NETT Coordinators

Researchers, Caregivers, or Both?

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The National Emphysema Treatment Trial (NETT) required the coordinated evaluation and treatment of thousands of patients with emphysema simultaneous with data collection to evaluate the safety and efficacy of surgery versus medical treatment for emphysema. These tasks were performed by a multidisciplinary team led by the clinic coordinator at each NETT center. The clinic coordinators functioned as members of the research team as well as communicators, managers, and members of the patient care team. The clinic coordinators' ability to balance these roles was instrumental to the successful completion of NETT, as evidenced by randomization of 1,218 subjects with only 10 subjects being lost to follow-up. Striving to achieve recruitment goals and working to retain study subjects was very labor intensive. The coordinator role was complicated by the study population's severity of illness combined with the complexity of the NETT protocol. Management of the study subjects' medical condition had to be balanced with the management of a multicenter, randomized clinical trial to ensure quality data collection and protocol adherence.

Keywords: research coordinator; emphysema; lung volume reduction surgery

The National Emphysema Treatment Trial (NETT) was a prospective, randomized clinical trial of medical therapy alone versus medical therapy plus lung volume reduction surgery (LVRS) for severe emphysema. The trial was cosponsored by the National Heart, Lung, and Blood Institute and the Centers for Medicare and Medicaid Services (CMS). Between October 1997 and July 2002, 3,777 patients with emphysema were evaluated at the 17 NETT centers, with 1,218 being randomized to treatment (608 to LVRS and 610 to medical therapy). The protocol required comprehensive medical evaluation to ensure suitability for LVRS, exclusion of comorbid conditions that would impact analysis of the efficacy of LVRS or ability to complete follow-up visits, and compliance with standard emphysema medical therapy (1). Patient recruitment and retention were complicated by the need for complex testing in severely impaired patients and tight time lines for each phase of the protocol. Screening had to be completed within 42 days of initiation of pulmonary rehabilitation, and randomization had to be completed within 21 days of the post-rehabilitation evaluation. Patients frequently had exacerbations of the underlying disease that delayed testing and required consider-

able test rescheduling. Successful conduct of the trial required management of the subjects' medical therapy while complying with study protocol. The coordinator was the key person to assure that these two goals were met without compromise to either.

NETT was initiated in a highly charged atmosphere in which many patients, physicians, and medical staff were biased toward surgical treatment. It was the perception of many that CMS had rescinded coverage of LVRS as a cost-cutting measure. The lack of precedents of sponsorship of clinical trials by CMS to evaluate the efficacy of any procedure made acceptance of NETT in the community more difficult.

The success of any trial relies heavily on the staff who works with the investigators. Although each and every person who works with subjects enrolled in a trial has an important role in maintaining the integrity of the trial, the clinic coordinator is the front line representative of the trial to subjects, referral physicians, the medical staff treating and testing the study subjects, and the study coordinating center. While the specifics of trials differ, the role of the coordinator for each trial is much the same and is multifaceted, with the coordinator having both research and patient care responsibilities. The researcher roles are to ensure adequate recruitment and retention, adherence to study protocols and procedures, and quality data; the patient care roles are those of advocate, educator, caregiver, and counselor. Studies have documented the relationship between coordinators and improved subject recruitment, enhanced subject retention, and increased study efficiency (2). For any clinical trial to be successful, the dual, and sometimes conflicting, roles of researcher and caregiver have to be balanced.

SUPPORT FOR THE CLINIC COORDINATOR POSITION

The original NETT contract budgeted funding for one clinical coordinator at each site. As investigators and coordinators initiated the protocol at NETT centers, it became apparent that more than one coordinator was needed to manage the workload created by NETT. Scheduling, patient management, data collection, and recruitment and retention activities were labor intensive. After the investigators and coordinators identified staffing as impedance to recruitment, the NHLBI worked with each NETT center to ensure that adequate funding was available to assist with the overall management of the trial. In the summer of 1999, the NHLBI initiated a program of capitation payments for completion of patient visits as a way of providing additional funding for NETT activities at rates linked to a clinic's recruitment and retention performance: \$2,500 per randomization; \$1,000 per each 12, 36, 48, 60 months in-person visit completed; and \$1,200 per each 24 months in-person visit completed. The capitation payments could be spent only on activities consistent with the NETT contract work scope, but the choice of activities was left to the discretion of the principal investigator—for example, the payments could be used to reimburse for patients' travel expenses, fund recruitment activities, or supplement staffing for NETT-related activities.

