MANAGEMENT OF MULTICENTER CONTROLLED CLINICAL TRIALS

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Multicenter controlled clinical trials require a synthesis of the scientific method and the precepts of modern management. The management tasks associated with these studies are akin to those found in other kinds of complex corporate endeavors. It is recommended that clinical investigators become more knowledgeable about management concepts and methods and management specialists be given a major role in the planning and conduct of large-scale clinical trials.

Controlled clinical trials are fast emerging as a critical link between biomedical science and the health care system. They are applied research conducted fully within the milieu of patient care and are unsurpassed as a means for validating the safety and efficacy of therapies. The results of clinical trials, therefore, are meaningful not only to laboratory and clinical investigators, who hope to see their therapeutically relevant findings applied for the benefit of the ill and the disabled, but also to health care providers, patients, health educators, officials of regulatory agencies, manufacturers of drugs and devices, administrators of health insurance programs, and others who are concerned with the quality of health services.

Although controlled clinical trials vary considerably as to scope and complexity, depending on the disorder and therapies involved and questions being asked, a substantial number of these studies must include hundreds or thousands of patients if there is to be a reasonable chance of achieving statistically significant results. A study population of this magnitude typically is far in excess of the number of eligible patients that any one clinical facility can identify and serve. Thus, a coordinated effort among several facilities is usually the approach of choice. This chapter summarizes the special characteristics of multicenter controlled clinical trials and the issues and opportunities encountered in managing them.

Scientific Management

Like other types of research, the multicenter controlled clinical trial is well-rooted in the fundamental principles of scientific investigation. There is close

attention to stating the hypothesis and specifying the experimental approach and methods, including various special techniques to guard against biased judgments and actions by investigators and patients. Key methodological issues are generally described in great detail prior to the enrollment of patients in these studies, including:

- The eligibility and exclusion criteria that are to be followed in selecting patients;
- The protocols for administering the therapies that are to be compared*;
- The patient characteristics to be measured at appropriate intervals throughout the study to determine the relative safety and efficacy of the alternative therapies;
- The plans for data acquisition and analysis; and
- The operational procedures for achieving maximum objectivity on the part of everyone involved—e.g., randomly allocating patients to the different therapies and preventing those who examine patients for the purpose of collecting data for the study from knowing which therapy has been administered to whom.

Because the geographical separation among participants in a multicenter trial makes comprehensive manuals of operations and other written communication mandatory, the elements of the scientific method are often more prominently displayed in these studies than in less complicated research.

Similarity to Corporate Management

But the multicenter controlled clinical trial is not only a paradigm of rigorous investigation; it also is a formidable managerial challenge. This class of studies involves multiple performers with varied skills and motivations who are geographically distributed yet committed to a common purpose. As such, a multicenter trial is akin to the complex corporate endeavors that occur frequently in business, industry, and elsewhere in large public and private organizations. Notwithstanding their prominent scientific and medical attributes, large-scale clinical trials offer fertile ground for the successful application of modern management concepts and techniques.

If one looks generically at the question of how complex corporate endeavors are conducted—leaving aside their individual purposes, subject matters, and

*In the interest of brevity, letting a disease run its natural course (in those cases where such action is medically and ethically defensible) is included implicitly in this account as one possible form of therapy.

technologies—one finds a strong recurring theme. Generally speaking, the successful management of essentially any complex corporate endeavor can be said to require the following:

- Objectives that are unambiguous, rigorously justified, few in number, and, whenever possible, quantitatively expressed;
- A detailed "game plan" strongly keyed to these objectives;
- Well-defined responsibilities and interrelationships for the participants (i.e., clear-cut accountability);
- Well-developed communications systems, both within the activity and between it and others;
- Systems and procedures for monitoring progress toward the stated objectives, including milestones that are reasonably frequent, strategically important, and readily determined; and
- Regular assessments of objectives and approach, with a view toward keeping the activity responsive to the potential new opportunities and problems that inevitably appear in an ever-changing social and technological environment.

An excellent exposition of these and other basic tenets of management is given in Drucker's book *Management: Tasks, Responsibilities, Practices* [1].

