special report

Rationale and Design of the National Emphysema Treatment Trial

A Prospective Randomized Trial of Lung Volume Reduction Surgery

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The National Emphysema Treatment Trial is a multicenter, randomized clinical trial of medical therapy vs medical therapy plus lung volume reduction surgery (LVRS) for the treatment of patients with severe bilateral emphysema. LVRS will be accomplished by bilateral stapled excision via median sternotomy or video-assisted thoracoscopic surgery. Every patient will complete 6 to 10 weeks of pulmonary rehabilitation prior to randomization and will participate in a maintenance program of pulmonary rehabilitation after randomization. The primary outcome to be assessed by the trial is survival. Additional outcomes to be assessed are maximum exercise capacity, pulmonary function, oxygen requirement, distance walked in 6 min, quality of life, respiratory symptoms, and health-care utilization and costs. In addition, selected clinics will evaluate lung mechanics and respiratory muscle function, partial and maximal flow-volume curves, gas exchange during maximal exercise, and right heart function. The trial is targeted to enroll patients with severe emphysema who have no significant comorbid conditions; each patient will be randomized to one of the two treatment groups. The study duration is 4.5 years with a close-out period of 6 months. ***(CHEST 1999; 116:1750–1761)***

Key words: emphysema; lung function; lung volume reduction surgery; maximum exercise capacity; median sternotomy; medical vs surgical treatment; pulmonary rehabilitation; randomized clinical trial; video-assisted thoracoscopic surgery

Abbreviations: HCFA = Health Care Financing Administration; LVRS = lung volume reduction surgery; MS = median sternotomy; NETT = National Emphysema Treatment Trial; NHLBI = National Heart, Lung, and Blood Institute; QWB = Quality of Well-Being Scale; SF-36 = Medical Outcomes Study Short Form 36-item questionnaire; SGRQ = St. George's Respiratory Questionnaire; SOBQ = The University of California, San Diego Shortness of Breath Questionnaire; VATS = video-assisted thoracoscopic surgery

The purpose of this paper is to present the design for the National Emphysema Treatment Trial (NETT). This trial is a collaborative effort of 17 clinical centers, a study coordinating/statistical center, the National Heart, Lung, and Blood Institute (NHLBI), and the Health Care Financing Administration (HCFA). The study protocol and procedures were finalized from 1997 to 1998, screening began in October 1997, and randomization began in January 1998.

Terminology

Emphysema is a condition of the lung characterized by abnormal, permanent enlargement of airspaces distal to the terminal bronchiole, accompanied by destruction of their walls in the absence of obvious fibrosis.[1] The cardinal physiologic defect in emphysema is a decrease in elastic recoil. This decrease in elastic recoil results in the principal physiologic abnormalities of emphysema: decreased

*A complete list of NETT investigators is located in the Appendix.

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maximum expiratory airflow, hyperinflation, and air-trapping. The destruction of the alveolar-capillary membrane surface leads to a reduction in diffusing capacity. Emphysema is usually the result of cigarette smoking, although it can occur occasionally without this exposure, notably in α_1-antitrypsin deficiency. It is a chronic progressive disorder that ultimately leads to disability and early death. Emphysema is estimated to be present in 2 million adults in the United States, and, along with other forms of COPD, accounts for $>$ 90,000 deaths annually.[2]

Present State of Treatment for Emphysema

Guidelines for the diagnosis and management of emphysema have been recently promulgated.[1,3] The goals of therapy in emphysema, as in other forms of COPD, are to halt the progressive decline in lung function, prevent and shorten exacerbations of the disease, improve exercise capacity and quality of life, and prolong survival. The only treatment that has been shown to alter the rate of progression of COPD is cessation of smoking.[4] Influenza immunization and pneumococcal vaccination are recommended for the prevention of intercurrent life-threatening infections.[5,6] As a rule, exacerbations of disease are treated with antibiotics, steroids, and bronchodilators. Although these interventions are believed to shorten the duration of individual episodes and to minimize symptoms, there is little evidence that they either alter the natural history of the disease or reduce mortality.[7,8] Bronchodilators improve lung function, exercise capacity, and quality of life in patients with COPD but are of limited benefit to patients without reversible airway disease.[9] Pulmonary rehabilitation, including aerobic exercise conditioning, education, and psychosocial support, improves exercise capacity in patients with COPD and may reduce the rate of hospitalization.[10–13]

