A cooperative network of trained sites for the conduct of a complex clinical trial: A new concept in multicenter clinical research

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Background The purpose of this report is to present a model of physicians in full-time clinical practice participating as investigators in multicenter clinical trials, sponsored by a pharmaceutical or medical device company.

Methods This gas-exchange substudy was conducted as a pilot study to establish the feasibility of the 10-member EXERcise testing group of the Duke University Cooperative Cardiovascular Society (EXERDUCCS) consortium to perform a complex multicenter trial using cardiopulmonary exercise testing.

An active interchange of information was established involving the principal investigator for the substudy, a dedicated full-time project coordinator, a medical director of the overall EXERDUCCS network site, the project coordinator for the sponsor, and all the participating EXERDUCCS investigators and coordinators.

Results The sponsor set as a goal of enrollment of 6 subjects per site, and 8 of the 10 sites met this goal. As a result of the successful enrollment and completion of the study and substudy by the EXERDUCCS sites, the sponsor subsequently increased the payment stipends to the sites to compensate for the extra work and expense incurred.

Conclusions This cooperative experience accomplished several goals: (1) it allowed a complex clinical trial to be successfully completed in a time frame which would not have been possible using only single unconnected sites; (2) it educated the physician-investigators (and their personnel) in exercise cardiopulmonary; and (3) it prepared the sites for future clinical trials involving this methodology. (Am Heart J 2006;151:451–6.)

In an earlier era of medicine, physicians sometimes combined their private practices with individual endeavors in clinical research, occasionally resulting in useful discoveries. However, more recently, physicians typically chose between full-time clinical practice and an academic-research career, with few being able to successfully combine the 2 unless they were clinician-investigators in an academic medical center. In the past few years, however, an increasing number of physicians in full-time clinical practice have chosen to participate as investigators in multicenter clinical trials, usually sponsored by pharmaceutical or medical device companies. The development of this form of collaboration between industry and physicians in private practice has benefited both, as well as provided an efficient mechanism for testing new drugs and devices on a large scale. The results of these multicenter clinical trials have increasingly contributed to the advances in “evidence-based medicine.”

Although many such trials have been conducted at academic centers, many others have been accomplished using patient enrollment by physicians in private practice. In most instances, these physicians have been recruited by the pharmaceutical companies directly or via intermediaries known as contract research organizations. Typically, the physicians engaged in these studies (other than the principal investigator [PI]) have no special training in research. However, no special skills are usually required to perform these studies other than those routinely used in clinical practice appropriate...
to the specialty involved. These investigators, working independently, are therefore able to successfully participate in “routine” clinical trials.

There are, however, certain intrinsic limitations to this approach. These investigators lack the formal interrelationships to facilitate the cooperative networking that may be required for more complex trials or trials that require special skills. In the academic centers, where such skills might be available, it may not be possible, however, to recruit sufficient numbers of subjects to complete the required enrollment.

In 1987, an organization of physicians was formed for the purpose of conducting national multicenter clinical trials in cardiology. This group consisted primarily of former cardiology fellows at Duke University Medical Center (DUMC). Full-time faculty members of DUMC were responsible for selecting and obtaining the studies from sponsoring companies and making them available for the physicians/investigators in this organization. Since its inception, this group, which became known as “DUCCS” (Duke University Cooperative Cardiovascular Society), has participated in many clinical trials and subtrials, resulting in peer-reviewed publications.3-9

A substudy of a multicenter clinical trial in congestive heart failure was designed by a member of the faculty of DUMC. This investigation required a complex study protocol that included the use of cardiopulmonary exercise (CPX) testing to measure maximum oxygen uptake (MV\textsubscript{O2}) and aerobic threshold during exercise.7

It was hypothesized that the use of this test would supplement the role of routine exercise testing in the evaluation of pharmacological therapy in the treatment of patients with heart failure by providing an accurate and objective measure of cardiac performance.10-13

Although the PI of this substudy had extensive experience with this methodology, CPX testing is not generally familiar to most cardiologists, including the members of DUCCS. It was therefore proposed that interested investigators and their study coordinators in the DUCCS organization be trained in this technique as a prerequisite to participate in this substudy. This group of investigators would subsequently be known as the “EXERDUCCS” (EXERCise testing group of DUCCS).