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STUDY START UP

From the announcement of the NETT centers in December 1996 until the first patients were screened in late 1997, much ground work was done to prepare each clinical center for the trial. The clinic coordinator was charged early on with learning the NETT protocol and ensuring that each staff member on the NETT team was adequately prepared and certified to perform the tests according to the protocol. Responsibility for protocol adherence ultimately rests with the principal investigator, but ensuring that it is achieved falls primarily to the clinic coordinator. The NETT Coordinators had vast medical experience, with 70% being Registered Nurses, 18% being Respiratory Therapists, and 12% reporting having had other responsibilities in health care before NETT. Interestingly, most NETT coordinators had no research experience before NETT, while most had either experience with lung volume reduction surgery or pulmonary medicine before becoming involved in the clinical trial.

RECRUITMENT AND RETENTION OF PATIENTS

Recruitment for clinical trials is always a challenge, and NETT was no exception. At the onset, there was optimism that recruitment goals would be met easily. Because CMS had issued a noncoverage policy for LVRS in late 1995, each site had lengthy lists of patients with emphysema waiting for the trial to start so that they could possibly receive LVRS. In reality, recruitment was disappointing. The “waiting list” was shortened by deaths and the fact that many patients were too sick to participate. The hope of having a large reserve of patients waiting to enroll into NETT quickly evaporated, and recruitment lagged at most centers. Coordinators identified issues hindering recruitment, such as: travel distance from the NETT centers; need to complete procedures over several days (up to a week for a screening visit and start of pulmonary rehabilitation); the rigors of the required testing on this patient population; and indirect costs associated with participation (travel, meals, housing, lost work day by accompanying spouse, etc.).

One strategy to enhance recruitment included allowing use of NETT-certified satellite pulmonary rehabilitation centers to carry out the NETT pulmonary rehabilitation program, after initiating the program at the NETT clinical center. In addition, travel reimbursement funds were allocated in 1998. In 2000, the NHLBI approved funding for a national advertising campaign with the goal of educating both physicians and patients about the NETT. This campaign involved printed material, TV ads, websites, and advertising for subjects in local newspapers. The yield from the campaign was disappointing. Many people inquired but few ever made it to randomization. Since that time there has been much discussion about the fact that the advertising campaign generated relatively few randomizations despite its direct appeal to the patients and referring physicians. Possibly initiation of advertising for the trial earlier might have yielded different results. The lack of enthusiasm among the medical community impacted recruitment in NETT. Conflicting reports of the risk and benefits of LVRS made some patients reluctant to participate and some physicians reluctant to refer patients for the trial. Others in the medical community felt disenfranchised by the randomization process as many had previous positive experiences with LVRS and thus did not value the need for a randomized clinical trial to evaluate the safety and efficacy of the procedure. Advertising alone could not change the lack of enthusiasm in the medical community at large. Furthermore, the advertising campaign was followed in May 2001 with the early release of data from NETT, which identified a group of patients who were considered at high risk for mor-

tality after LVRS with little chance of functional benefit (3). While the information was readily accepted in the medical and scientific community as confirmation of safety concerns related to groups which some thought were at higher risk from LVRS all along, the lay press generally interpreted the results as “emphysema surgery kills.” Few patients and few physicians grasped that the results pertained to a small subgroup, and many quite frankly saw the results as a failure of LVRS, rather than as a modification of the inclusion/exclusion criteria for the procedure, thus further complicating the recruitment efforts for NETT.

Retention of NETT patients was very successful. NETT was a long-term trial with all enrollees followed for a minimum of 6 months and some for as long as 7 years when patient contact ended in June 2004 (mean follow-up was 29.2 months in December 2002) (1). The clinic coordinators established close relationships with the patients and worked to educate the subjects about the protocol from the screening and rehabilitation phase to the randomization phase and through follow-up. Coordinators recognized that the patient’s understanding of the research study, including the schedule of visits, laboratory tests, and procedures, was critical to retention of the subject over the life of any study (4).

INFORMED CONSENT PROCESS

NETT had a complex protocol with potentially serious consequences and obligations for the patient who enrolled: gravity of the risks of surgery (mortality, disability, prolonged and painful recovery); commitment to two sets of selection evaluations consisting of pulmonary function and exercise testing, interviews, questionnaires, laboratory tests and radiographic imaging studies, all to be completed prior to randomization to treatment; a 6- to 10-week rehabilitation program that was to be supplemented by a daily exercise regime that the patient was to maintain through screening and for the duration of the trial; potential for out-of-pocket expenses for the patient associated with the study visits and procedures and treatment (Medicare co-payments and deductibles); study duration of possibly 5 years (later extended for 2 additional years); transfer of personal identifiers outside of the clinic to the coordinating center as part of the Medicare reimbursement process, etc. Because of this complexity, NETT used three separate consent forms, each marking entry into a new phase of the study. Each consent specified the procedures, requirements, obligations, risks, and benefits of the new phase. The requirement for three separate consents was to assure that each patient was truly informed about the study before randomization.