Long-term domiciliary oxygen therapy in hypoxemic patients is the only treatment for COPD that has been documented to decrease mortality rates.[14,15] Adjunctive forms of therapy, such as the use of mucolytics to control respiratory secretions or narcotics to reduce the sensation of dyspnea, have been used in selected COPD patients.[16] In patients with α_1-protease inhibitor deficiency, protective serum levels of the enzyme may be restored by regular infusions of exogenous α_1-protease inhibitor,[17] but it is unclear whether restoring serum levels protects against progression of the disease or prolongs survival.[11] In patients with far-advanced COPD, single or double lung transplantation has been used as a last resort, but this option is limited by the small number of donor organs.

Surgery for Emphysema

The failure of medical treatment to produce prolonged improvement of symptoms has prompted the introduction of various surgical procedures over the last 90 years in an attempt to improve symptoms in patients with emphysema.[18] Based on the premise that patients with severe emphysema have lungs that have become too large relative to the size of their chests, several different surgical procedures, including pneumoperitoneum formation, phrenic nerve paralysis, thoracoplasty, or excision of costal cartilage combined with a partial sternotomy, have been tried in uncontrolled series of patients.[18] Other operations have included denervation of the lung and stabilization and fixation of the trachea, and procedures to correct gastroesophageal reflux disease. These surgical procedures produced minimal or no benefit to the patients.[18]

In 1957, Brantigan and Mueller[19] reported the surgical excision of lung tissue to reduce the volume of the hyperinflated lung parenchyma, so-called "lung volume reduction surgery" (LVRS). Although 75% of patients reported clinical improvement, the lack of objective documentation for benefit from the procedure and an operative mortality of 18% prevented widespread acceptance of the procedure.

In more recent years, the concept of reducing lung volume surgically in patients with emphysema has been reexplored. In 1991, Wakabayashi et al[20] reported using a carbon dioxide laser to shrink bullous areas of the lung using a thoracoscopic approach. In 1995, Cooper et al[21] reported a modification of the volume reduction operation of Brantigan and Mueller,[19] in which lung tissue was resected from both lungs via a median sternotomy (MS). In the initial 20 patients reported, there was no operative mortality, and the operation produced an 82% mean increase in the FEV_1 and significant improvement in the distance walked in 6 min. Moreover, many patients were able to discontinue the use of supplemental oxygen. Subsequent randomized prospective studies suggested that the results using stapled resection were superior to those obtained by laser ablation[22] and that bilateral resection was superior to unilateral resection.[23]

Existing Data on LVRS

A number of studies have reported their results following bilateral LVRS.[23–29] From this combined experience, 738 patients showed a 61% mean improvement in FEV_1 and a 45.7% mean improvement in the distance walked in 6 min; 62% of the oxygen-dependent patients became oxygen independent. The operative mortality in these series ranged from 2.5 to 10%, and the mean length of stay ranged from 10.9 to 17 days.

The favorable results reported in the series reported earlier contrasted with data collected from 722 Medicare claims that used the LVRS billing code between October 1995 and January 1996.[30] Mortality rates 3 and 12 months postsurgery were 14.4% and 23%, respectively. For these patients, acute-care hospitalizations and use of long-term care and rehabilitation services were greater postsurgery than presurgery (304 stays for 160 patients postsurgery vs 197 stays for 123 patients presurgery; the inpatient stay associated with the LVRS was excluded from these analyses). The average number of days hospitalized was greater postsurgery than presurgery.

During the development of the NETT protocol, the historical experience with LVRS at the original 18 clinical centers was reviewed by the NETT Coordinating Center at the request of the NETT Steering Committee. The centers collectively reported 1,741 patients who had undergone LVRS by bilateral, unilateral, laser, and excision procedures. The number of patients per center undergoing LVRS ranged between 13 and 371. Data were requested on baseline prognostic variables (*eg*, age, sex, and pulmonary function tests), pulmonary function tests performed 6 months postoperatively, the 6-min walk test, vital status, and duration of survival. Investigators also were asked to assess each patient for whether they had benefitted from the LVRS; each investigator could use their discretion regarding the criteria for the assessment of benefit or lack of benefit. Analyses were conducted on all 1,741 patients regardless of the type of procedure used for LVRS.

