and nationally important. At this point approval and funding are limited to a planning activity phase. This phase may be completed in as little as one year, but may take as long as two or three years (Weiss et al. 1983a).

The scientific as well as interpersonal (Boen and Zahn 1982) composition of the study Planning Committee is critical to the eventual successful completion of the planning process. In addition to the medical/scientific, clinical, and statistical knowledge that the various members of the committee provide, there must also be some experience and expertise with respect to ethics in human studies (Faden, Beauchamp, and King 1986), forms design, MRCT budgeting, and if appropriate (for the particular MRCT) pharmacy (if new or investigative drugs or devices are involved in the trial that may require FDA approval), quality-of-life (specific to the disease process under investigation) measures, and cost benefit and/or effectiveness analysis (Eisenberg, Glick, Buzby, Kinosian, and Williford 1993). Much of this experience and expertise is brought to the planning activity by or through the CC statistician.

After the appropriate composition of the Planning Committee has been determined by the study chairman and statistician and members have been selected and agreed to serve, familiarizing the committee with both the relevant medical and MRCT literature is accomplished prior to the first (of two or more) planning meetings. The primary goal of the planning phase is to develop and produce a protocol that can survive the review process, particularly the final scientific review by the Cooperative Studies Evaluation Committee (CSEC). For the statistician this planning phase marks the beginning of a potentially long and productive collaborative relationship. As early as 1979, Ederer (1979) recognized the broadness of the statistician's role, as well as the complexity of the relationship when he stated "... (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. 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" (p. 116).

It is perhaps this identification as "more than a consultant," that is, a "full fledged partner of the investigative team" that best defines to the entire Planning Committee this enhanced consultative role. If the study chairman and other members of the committee are unfamiliar with the mechanics and methodology of the MRCT, the statistician provides a knowledgeable and instructive presence on the committee during the planning phase. A scientifically expert, specific to the disease under study, and assertive Planning Committee with diverse viewpoints provides a stimulating and educational forum for all the members, and the level of exhaustion is generally high at the conclusion of any day's planning session. However, the statistician must ensure that whatever decisions are finally determined and agreed upon integrate seamlessly into the MRCT paradigm and protocol.

Because the CC statistician is largely responsible for the integration of the various and complex aspects of the modern MRCT, the traditional statistical consulting role, which included the issues of design, sample size, endpoint definition, and statistical analysis, etc., has been expanded. Thus the statistician, in addition to his or her statistical knowledge, must become familiar with the medical/disease area, and must be prepared to coordinate the committee's decisions with respect to the activities of the CC in the process of implementing the study protocol. That is, the statistician's role is expanded to include, and bring to the planning committee's deliberations, knowledge of all of those areas and activities in which the CC's MRCT expertise and experience can be used, exploited, and incorporated

into the resulting protocol and its implementation. These additional areas with which the CC statistician must thus be knowledgeable include human studies (ethics), MRCT budget, case forms design, patient availability, recruitment and follow-up, data processing and management, and report and manuscript generation. Several of these areas are those with which the academic consulting statistician who is not attached to a unit that has the facilities of a CC must perforce avoid—particularly those related to data processing and management (Hand and Everitt 1987, chap. 5).

Once the planning process has been completed and a protocol has been written, the chairman and planning committee have become personally familiar and comfortable with their CC statistician and his or her role, and will be much more aware of the variety of ways that the statistician and the CC will be involved with implementing and facilitating the protocol-defined MRCT. However, throughout the course of the MRCT this knowledge and dependency on the statistician and the CC will continue to evolve and increase.

4. IMPLEMENTATION AND FINAL ANALYSIS OF THE MRCT

If the planning phase has resulted in a protocol which has successfully navigated the peer reviewer infested waters, the chairman, steering or executive committee (ordinarily evolved from the original planning committee), and CC statistician, with all the facilities, expertise, and experience of the CC at their disposal, begin the task of guiding this monolithic endeavor through all of the usual MRCT shoals [which include poor recruitment, bad data, and various other problems (Collins, Bingham, Weiss, Williford, and Kuhn 1980)], as well as the unusual but not to be unexpected problems that are almost certain to occur. It is at this point that the statistician and the CC recognize that they have now embarked upon a commitment that may be as short as three years but can be as long as 15 years—or possibly even longer.

It is also at this point that the statistician brings the CC and designated study team into full operation and integration with the approved and funded MRCT. The process is initiated with: (1) an organizational and training phase, which is succeeded by (2) the patient recruitment and follow-up phase, and concludes with (3) the final database clean-up, final analysis, and manuscript preparation.

