Economic Analysis of Lung Volume Reduction Surgery as Part of the National Emphysema Treatment Trial

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Background. In today's cost-conscious health care environment, obtaining timely and accurate economic information regarding new medical technologies has become extremely important. The National Emphysema Treatment Trial, a multicenter, randomized controlled trial of lung volume reduction surgery (LVRS) plus medical therapy, versus medical therapy for patients with severe emphysema, includes a parallel cost-effectiveness analysis.

Methods. The analysis is designed to determine the cost-effectiveness of LVRS versus medical therapy for those who are eligible for the procedure. After describing theoretical foundations of cost-effectiveness analysis as they apply to this study, we describe the economic and quality of life data that are being collected alongside the clinical trial, methods of analysis, and approach to presenting the results.

Results. The cost-effectiveness of LVRS relative to medical therapy will be presented as costs per quality-adjusted life years gained.

Conclusions. This analysis will provide timely economic data that can be considered alongside the clinical results of the National Emphysema Treatment Trial. As one of the largest clinical trials to include a parallel, prospective cost-effectiveness analyses, this study will also provide valuable practical information about conducting an economic analysis alongside a multicenter clinical trial.


Lung Volume Reduction Surgery (LVRS), a promising new surgical therapy for patients with severe emphysema, has engendered considerable controversy since being reintroduced in 1994. After favorable results from a small study of patients with severe emphysema who underwent LVRS were reported at separate meetings in the spring and fall of 1994, several institutions throughout the country began offering LVRS programs and actively recruiting patients [1]. By December of 1995, Health Care Financing Administration (HCFA) records indicated that over 1,200 LVRS procedures had been performed on Medicare beneficiaries [2]. In December of 1995, the HCFA announced that Medicare would not pay for LVRS, on the grounds that insufficient safety and efficacy evidence were available to support reimbursement [3]. Subsequently, the HCFA and the National Heart, Lung, and Blood Institute (NHLBI) announced that they would cosponsor a multicenter, randomized controlled trial to evaluate the efficacy of LVRS. In October of 1997, patients began enrolling into what is now known as the National Emphysema Treatment Trial (NETT).

Should the NETT demonstrate that LVRS provides a significant and lasting improvement for those with emphysema, the financial impact on the health care sector may be substantial. Emphysema affects approximately 2.0 million Americans and is one of the fastest growing causes of morbidity and mortality in the United States [4]. The mean reimbursement for the more than 1,200 LVRS procedures performed on Medicare beneficiaries was $31,398 per procedure [2]. Given the prevalence of emphysema, even if a comparatively small proportion of individuals with this disease are eligible for LVRS, widespread adoption of this procedure could increase US health care expenditures by hundreds of millions of dollars [2, 5].

As efforts to control health care spending become increasingly intense, decision makers are forced to confront the reality that adopting new, cost-increasing technologies necessitates spending less in other areas of health care. In this context, some have argued that it is reasonable to consider the outcomes and costs for LVRS relative to outcomes and costs for other medical procedures [6-8]. The most common and accepted approach to compare the relative value of different interventions in
creating better health or longer life is cost-effectiveness analysis (CEA).

As clinical services provided for NETT are reimbursed by HCFA, NETT provides a landmark opportunity to complete a rigorous cost-effectiveness analysis. Recognizing this, the Agency for Healthcare Research and Quality agreed to support a CEA alongside NETT, and HCFA, NHLBI, and NETT investigators to provide data for the CEA. The parallel analysis of cost-effectiveness alongside the clinical trial has two important advantages. First, it is an efficient and timely way to obtain data on clinical, economic, and humanistic outcomes simultaneously. Timely economic data will be particularly useful to those who are responsible for health care budgets, since LVRS may become a widely used procedure for patients with severe emphysema if the NETT demonstrates a beneficial effect of the procedure. Second, performing a CEA alongside a randomized, controlled trial has high internal validity and low potential for bias. If one accepts the notion that economic considerations are unavoidable in clinical decision-making, the highest quality economic evidence should be used.