The analyses showed that considerable historical data were missing, making it difficult to draw statistical inferences. For example, only 25% of the 1,741 patients had sufficient baseline and follow-up data on prognostic variables for meaningful analyses. Inferences from the historical data were compromised not only by the missing values but also by the potential for strong biases in follow-up and functional assessment. In general, investigators seemed inclined to attribute benefit to the procedure, as seen in the requested subjective assessment of benefit or no benefit. Logistic regression techniques were used on one half of the historical data set to identify baseline characteristics that would be predictive of benefit. The other half of the data set was used to determine the sensitivity and specificity of the characteristics identified as predictive of benefit. The best sensitivity and specificity for prediction of benefit were approximately 62% and 64%, respectively. In summary, the historical data did not provide convincing evidence for efficacy for or reliable characterization of a subset of patients likely to benefit from LVRS.

Rationale for the Trial

As indicated above, published reports on LVRS deal with relatively small numbers of selected patients without long-term follow-up or comprehensive assessment of risks, benefits, and costs. In these reports, there is considerable variability in baseline assessments, the types of surgery performed, the procedures involved in preoperative, intraoperative, and postoperative care, and the type and completeness of follow-up evaluations. In addition, although selection criteria were not standardized, only a small proportion of the patients who were evaluated for LVRS actually underwent the procedure. The natural history of these patients, with or without surgery, has not been carefully followed.

Investigators at a number of medical centers across the United States tried to reproduce the data given in the initial reports of success with LVRS. At several of these sites, mortality rates were inordinately high, raising questions about the risk/benefit ratio of medical therapy vs medical therapy plus surgical intervention. Among the questions raised were the following: How long would the benefit from surgery last? What is the optimal technique for performing the procedure? What are the clinical outcomes beyond the first few months after surgery? Can a subset of patients who would benefit from the procedure be defined?

Thus, key questions remain about whether the benefits of LVRS outweigh the associated risks and costs, and about issues of efficacy, safety, and patient selection. These questions are particularly pertinent for this group of individuals, who suffer from advanced emphysematous lung disease and who are willing to try any new form of treatment that has the potential for relieving their considerable discomfort in breathing.

Outcome Measures

Primary Measures

The two primary outcome measures chosen for the NETT are survival and maximum exercise capacity. Although many investigators favored palliation (measured by dyspnea scores, quality of life, and exercise capacity) as a more appropriate primary outcome measure than mortality, survival was chosen as the primary outcome for three reasons: (1) it is clinically significant, because patients with severe emphysema have a high mortality rate; (2) it can be objectively assessed and is easily quantified; and (3) a statistical design for differences in survival ensures a sufficient number of participants for other important outcome measures.

The other primary measure of outcome, the maximum exercise capacity, was chosen as a measure of integrated cardiopulmonary and physical performance. It is determined by maximal, incremental, symptom-limited exercise using a cycle ergometer. This test affords several advantages over the 6-min walk test: it is easier to standardize, it is more reproducible, it is not difficult to administer, and it entails less of a learning effect. Exercise capacity was favored over pulmonary function tests as a primary measure of outcome because studies to date have not documented a consistent relationship between improvement in functional status and changes in pulmonary function, particularly in patients treated medically.

Secondary Measures

The following secondary measures will be in used in the assessment of outcomes.

Quality of Life and Related Disease-Specific Symptoms: These are possibly the most important outcome measures to the patients participating in the trial, and will be measured both by general and disease-specific instruments. General quality of life will be assessed by the Medical Outcomes Study Short Form 36-item questionnaire (SF-36)[31] and the utility-weighted Quality of Well-Being Scale (QWB).[32] The SF-36 is widely used; its inclusion in the NETT battery will allow the comparison of results from NETT with results from other studies. The QWB is widely used to provide an estimate of quality-adjusted life years, an important measure for the cost-effectiveness analysis. Disease-specific quality of life will be assessed using the St. George's Respiratory Questionnaire (SGRQ),[33] an instrument that has been developed and validated in patients with COPD. The University of California, San Diego Shortness of Breath Questionnaire (SOBQ),[34] and the modified Borg scale for perceived dyspnea[35,36] will be used to assess dyspnea, the most important symptom of chronic lung disease. The SOBQ is sensitive to small changes in perceived breathlessness and provides information about breathlessness during the daily activities of patients that can be helpful in their clinical evaluation and in their management in rehabilitation. The modified Borg scale is used at the start and close of the 6-min walk testing and the maximum exercise testing to obtain ratings of perceived dyspnea and muscle fatigue before and after exercise. The SF-36, QWB, SGRQ, and SOBQ are self-administered scales that can be completed within 60 min.