Methods

Inquiries were sent out to all DUCCS investigators to determine their interest in performing cardiopulmonary testing as part of a substudy in a new heart failure trial. A total of 13 investigators in 12 states opted to participate in training and were invited to attend an initial educational and training session at DUMC. More intensive sessions were subsequently held at 1 of the equipment manufacturer’s site and at local investigators’ sites. In addition, the PI wrote a manual, Cardiopulmonary Exercise Testing: A Lecture Series on Interpretation for the Cardiologist,14 and personally visited all sites to ensure quality control after they had acquired the necessary equipment (either a Medical Graphics [Minneapolis, Minn] or Sensorimedics [Anaheim, Calif] metabolic cart).

It was hoped that such a collaborative effort would benefit the academic center (DUMC) and the individual DUCCS sites, both in terms of patient enrollment and in educating the investigators at the DUCCS sites how to use an unfamiliar methodology for this and future studies in heart failure. Because each of the DUCCS sites was geographically distant from the others, there was no concern regarding competition for the same patient population.

A minimum of 3 normal subjects at each site underwent maximum exercise testing using a bicycle ergometer and a ramped protocol. The raw data generated by the gas exchange analyzer were sent to the PI at DUMC for review. Gas exchange variables consisted of MV\textsubscript{O2}, carbon dioxide production, and ventilation measured and averaged every 15 seconds. For the purpose of data analysis at the coordinating center, MV\textsubscript{O2} during the third minute of each workload was averaged for each subject, and the average for all 3 subjects was calculated for each workload. Thus, the MV\textsubscript{O2} workload was determined for each site and compared with standardized data from the published literature. If the collected data were found to be within 2 SDs of the published age-adjusted standards, these sites were certified as capable of participating in the substudy and were permitted to enroll patients. If not, further validation was required until a satisfactory performance was achieved. All sites ultimately met these requirements.

Study protocol

The gas-exchange substudy was conducted both as a pilot study to establish the feasibility of the 10-member EXERDUCCS consortium to perform a complex multicenter trial using CPX testing and to collect usable research data in a national multicenter clinical trial in patients with congestive heart failure.

Subjects were recruited at each site who met the following baseline criteria: symptomatic congestive heart failure (New York Heart Association classes II-IV), angiotensin-converting enzyme inhibitor drug-naive or intolerant (cough), angiotensin receptor-blocking drug-naive, and left ventricular ejection fraction of 40% or less. After informed consent was obtained, 5 baseline exercise tests were performed on each subject using the Modified Naughton protocol on a motorized treadmill at intervals of 3 to 10 days.14 Patients whose treadmill exercise tests were limited by fatigue and or dyspnea and whose exercise time was between 2 and 10 minutes’ duration and reproducible within 60 seconds were eligible for randomization to receive placebo or active drug (an angiotensin receptor blocker). During this double-blind randomization phase, exercise tests were obtained during weeks 8, 11, and 12 of treatment.

At the sites involved in the CPX testing (EXERDUCCS sites), 3 of the 5 baseline stress tests (tests 1, 3, and 4) were performed using CPX testing, as were 2 of the 3 tests during the treatment phase (tests 6 and 7). The gas analysis protocols were the same as described above for the normal subjects.

An active interchange of information was developed which continued throughout the developmental, recruitment, and study periods, involving a dedicated full-time project coordinator at DUMC (whose salary was derived entirely from
contributions from the EXERDUCCS investigators out of study payments supplied by the sponsor), the PI for the substudy, a medical director of DUCCS, the project coordinator for the sponsor, and all the participating EXERDUCCS investigators. In addition to regular phone calls and periodic personal visits to the sites, a newsletter (the Gas Gazette) was developed and circulated regularly to all sites (Figure 1).