In the specific case of multicenter controlled clinical trials, one can easily find instances in which each of the foregoing tenets apply and begin to understand the consequences of ignoring them. Moreover, one can identify a variety of events and processes associated with this type of research that are primarily management tasks, even though they obviously involve scientific and medical considerations, including:

- Achieving technical consensus among the investigators and advisers with respect to the study protocol;
- Matching staff and facilities to the tasks at the participating centers;
- Establishing procedures to ensure that patients are well-informed about the purposes of the study and the nature of the care they will receive, as well as their rights and obligations as participants; are accorded high quality care throughout the period of their participation; and are spared unreasonable risks;
- Tracking overall progress of the study, using such measures as patient recruitment and dropout rates;
- Achieving technical consensus with respect to interpretation of the study data initially among the data monitors and eventually among the investigators; and

- Communicating the results of the study to the participating patients, the scientific community, and the public at large.

Indeed, inadequate attention to the management aspects of such tasks can produce deficiencies in a study that are as serious as those resulting from substantive errors or misjudgments about the scientific and medical aspects. Both good science and good management are required for multicenter trials to achieve their objectives within reasonable time and cost estimates.

The Diabetic Retinopathy Study

The organizational complexity of multicenter trials is illustrated by the Diabetic Retinopathy Study [2,3] of the National Eye Institute (NEI). This project was initiated to evaluate "light beam surgery" (photocoagulation) as a treatment for diabetic retinopathy, one of the leading causes of blindness in industrialized societies. To date, the study has shown that this therapy is effective in preventing severe visual loss in diabetics who have relatively advanced pathological changes in their retinal vasculature and in retarding the progression of the disease from its early to its advanced stages [4,5]. The trial is continuing, with the objectives of describing the long-term effects of treatment and comparing the two different modalities of photocoagulation that have been used (i.e., the xenon arc and the argon laser).

The Diabetic Retinopathy Study involves over 1,700 diabetic patients, 15 clinical centers, a coordinating center, and a retinal photograph reading center. The study chairman is a university-based ophthalmologist with special expertise in diabetic retinopathy and clinical research methods. He is assisted by a group of NEI staff members (the NEI project team), an executive committee made up principally of selected study participants, and a variety of intrastudy committees concerned with such topics as clinic monitoring, natural history data analyses, and scientific publication of study findings. The study chairman and the NEI project team, in turn, interact closely with a data monitoring group and a policy advisory group; none of the data monitors participates in caring for study patients or in collecting study data, and policy advisers are not involved in any way beyond their role as counselors to the Director, NEI. Final responsibility for the study, including such major decisions as changing the protocol in the light of interim findings, rests with the Director, NEI. Figure 1 summarizes the functional relationships among these several groups and individuals. Those activities that are principally management tasks tend to be concentrated in the components symbolized by the enclosures with curved sides.

Figure 2 shows the composition of the NEI project team for the Diabetic Retinopathy Study. The project officer, a senior epidemiologist, is the leader of the group and principal spokesman for the NEI with respect to the study. The co-project officer, a widely experienced management specialist, is responsible for not only fiscal and administrative matters but also for a substantial