Cost-effectiveness Analysis: This analysis will be performed using incremental quality-adjusted life years as the denominator and incremental costs as the numerator. Costs will include resources consumed during the course of care; values or prices will be assigned to each resource. Costs of therapy include medical and surgical care, nonmedical care related to the treatment, the time of family or friends (valued to dollars) for caring for the patient, and the value of the patient's time obtaining treatment. The analysis will be completed both from this general societal perspective and from the Medicare perspective. The latter includes only the costs that Medicare covers. Details about the cost-effectiveness analysis will be published elsewhere.

Pulmonary Function and Gas Exchange: These will be assessed in all patients at the time of the initial evaluation and at all follow-up visits. Tests will include spirometry, plethysmographic determination of the functional residual capacity, the single-breath diffusing capacity, arterial blood gas levels at rest, and the maximal inspiratory and expiratory mouth pressures. Selected clinics will assess pulmonary mechanics in greater detail, including determinations of lung elastic recoil pressures, flow-volume relationships, pulmonary resistance, respiratory muscle function, and arterial blood gas levels during maximum exercise.

Radiologic Studies: These studies will include standard chest radiographs, volumetric and high-resolution CT scans, and nuclear perfusion scans. Chest radiographs and CT scans will be performed at the time of initial evaluation and at two follow-up visits; perfusion scans will be performed at the initial evaluation only. CT scans will be used to verify the presence of emphysema and to assess the distribution and severity of the disease.

Oxygen Requirement: The requirement of patients for supplemental oxygen will be assessed on entry into the study and in follow-up. This will be done by adjusting the oxygen concentration of inspired air to maintain the oxygen saturation of arterial blood at $> 90\%$ while the patient walks on a treadmill, on a level grade, at one mile per hour.

6-Min Walk Distance: This exercise parameter is included largely because of its widespread use by investigators who have previously reported on the results of LVRS. However, it has been designated as a secondary, rather than a primary, measure of outcome because the test is difficult to standardize.[37] The test will be performed initially and during follow-up.

Cardiovascular Measures: All patients will undergo echocardiographic studies at the time of initial assessment. All patients with evidence of abnormally high pulmonary arterial pressures will undergo right heart catheterization as part of their evaluation for inclusion in the trial. Patients with pulmonary hypertension are ineligible, because of the possibility of increased surgical risk. All patients will undergo at least one follow-up echocardiographic study. At selected clinics, patients will undergo initial and follow-up right heart catheterization.

Attention and Psychomotor Functioning: The Trail Making Test[38,39] will be used at baseline and at annual follow-up visits to evaluate changes in cognitive ability or performance over time. The test is included because it is informative, simple to administer, and sensitive to hypoxia.

Study Design

The NETT is a randomized clinical trial that compares medical therapy for emphysema with medical therapy plus LVRS. The only patients who can enroll are Medicare beneficiaries or those whose insurance carrier is willing to cover the costs of participation in the trial.

The trial has three components:

1. *The main protocol*, which involves all enrolled patients at all participating clinical centers, and addresses the primary and secondary objectives of the NETT.
2. *Several substudies*, performed only at selected centers and involving only patients enrolled at those centers, addressing specific issues related to LVRS.
3. *Ancillary studies*, which are not part of the main NETT protocol, but involve either patients participating in the NETT or take advantage of information or materials obtained during the course of the NETT. These studies require approval from the NETT Steering Committee and separate consent from the patients.

Patient Participation

The recruitment goal for the trial is 2,500 patients; 6% of these are expected to be of minority background, and 30% are expected to be women. The study duration is set at 4.5 years with a 6-month close-out period.

Patients with moderate to severe emphysema who have been nonsmokers for 6 months prior to randomization and are judged to be free of other diseases, disabilities, or circumstances likely to interfere with therapy, data collection, or both for the duration of the trial, will be offered the opportunity to enroll in the NETT.