Results

Of the original 13 sites, 3 dropped out before or during recruitment of patients, leaving 10 enrolling sites. (Table I) One of these sites randomized 8 of the initial 15 patients. The PI and coordinator from this site then conducted a workshop for other site personnel and shared recruitment strategies via the Gas Gazette. These sites recruited and randomized (to placebo or drug treatment) a total of 81 patients (range 2-22) over a period of 14 months (Figure 2).

The sponsor set as a goal of enrollment of 6 subjects per site, and 8 of the 10 sites met this goal (Figure 3). Ten subjects were subsequently excluded from analysis as a result of incomplete collection of required ventilatory data. The remaining 71 subjects became the population for the substudy as well as for other studies.7,15

As a result of the successful enrollment and completion of the study and substudy by the EXERDUCCS sites, the sponsor subsequently increased the payment stipends to the sites to compensate for the extra work and expense incurred. The sponsor also retroactively paid DUCCS for the full salary of the study coordinator, and DUCCS reimbursed the contributing member sites. In recognition of the quantity and quality of the substudy data, the sponsor provided supplementary funding for a DUMC statistician to perform data analysis. This enabled the EXERDUCCS investigators to produce results leading to 3 manuscripts, 2 published7,15 and another in preparation. In addition, the sponsor subsequently offered the EXERDUCCS sites another study using the same drug.16 Subsequently, another sponsor used the interested EXERDUCCS sites for another drug study using CPX testing in heart failure patients, and this study is currently in progress.

Discussion

The conception, organization, and operation of the exercise subgroup of the DUCCS organization (which became known as the EXERDUCCS group) represent a unique approach to the feasibility and practicality of training and using independent physicians in private practice in different areas of the country into a cooperative group to conduct highly specialized clinical research using a methodology previously unfamiliar to

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<td>Barbara Kuzil</td>
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the physicians and their research assistants. The functions of each of the key components of this collaborative clinical research network should be emphasized.

The academic substudy PI

The special diagnostic method required for this study, CPX testing, is the primary academic focus of this academic faculty member. He used this expertise to work with the sponsor to design the substudy protocol, and then to “clone” himself at each of the network sites. This required developing a detailed educational manual and then personally visiting each perspective study site. He provided hands-on training for the site PI and study coordinator. He also served as a site PI and led his site to meet the substudy enrollment requirements, thus leading by example.

The substudy coordinator

This individual was a trained exercise physiologist who worked full time in the coordinator role. Because of her professional expertise, she personally provided technical consultation to all site personnel. Because of
her full-time status, she developed personal knowledge of all site PIs and coordinators. She initiated phone communication with each site regularly and edited a regularly published substudy newsletter. She filled the important role of liaison between the sponsor and the site PIs and coordinators. This role served as a buffer between the less personal demands of the sponsor on the network personnel. When the sponsor proposed deadlines for enrollment, the substudy coordinator could negotiate appropriate “slack” for all of her network members.

The EXERDUCCS network medical director

This person had known each network PI individually from past academic and social interaction. He lacked expertise in the substudy methodology but provided the substudy coordinator with insights into the personal characteristics of each site PI. His knowledge of the past relationships among site PIs guided his suggestions for establishing intersite communications within the network. He also maintained communication with the sponsor’s project director throughout the course of the study to initiate negotiation favorable to the network.

The lead site PI

The PI at 1 of the sites emerged during the early enrollment period as having most rapidly ascended the substudy learning curve. He could have elected to further widen the gap between his site and the others; however, he elected to sacrifice this personal accomplishment for the goal of overall network performance. He worked with the network coordinator to organize a symposium at his site for the PIs and coordinators. He personally called many of those who could not attend and communicated with the entire group through the substudy newsletter. This leadership, by example and by mentoring, by the PI of 1 of the nonacademic study sites provided the model, the challenge, and the skills for the other network sites’ personnel.