In advance of the actual implementation of any MRCT, estimating the percent of resources required of the CC as a whole, and the amount of the statistician's time in particular, involves several factors related to the size and/or complexity of the trial. Chief among these is the amount of data per patient and the number of separate facilities randomizing patients and submitting data. For example, considering the later variable, the majority of trials coordinated at the Perry Point, Maryland, VAMC CC have between 10 and 20 (one has 31) participating sites, and the workloads are roughly comparable and generally predictable. However, one recently implemented MRCT has over 300 participating medical centers in the United States and Canada. This particular trial is a collaborative effort between the VA and the National Heart, Lung and Blood Institute (NHLBI), and was constituted in the manner of what has been termed the "large simple trial (LST)" (see Williford, Collins, Garg, Gorlin, and Yusuf 1992). The so-called LST, a recent major modification of the MRCT paradigm, was designed in part to reduce the escalating cost of the more standard MRCT. Briefly, the LST requires a large number of patients (at least several thousand), hence a large number of participating sites (hospitals, clinics, and private practices), but the amount of data per patient is severely limited. Although the amount of work required of each participating site is relatively small, the resulting workload for the statistician and the CC staff, communicating with and managing data from over 300 sites versus the usual 20 or so, is increased several-fold and perforce drastically changed in manner. The manner of communicating, both written but particularly verbal, to committees of size 40 or 50 versus 5 or 10 and study groups of several hundred versus 30 or 40 are fundamentally different in nature. Ignoring the difficulties bound to exist between different private and/or governmental agencies or organizations in management style and even MRCT interpretation, this LST trial is only one example of the recent evolution of the MRCT paradigm, and each evolution requires the implementation of a variety of new statistical and management techniques by the CC statistician, both data and personnel.

Monitoring the MRCT in general and the data received in particular is the primary task and responsibility of the CC statistician during the course of the trial. Both the accuracy and integrity of the data are of paramount concern. No amount of sophisticated statistical data manipulation or analysis can overcome a flawed and questionable data base. The results of such problems in the breast cancer MRCT study are presently cause for a spate of news stories in both the major science and national news media (Anderson 1994b; Gorman 1994; Recer 1994; Twedt 1994; *Wilmington News Journal* 1994).

Any MRCT is subject to the usual errors in data transcription. The majority of these types of errors can be eliminated with the use of appropriate statistical software editing during the course of the trial. At the Perry Point CC all study databases are edited, according to the size of the data flow, at least once and sometimes twice each month. However, this is only the first step in such data management. Written and verbal communication between the CC statistician and data management personnel and participating medical centers is continuous and intense, particularly in the early stages of a trial. Periodic meetings are held in which the CC statistician and study team meet with all of the participating investigators and data coordinators to discuss the study case report forms and editing procedures and results. In the VA CSP visits to participating sites by the statistician and a member of the CC's Human Rights Committee are performed routinely. Study patients and participating study personnel are interviewed by the visiting team and the study case report forms are reviewed. No amount of such monitoring and oversight can guarantee against such fraud as occurred in the breast cancer MRCT; however, it can minimize error and help guard against the deliberate submittal of fraudulent data.

Another, but at least to the CC statisticians more familiar and congenial task, and one more closely related

to their academic training and subsequent statistical consulting experience, is the actual scrutiny and examination of the enormous amount of data that has been collected and edited but remains to be analyzed and summarized. "The first thing to do with data is to look at them. There are those who claim the ability to spot odd values or relationships in a large table of figures at 20 paces. However, for humbler mortals, this usually means tabulating and plotting the data in many different ways to 'see what's going on' " (Crowder and Hand 1990, p. 130). Thus, after following the foregoing advice, the CC statistician must prepare reports and presentations for the study monitoring committees that are simple, concise, and as transparent as possible, keeping in mind the various levels of data and statistical expertise encountered among the several members of the committees. These reports will naturally evolve in size and sophistication, always related to the desires, requirements, and requests of the committees, over the tenure of the MRCT. The final report should provide the basis for the statistical results and clinical conclusions eventually published in the MRCT's initial manuscripts.

5. DISCUSSION

It should be obvious from the foregoing discussion that the experienced CC MRCT statistician must bring an unusual and enhanced assortment of skills to this large, complex, and often long-term endeavor. There are the usual ones of the skillful consulting statistician that include the requisite statistical knowledge for the project at hand, familiarity with the scientific area under study, and good interpersonal and communication (verbal and written) skills as well as curiosity and a continuing willingness to learn.

Because of the large number of people involved in planning and implementing the MRCT and due to the large, complex, and long-term nature of the MRCT process, the necessity of these skills for the CC statistician, particularly those involving interpersonal communication both in the CC and the committees and groups internal to the CC, as well as between the CC and the external committees and groups are of necessity important. Also, the scale of the effort for the CC statistician is undoubtedly magnified in the MRCT effort. However, in addition to those outlined above for the consulting statistician, there are those specifically related to the coordinating center team aspect of the CC and the multicenter nature of the MRCT, particularly those related to the size and complexity of the data processing and management task. Thus perhaps it is being both familiar and knowledgeable with respect to all aspects of the expertise that the CC and its study team bring to the MRCT process, as well as being able to foresee and efficiently employ at the right moment the appropriate individual and organizational expertise, that in general terms best describes the work of the MRCT CC statistician.

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