At all clinical centers, participants, after enrollment and pulmonary rehabilitation, will be randomized to a program of medical therapy or to a program of medical therapy plus LVRS in a 1:1 ratio. At those clinical centers that offer LVRS by both MS and video-assisted thoracoscopic surgery (VATS), those patients randomized to the surgical arm will participate in a second randomization between the two surgical approaches, also in a 1:1 ratio.

Screening Process

Patients may either self-refer for evaluation at a NETT clinical center or be referred by their physician. Patients, their physician, or both will be asked to provide a brief history, chest radiograph, ECG report, and the results of spirometry. These data will be reviewed at the clinical center. Those patients without identifiable contraindication will be invited to the clinical center for evaluation and testing. All patients who initiate screening at a NETT clinic are included in the NETT registry. Patients who are found to be ineligible for randomization remain in the registry and will be followed for vital status.

Patients invited for further evaluation will undertake a process designed to establish eligibility to be enrolled in the NETT and provide the baseline assessments that will serve as reference data for the duration of the trial. The evaluation process is outlined in Tables 1, 2.

The patient selection criteria for the NETT were formulated to achieve two broad goals:

1. Enrollment of patients with emphysema; patients with either heterogeneous or homogeneous emphysema will be included.
2. Exclusion of patients at high risk for perioperative morbidity or mortality, as well as patients unlikely to be able to complete the trial.

Inclusion Criteria

The inclusion criteria were designed to enroll patients with severe obstructive lung disease primarily due to emphysema. The criteria were formulated to include patients with a diverse distribution of emphysema to examine the effect of the anatomic distribution of disease on the response to therapy. The inclusion criteria include the following: (1) radiographic evidence of bilateral emphysema; (2) studies demonstrating severe airflow obstruction and hyperinflation; and (3) participation in pulmonary rehabilitation with the attainment of preset performance goals (Table 3).

Table 1—*Evaluation and Screening Procedure for NETT Enrollees*

Initial screening: review of data and confirmation of coverage by a NETT participating center
Consent No. 1: consent to screening and inclusion in registry; understanding of trial design
Assessment of eligibility
Completion of prerehabilitation assessment: exercise test, oxygen titration, 6-min walk, quality-of-life instruments, substudy testing
Determination of study eligibility and consent No. 2: consent to participate in pulmonary rehabilitation
Pulmonary rehabilitation: 6–10 weeks of supervised pulmonary rehabilitation, attendance requirements
Postrehabilitation assessment*
Review of eligibility: if eligible, then perfusion scan and pulmonary mechanics tests are performed
Consent No. 3: consent to randomization and follow-up

*See Table 2.

Exclusion Criteria

Exclusion criteria were formulated with the goal of excluding certain patients with emphysema who have the following characteristics: (1) characteristics that place them at high risk for perioperative morbidity and/or mortality; (2) disease considered to be unsuitable for LVRS; and (3) medical conditions or other circumstances that make it likely that the patient would be unable to complete the trial (Table 4). The exclusionary criteria relating to cardiologic issues are based on the work of Goldman et al.[40]

Treatments in the NETT

Medical Therapy

Medical therapy will closely follow the guidelines proposed by the American Thoracic Society.[1] A NETT pulmonary physician will provide recommendations for medical therapy for each participant in the trial. Overall responsibility for medical management will remain with the patient's primary-care physician. Medical treatment will include the following.

Table 2—*Trial Outcomes Assessment*

Outcomes	Assessments
Quality of life/ symptoms	SGRQ; SF-36; QWB; SOBQ; modified Borg scale for perceived dyspnea
Pulmonary function	Spirometry; lung volumes; arterial blood gas levels; inspiratory and expiratory mouth pressures; oxygen titration
Exercise	Cycle ergometry exercise tolerance test; 6-min walk
General medical	History; physical examination