This cooperative experience accomplished several goals: (1) it allowed a complex clinical trial to be successfully completed in a time frame which would not have been possible using only single sites consisting of investigators already trained in the necessary methodology; (2) it educated the physician-investigators (and their personnel) in exercise cardiopulmonary physiology in healthy subjects and in patients with heart failure and prepared them to use this technique in their clinical practices for the evaluation of dyspnea and cardiopulmonary fitness; and (3) it prepared the sites for future clinical trials involving this methodology. (4) From a financial standpoint, the individual sites benefited in several respects: (a) they were able to participate in a paid substudy that would otherwise not have been available to them without the specialized training provided by the academic center PI; (b) each of the individual sites received an increase in payment stipends as a result of the performance of the consortium as a whole; (c) the individual sites were offered additional funded studies by the sponsor based upon the success of this study; (d) the individual sites were able to use group purchasing power to acquire the cardiopulmonary equipment at a discount; (e) a number of the sites were able to use their new equipment and expertise obtained from this study for nonstudy-related reimbursable clinical testing in their practices; (f) from the standpoint of the academic center, the additional reimbursement from the sponsor paid in part for the salaries of the substudy coordinator and statistician, which had previously been paid for jointly by the sites and the academic center.

Limitations

The feasibility and success of this cooperative arrangement between the EXERDUCCS sites and DUMC were facilitated by the ongoing cooperative relationship between the DUCCS organization and its parent academic institution, DUMC. Therefore, no new professional and personal relationships were required to accomplish the goals of this clinical trial. DUCCS emerged from a social postgraduate educational organization of former DUMC cardiovascular fellows, known as the “Duke University Cardiovascular Fellowship Society.” The development of the DUCCS organization was essential to the new goal of participating in selected multicenter clinical trials under the guidance and assistance of the academic center where the investigators had received their training. The Organizational Document of DUCCS listed the 3 goals of the organization as: “(1) to extend the activities of the Duke University Cardiology programs beyond the walls of the institution, (2) to develop an organization for conducting collaborative clinical research projects, and (3) to develop a Comprehensive Community Data Bank.”

For sites to join and remain members of DUCCS, initial and subsequent financial contributions were required from each site. In addition, there was a “tax” on subsequent study revenues to partially subsidize the administrative expenses (mainly salaries) of DUCCS personnel working at DUMC. This often resulted in a lower reimbursement to DUCCS sites compared with nonaffiliated independent research sites participating in the same studies.

It is not clear whether the DUCCS model would work as well for other sites wishing to form a consortium for clinical trials, in which there was no underlying relationship to an academic center, or a commitment of the academic center to supporting these sites. Moreover, in today’s economic milieu it is difficult for clinical trial sites to invest financially in the formation and maintenance of such an organization for the goal of being able to participate in the type of highly specialized study described in this article. This report does indicate that it
is feasible to use this model to build a successful network for specialized studies. Accordingly, appropriate funding and support from industries and/or government funding agencies are key to its success and are highly recommended.

From the standpoint of the academic center, there are also certain potential disadvantages in affiliating with geographically distant as well as independently run clinical research sites. It would seem inherently obvious that it would be easier and more practical to run a clinical trial at a central location, with a staff PI and clinical trial coordinators. However, with the highly selective study populations required for certain trials, it is often difficult to recruit enough patients in the required period at 1 central location. Moreover, the patient population available to an academic center such as DUMC does not reflect the desired diversity of a "real world" patient population seen at a consortium of individual clinical trial sites across the country. Thus, the advantages of the DUCCS multicenter model would seem to outweigh the disadvantages of administration of such an organization from the viewpoint of the academic institution.

From the perspective of a study sponsor, an academically oriented network of practice-based study sites facilitates completion of a challenging study with a high level of data quality. The academic center is able to fulfill its continuing education mission by enhancing its relationship with its former trainees.

At a time when increasing pressures of clinical practice are resulting in physician frustration, discouragement, and "burnout," the opportunity for engaging in new and challenging clinical trials offers clinicians an alternative activity, which is both academically interesting and productive. The success of the EXERDUCCS group of DUCCS should lead to further acceptance of the validity and practicality of using practicing physicians to participate in the types of research that traditionally have been confined to academic centers.

We thank Christine Lin for her assistance with the database.

References