The first consent was obtained at the start of screening, the second just before start of the rehabilitation phase, and the third just before randomization. Patients assigned to LVRS signed a fourth consent, the center’s institutional consent for surgery.

The coordinator’s role in the consent process was to ensure that the procedures, risks, and obligations were clearly understood by the patient. Since NETT was assessing the efficacy of LVRS, it was imperative that the patient be educated about the surgery and its potential risks and benefits. While most patients claimed to know a lot about LVRS, much education was needed to ensure that the consent before randomization was indeed an informed consent. The ability of the coordinator to teach the patient about the goals of emphysema treatment, coupled with the ability to empathize with the patient, enhanced recruitment and retention. The coordinator became the patient’s advocate and constant ally while navigating the complex protocol. Study visits were conducted every 6 months for the first year and then yearly thereafter. There were also telephone contacts monthly, then every 2 months, and finally every 3 months until the end of the trial. These frequent contacts

fostered the relationship between the coordinators and subjects. The combination of data collection with medical therapy for their underlying condition further enhanced the patients' continued follow-up with the study, as there was a benefit to returning to the NETT center because the NETT staff would work with the patients and referring medical staff to fine-tune the patient's medical regime.

A consequence of the close bond developed with study subjects was the emotional toll related to the loss of subjects over time. Telephone contacts often yielded information about the death or major illness of an NETT subject and became a source of loss among coordinators and other study staff in NETT.

RANDOMIZATION

Many times the discussion of the randomization process fell to the clinic coordinator. Though much effort was spent in explaining the randomization process to patients, many patients failed to understand that the selection of LVRS or medicine would be purely by chance. A lack of complete understanding of "randomization" is evident in many studies of randomized trials (5). The fact that the trial subject lacked control to choose LVRS or medical therapy caused frustration, anger and, at times, disappointment. As with subjects assigned to placebo or usual treatment in other randomized trials, the NETT subjects assigned to medical therapy felt that they somehow had LVRS "snatched away from them" (5).

It was the clinic coordinator who often communicated the outcome of randomization and dealt with the ensuing emotions. Those randomized to LVRS often experienced extreme happiness and immense hope, and it was the coordinator who had to temper those feelings with reminders that LVRS carried possible risks. At times those randomized to LVRS felt guilt that they had been chosen over one of their peers in rehabilitation. A few patients randomized to LVRS found that they were unwilling to accept the risks of surgery and refused to proceed with surgery. Those randomized to medicine often exhibited grief, anger, and despair and shared feelings that all hope was lost to improve their quality of life. Each side of the proverbial "coin" required that the coordinator interact with and educate the patients again regarding the responsibilities that faced subjects after randomization and the uncertainties in the test treatment and the underlying purpose behind the trial. Often it was the coordinator's ability to empathize with a patient that was the key to the retention of subjects randomized to medical therapy in NETT. While the coordinator had to focus on getting a patient to return for follow-up, she/he also had to recognize and validate the patient's feelings of disappointment with the assigned treatment. Such validation was important to the relationship and thus helped in getting patients to return for follow-up, as evidenced by the fact that out of the 1,218 patients randomized in NETT, only 10 were completely lost to follow-up.

In addition, each clinic coordinator had to deal with his or her beliefs about whether randomization was ethical given their own experience with LVRS before NETT. There was much discussion regarding investigators' "equipoise" during the planning phase of NETT, but little to no discussion at study-wide meetings regarding the coordinators' equipoise with regard to LVRS, either among investigators or among coordinators. The need for equipoise was important in the informed consent and randomization process. To educate and support the study subject, the coordinator needed to value the need for a randomized, clinical trial to test LVRS. Strong feelings either way would have been detrimental to the overall success of NETT. Each coordinator was left to reconcile his/her issues regarding whether LVRS was beneficial and therefore how he/she felt about

randomization to treatment in NETT. As NETT progressed, coordinators realized that some subjects who had been randomized to medical treatment were clinically declining to a degree that would render them ineligible ever to receive LVRS. Likewise, the coordinators also had to deal with the issue of those patients who were randomized to LVRS before the identification of the "high risk" group and who would never have received LVRS if enrolled later in NETT.