Table 3—*Inclusion Criteria

Assessment	Criteria
History and physical examination	Consistent with emphysema BMI, ≤ 31.1 kg/m^2 (men) or ≤ 32.3 kg/m^2 (women) at randomization Stable with ≤ 20 mg prednisone (or equivalent) qd
Radiographic	HRCT scan evidence of bilateral emphysema
Pulmonary function (prerehabilitation)	FEV_1, ≤ 45% predicted (≥ 15% predicted if age ≥ 70 years) TLC, ≥ 100% predicted RV, ≥ 150% predicted
Arterial blood gas level (prerehabilitation)	P_{CO_2}, ≤ 60 mm Hg (Denver criterion: P_{CO_2}, ≤ 55 mm Hg) P_{O_2}, ≥ 45 mm Hg (Denver criterion: P_{O_2}, ≥ 30 mm Hg) on room air
Cardiac assessment	Approval for surgery prior to randomization by cardiologist if any of the following are present: unstable angina; LVEF cannot be estimated from the echocardiogram; LVEF < 45%; dobutamine-radionuclide cardiac scan indicates coronary artery disease or ventricular dysfunction; arrhythmia (> 5 PVCs per minute; cardiac rhythm other than sinus; PACs at rest)
Surgical assessment	Approval for surgery by pulmonary physician, thoracic surgeon, and anesthesiologist postrehabilitation and prior to randomization
Exercise	Postrehabilitation 6-min walk of ≥ 140 m; able to complete 3 min unloaded pedaling in exercise tolerance test (pre- and postrehabilitation)
Consent	Signed consents for screening, rehabilitation, and randomization
Smoking	Plasma cotinine level ≤ 13.7 ng/mL (or arterial carboxyhemoglobin ≤ 2.5% if using nicotine products) Nonsmoking for 4 mo prior to initial interview and throughout screening
Rehabilitation	Must complete prerandomization assessments, rehabilitation program, and all postrehabilitation and randomization assessments

*Patients must meet all criteria to participate in the study. BMI = body mass index; HRCT = high-resolution computed tomography; LVEF = left ventricular ejection fraction; PAC = premature atrial contraction; PVC = premature ventricular contractions; RV = residual volume; TLC = total lung capacity.

Smoking Cessation: Although eligibility for participation in NETT requires smoking cessation for at least 6 months before randomization and biochemical validation at the time of screening, it is anticipated that some participants may resume smoking during NETT. Relapses will be treated in line with the Agency for Health Care Policy and Research guidelines, including counseling, referral to group programs, and nicotine replacement therapy.

Table 4—*Exclusionary Criteria

History	Criteria
Previous surgery	Lung transplant
	LVRS
	MS or lobectomy
Cardiovascular	Dysrhythmia that might pose a risk during exercise or training
	Resting bradycardia (< 50 beats/min); frequent multifocal PVCs; complex ventricular arrhythmia; sustained SVT
	History of exercise-related syncope
	MI within 6 mo and LVEF < 45%
	Congestive heart failure within 6 mo and LVEF < 45%
	Uncontrolled hypertension (systolic, > 200 mm; diastolic, > 110 mm)
Pulmonary	History of recurrent infections with clinically significant sputum production
	Pleural or interstitial disease that precludes surgery
	Clinically significant bronchiectasis
	Pulmonary nodule requiring surgery
	Giant bulla (> 1/3 volume of lung)
	Pulmonary hypertension: peak systolic PPA, ≥ 45 mm Hg (Denver criterion: ≥ 50 mm Hg) or mean PPA, ≥ 35 mm Hg (Denver criterion: ≥ 38 mm Hg). (Right heart catheter is required to rule out pulmonary hypertension if peak systolic PPA on echocardiogram is ≥ 45 mm Hg)
	Requirement for > 6 L O_2 to keep saturation ≥ 90% with exercise
Radiographic	CT evidence of diffuse emphysema judged unsuitable for LVRS
General	Unplanned weight loss of > 10% usual weight in 90 d prior to enrollment
	Evidence of systemic disease or neoplasia expected to compromise survival during 5-yr period
	6-min walk distance ≤ 140 m after rehabilitation
	Any disease or condition that interferes with completion of initial or follow-up assessments
	Unwillingness or inability to complete screening or baseline data collection procedures

*The presence of any one criterion makes the patient ineligible for the study; MI = myocardial infarction; PPA = pulmonary artery pressure; SVT = supraventricular tachycardia. For other abbreviations, see Table 3.

Bronchodilators: In general, treatment will include both an anticholinergic bronchodilator and a β_2-agonist. The preferred route of administration is by metered-dose inhaler.

Oxygen Therapy: Oxygen will be administered chronically to maintain the level of arterial oxygen saturation at ≥ 90% during activities of daily living.

Immunization: Influenza immunization and pneumococcal vaccination are to be used in accord with Centers for Disease Control and Prevention guidelines.