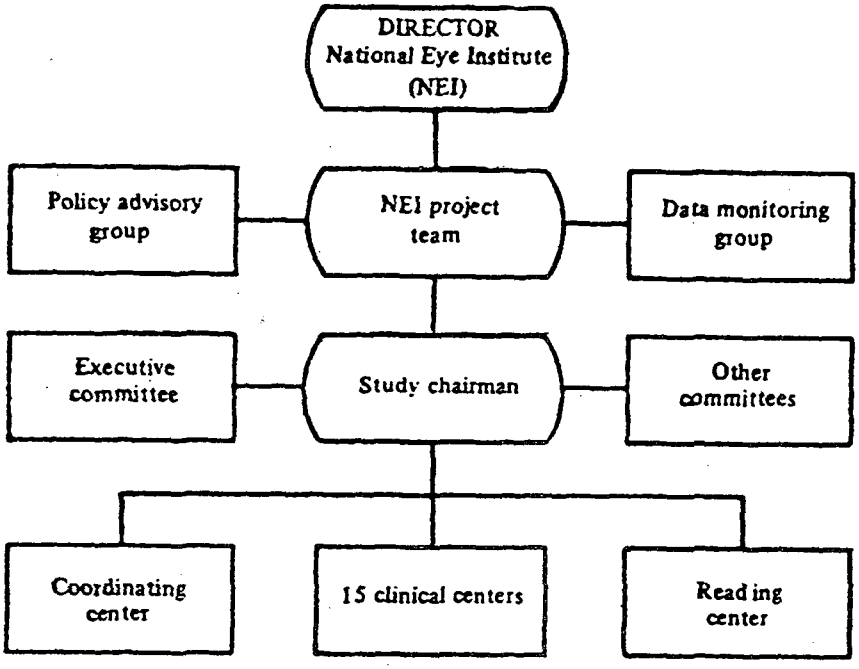

FIGURE 1. The Diabetic Retinopathy Study: Functional relationships

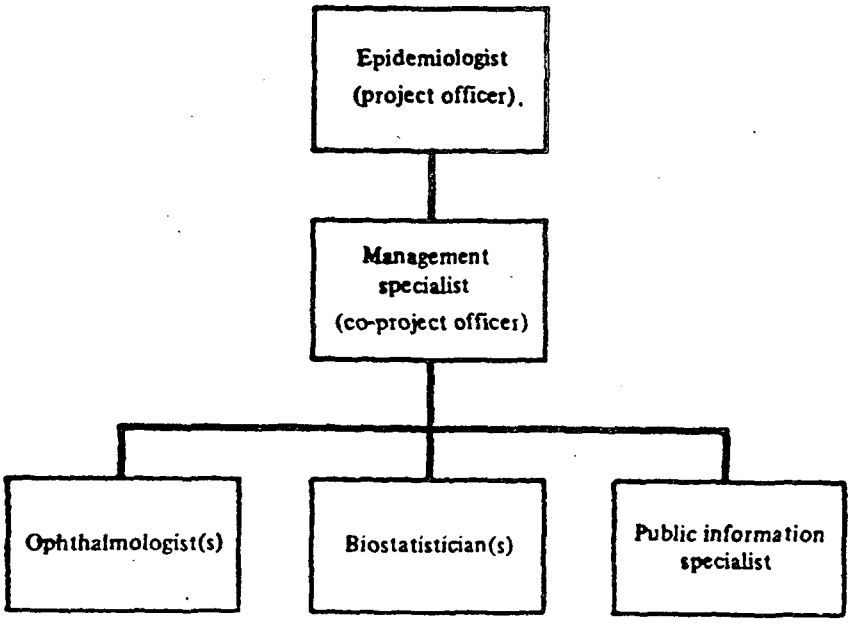

FIGURE 2. The Diabetic Retinopathy Study: NEI Project Team

portion of the day-to-day operational activities in support of the study chairman and the participating centers and advisory groups. The other project team members contribute a wealth of expertise in relevant areas such as ophthalmology, biostatistics, and public relations and information methods. This ad hoc, task-oriented cadre of individuals drawn from various operating components of the NEI has many of the attributes of the new product development teams that are commonplace in industrial management and has been an efficient and effective forum for planning, coordinating, and evaluating study activities. In addition, by accommodating multiple ophthalmologists and biostatisticians as such opportunities appear, the project team has proved to be an excellent on-the-job training mechanism for individuals interested in learning the methods of controlled clinical trials.

On the basis of our experiences with the Diabetic Retinopathy Study and other multicenter controlled clinical trials, the senior staff of the NEI believe that the management aspects of such studies deserve much more attention than they have been traditionally accorded. Furthermore, we conclude that

- Multicenter clinical trials require a synthesis of the scientific method and the precepts of modern management;
- Clinical investigators should become more knowledgeable about management techniques; and
- Management specialists should have significant involvement in the planning and operations of multicenter clinical trials.

If these considerations are made a prominent part of the design and conduct of multicenter trials, we are confident that much can be done to assure high-quality results of considerable scientific and social importance, while reducing the interval between concept and conclusion to the minimum that is realistic and maintaining the costs within acceptable limits. With so many facets of the health care system so much in need of the best that biomedical science can offer, we could have no more compelling calling.

References

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