TRIAL MANAGEMENT

NETT required immense cooperation across multiple disciplines. The clinic coordinator interacted regularly with pulmonary function technicians, exercise physiologists, pulmonary rehabilitation coordinators, radiology and nuclear medicine technicians, radiologists, pulmonologists, anesthesiologists, cardiologists, and surgeons to ensure that the testing procedures were conducted according to NETT standards and within the NETT timeline, but within the daily operation of each of these specialty departments. Timely completion of all data collection forms and coordination of data entry for several hundred form items were required at each NETT visit.

Since CMS had agreed to pay the costs of the clinical services associated with study participation for Medicare beneficiaries enrolled in NETT, every NETT test, visit, and LVRS procedure generated patient-specific bills to Medicare. Because the bills were subject to a different review process than bills for usual Medicare benefits, bills for NETT services had to be prepared in highly specific ways. The specifics around NETT billing and reimbursement required ongoing coordination between study staff; hospital, facility, and physician office billing staff; Medicare carriers and intermediaries; and CMS. The responsibility of such coordination often fell to the clinic coordinators. Bills to Medicare for NETT services in turn generated explanations of benefits to patients that specified their co-payment and deductible obligations for the NETT services and, until physicians and facilities received assurance that they could waive the co-payments and deductibles associated with NETT services, explanations of benefits led to bills to patients for NETT services. Coordinators had to advocate for patients who were receiving an immense amount of paperwork regarding bills for services while they were enrolled in NETT. Medicare is required by statute to charge co-payments and deductibles for services covered by Medicare, and hospitals, physicians, and facilities are required by law to bill patients for these co-payments and deductibles. Testing was required by the protocol and paying out of pocket for some was a real burden. At times patients resented having to pay for care rendered because they were enrolled in a clinical trial. To accommodate such concerns, early on in NETT (but after recruitment and randomization had begun), centers applied for an advisory opinion from the Office of the Inspector General (OIG) in the Department of Health and Human Services on the legality of physicians and institutions providing NETT services not charging NETT patients for the co-payments and deductibles associated with NETT services. The OIG issued their opinion that, in the context of NETT, it would not be illegal if patients were not billed for co-payments and deductibles for NETT services (http://oig.hhs.gov/fraud/docs/advisoryopinions/2000/ao00_5.htm). Armed with this document, most NETT sites felt comfortable with waiving co-pays and deductibles for NETT services.

CAREGIVER ROLE

Before randomization and throughout the trial, each patient was required to have optimal medical management of their

emphysema. Patients had to be educated on changes in their medical regimen, oxygen use, and expected follow-up appointments, and the primary physician also needed to be kept informed about changes to his/her patient's medical regimen. Each NETT center had to develop and nurture relationships with their patients' private physicians to assure their compliance with the study protocol. In effect, the physicians had to be educated as well as the patients.

Patient care was challenging and demanding, as NETT enrollees had severe emphysema with limited ability to perform activities of daily living and poor quality of life. Optimization of the medical management of the emphysema patients referred for NETT was a large part of the clinic coordinator's responsibilities. Changes to the patient's routine required that the coordinator evaluate the learning needs of each patient and follow-up with education as needed. There were also times when the clinic coordinator had to educate patients how to navigate the health care system so that they received the best possible care available.

The coordinators also had a role in the quality of care that the patients randomized to LVRS received while hospitalized after the procedure. The NETT coordinators routinely followed the LVRS patients during their hospitalization to collect pertinent NETT data, but more importantly often acted as the coordinator in the postoperative care of the patient. The coordinator interacted with the interdisciplinary team and the patients during their postoperative course so as to ensure quality care was rendered to the patients entrusted to them.

CONCLUSIONS

Maintaining quality patient care while also maintaining a quality study was challenging. The successful balance of the clinic co-

ordinator's roles of researcher and patient care provider was essential to the overall conduct of NETT. As coordinators, the staff was given the opportunity to provide necessary care, education, and support to patients with severe emphysema who had chosen to enroll as study subjects in NETT. At the conclusion of NETT, there were many rewards for the coordinators. They helped to validate the safety and efficacy of LVRS while conducting a randomized, clinical trial with an acceptable recruitment rate and exceptional subject retention. While the role of coordinator is similar in most trials, not many can say that they participated in a trial that changed a national coverage policy for a procedure like LVRS for patients suffering from such a debilitating disease as emphysema. In the end, NETT was a huge success for all those involved.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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