Additional Measures: Additional measures will be tailored to individual needs. These may include bronchodilators such as theophylline, administered orally, corticosteroids, administered by inhalation or orally, and antibiotics for the treatment of respiratory infections.

Pulmonary Rehabilitation: The rehabilitation program in NETT is designed to optimize the ability of the patient to perform the activities of daily living and to understand and manage the chronic disease. For participants undergoing medical therapy alone, the goal of the NETT rehabilitation program is to optimize exercise capacity. For participants undergoing medical therapy plus LVRS, the goals are to achieve as much physical fitness as possible before surgery to effect early postoperative mobilization and to provide a baseline of optimized preoperative exercise capacity for comparison with the postoperative exercise capacity.

All participants will engage in pulmonary rehabilitation, which will be conducted in three phases: prerandomization (16 to 20 sessions over 6 to 10 weeks); postrandomization (10 sessions over 8 to 9 weeks); and long-term maintenance (duration of the trial). The rehabilitation programs will be supervised by a NETT clinical center; portions of the program may be carried out at a NETT-certified rehabilitation facility closer to the participant's home. The long-term maintenance program will be conducted at home or at a fitness center with continued monitoring performed by a NETT clinical center.

Components of the pulmonary rehabilitation program include the following:

1. Comprehensive evaluation of medical, psychosocial, and nutritional needs
2. Setting of goals for education and exercise training
3. Exercise training (lower extremity, flexibility, strengthening, and upper extremity)
4. Education about emphysema, medical treatments, and NETT
5. Psychosocial counseling
6. Nutritional counseling

Surgical Treatment

Based on the consensus that the excision of lung tissue using LVRS is more effective than laser ablation or lung plication in relieving symptoms and improving pulmonary function, and to ensure consistency among participating centers, only stapled LVRS with excision will be used in the trial. In addition, all patients treated surgically will undergo bilateral reduction surgery because of the evidence

that the bilateral procedure affords greater and more consistent benefits than does the unilateral procedure.

The surgical approach will not be uniform at all the centers. MS will be performed at 8 of the 17 centers, bilateral VATS will be performed at 3 centers, and 6 centers will randomize patients to either MS or VATS. Patients will be scheduled for surgery within 2 weeks of randomization. If exacerbation of the patient's underlying disease or other illness causes delay beyond this time limit, surgery will be postponed until after the acute illness has subsided. Further pulmonary rehabilitation and additional testing may be required to ensure that candidates continue to satisfy inclusion criteria.

The surgical procedure is directed at excising functionally useless lung tissue. The areas to be resected are identified by preoperative CT scans and perfusion scans. Based on published experience, most patients can be expected to have heterogeneous disease, which is most severe in the upper lobes; in relatively few patients, emphysema will predominate in the lower lobes. The surgical procedure entails removal of approximately 25 to 30% of the total lung tissue from each side. Surgeons are permitted to reinforce the staple lines using buttress material to minimize the incidence and severity of air leaks. Removed tissue will be weighed, and portions will be stored for possible use in future studies. For each patient, details of the operation will be recorded that pay special attention to the extent of adhesions, intraoperative difficulties, and problems with intraoperative hemodynamics.

Intraoperative management of anesthesia has been standardized. Preoperatively, in MS patients, thoracic epidural catheters will be placed for intra- and postoperative pain control. It is expected that extubation will be performed within 2 h, either in the operating room or the recovery area. Patients will be admitted either to the ICU or to another designated unit in line with the standard of care for patients undergoing major thoracic surgery at the respective institution. Starting on the first postoperative day, patients will receive vigorous chest respiratory therapy and physical therapy to enhance mobilization.

Based on previous experience, the most significant postoperative complication is expected to be air leaks that last > 7 days. This problem is likely to affect $\leq 40\%$ of surgical patients regardless of the technique used for LVRS. Other significant complications to be anticipated include respiratory failure, especially if reintubation is necessary, cardiac dysrhythmia, and GI complications.

Individual centers may choose to discharge patients with air leaks controlled by the use of Heimlich valves on the chest tube(s). The date of discharge from the surgical facility, as well as the disposition of the patient (home or another inpatient facility, for example), will be recorded.

Statistical Considerations

This study is an unmasked, randomized, clinical trial with a prospectively accrued registry of patients. The trial consists of an equal allocation of prospectively randomized patients who receive medical therapy alone or medical therapy plus LVRS. The primary statistical objectives of the randomized trial are to estimate differences between the two groups in survival and maximum exercise capacity.

The primary treatment comparisons will be between medical therapy and LVRS of either type (MS or VATS). However, the structure and size of the trial will also permit important subset analyses to be conducted, as well as comparisons of morbidity, mortality, and other outcomes within the surgery group. These differences will be assessed with lower power than the primary comparison, but they should permit clinically important differences to be detected. An important objective of the trial is to gather information to characterize any subset of patients who might receive disproportionate benefit (or risk) from the surgical procedure.

Power and Sample Size

This trial is designed primarily to determine the difference in survival rates between the medical therapy and LVRS groups. The required sample size has been calculated to be 2,500 patients (*ie*, 1,250 patients per group).[41] The accrual rate required to reach the target of 2,500 patients in 4.5 years is 2.7 patients per clinic per month. Overall, the trial will have high power to meet other objectives such as detecting a difference in maximum exercise capacity (or other continuously distributed random variables).

Analyses

In the initial analysis for any variable, patients will be counted in the treatment group to which they were randomly assigned without regard to dropouts, drop-ins, or course of therapy (*ie*, the intention-to-treat principle). All events occurring from randomization on will be counted in the treatment group to which the patient was randomly assigned. Analyses will be conducted to assess whether any observed treatment effect is consistent across subsets of patients (defined by baseline characteristics, *eg*, age, race, and gender). Analyses will be conducted separately in the prospectively defined subset of patients who are thought most likely to benefit. This ap-

proach will be taken for analyses of mortality, complications, and functional outcomes.

Attempts will be made to define a subset of patients who benefit from treatment (either LVRS or medical therapy). "Benefit" will be defined objectively by a quantitative algorithm based on functional capacity, and all patients will be classified accordingly. The association between benefit and baseline prognostic factors will be assessed using a multiple logistic regression model. The model will be built on a random subset of patients (50%) and validated on the remaining patients. The sensitivity and specificity of the "best" such model will be calculated from the logistic classification method using standard methods. A similar procedure will be used to identify subsets of patients who may be at high short-term risk from treatment. These analyses will be conducted separately in medical and surgical patients, as well as in the combined group.

Patient Rights and Responsibilities

Consent Process

There are three separate consents. The first consent, for screening and patient registry, is to be signed at the first visit at the NETT clinic after review of records provided by the patient's private physician indicates that the patient is likely to have emphysema and may be eligible. The second consent, for pulmonary rehabilitation, is to be signed after the patient has completed the diagnostic and prerehabilitation assessments and has been judged eligible to enroll in the 6- to 10-week pulmonary rehabilitation program that is required before assessment for randomization in NETT is undertaken. The third consent statement, for randomization, is to be signed after the patient has completed the 6 to 10 weeks of rehabilitation and the postrehabilitation assessments and is found to be eligible for randomization, including judgment by the treatment team that the patient is suitable for surgery. Surgical consent will be obtained by a separate consent statement prepared and administered by each individual clinic, and will be required only for patients assigned to LVRS.

Participation in NETT and Impact on Participation in Transplant Program

Participation in the trial does not preclude a patient from undergoing or remaining on the active list for lung transplantation. Although individual patients may be asked by NETT staff to consider delaying a transplant at certain times during the protocol, the final choice will be made by the patient in consultation with their private physician and will be directed by their clinical situation.

Conclusion

The NETT is a multicenter randomized trial designed to assess the effect of LVRS compared to medical therapy on survival and exercise capacity in patients with severe emphysema. This trial will provide information on the role of LVRS in the management of emphysema, define the characteristics of which patients, if any, likely to benefit from LVRS, and serve as a basis for an HCFA decision on reimbursement for LVRS.

The NETT represents a novel paradigm for evaluating new medical and surgical treatments. The agreement between NHLBI and HCFA to cosponsor NETT specifies that NHLBI will provide scientific and administrative leadership and monitoring (and associated costs) and that HCFA will bear the costs of the clinical services associated with the protocol. The Agency for Health Care Policy and Research contributes support for the cost-effectiveness analysis. NETT could serve as a model for evaluating the benefit and appropriate use of new therapies.

Appendix: NETT Investigators

The members of the NETT Research Group (as of February 1999) are the following:

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