In this article, we provide an overview of the CEA that will be conducted alongside the NETT. We begin by summarizing the approach for performing a CEA of a new medical technology, and describe how it will be applied to the alternative treatments being studied in the NETT. We then describe how the findings from this study should be interpreted in the context of other economic analyses of medical interventions.

The National Emphysema Treatment Trial

The National Emphysema Treatment Trial (NETT) is a multicenter, randomized controlled trial of lung volume reduction surgery (LVRS) versus medical therapy (MT) for patients with severe emphysema [9]. Seventeen participating centers will randomly assign approximately 2,500 patients meeting inclusion criteria into two treatment arms: MT versus medical therapy with LVRS. At six centers, patients randomized to surgery will also be randomized as to surgical approach: LVRS via median sternotomy versus LVRS via video-assisted thoracoscopic surgery. Prior to randomization, all patients will undergo a 6 to 10 week period of pulmonary rehabilitation and optimization of their medical therapy. Since the trial has a fixed end date, follow-up postrandomization will range from 6 months to 5 years, depending on the date of entry into the protocol. The primary outcome measures for the trial are mortality and maximal exercise capacity as measured by a cycle ergometer. Other outcomes include measures of pulmonary physiology, emphysema-related quality of life measured by the St. Georges Respiratory questionnaire [10], and general health-related quality of life measured by the Quality of Well Being questionnaire [11].

The cost-effectiveness estimate for LVRS will be derived for costs and consequences that accrue over the time horizon of the clinical trial (5 years) utilizing data drawn directly from the trial. Costs will be estimated by tracking Medicare health care claims data for trial participants (provided by the HCFA) and applying national average prices to those claims, based on Medicare reimbursement levels. Health services not covered by Medicare (such as drugs) are being collected as part of the clinical trial, and will be incorporated into the analysis after applying average prices from national average wholesale price data. Health care costs for participants will be tracked during 6 months prior to entry into the study and through the duration of the trial. Survival and quality of life data for trial participants will be used to estimate the effectiveness of each arm of the trial, as described below. The cost, quality of life, and survival data will be used to derive lifetime cost-effectiveness estimates for LVRS compared to medical therapy.

Economic Analysis of Medical Technologies

The approach to performing cost-effectiveness analyses of medical technologies has become standardized in recent years, with principles and procedures for analysis and reporting results that should be adhered to as is done for clinical evaluations [12, 13]. Readers should now expect to find elements in reports of cost-effectiveness analyses indicating that a sound evaluation was performed (Table 1).

Research Question
We wish to determine whether LVRS is cost-effective compared to MT as therapy for patients with severe emphysema. When comparing a new therapy with an existing therapy for a given population with a given medical condition, cost-effectiveness is measured as the change in costs of care for new technology compared to the existing therapy, relative to the change in effectiveness of new therapy compared to the existing therapy. The difference in costs over the difference in effectiveness of LVRS versus MT, known as the incremental cost-effectiveness of LVRS, and can be derived using the following formula:

\[
\text{Incremental cost-effectiveness LVRS} = \frac{(C_{LVRS} - C_{MT})}{(E_{LVRS} - E_{MT})}. \tag{1}
\]
A second important aspect of determining the cost-effectiveness of LVRS versus MT is stating from whose viewpoint, or perspective we are evaluating cost-effectiveness. In this study, outcomes and costs will be estimated from two perspectives: the societal perspective (primary), and the health insurer perspective (secondary). The societal perspective, which includes all costs and health outcomes that flow from LVRS, is the most comprehensive and appropriate measure of cost-effectiveness [12]. It is also important, however, to recognize the health insurer perspective. Health insurers, who make the bulk of health care resource allocation decisions in the United States, generally consider only costs that they are directly accountable for when making resource allocation decisions for their insured populations. It will be important to compare the cost-effectiveness of LVRS from both perspectives, because it is possible that LVRS might be cost-effective from one perspective but not from another. In this case, policymakers may need to consider enacting policies that encourage utilization of LVRS in ways that maximize the benefits to society.

Medical Alternatives to LVRS

In cost-effectiveness analysis, it is important to define and justify the therapy or therapies that will be compared to the medical intervention of interest. Usually, the competing therapy is what would be considered the best alternative care of the patient prior to introduction of the new technology. In the NETT, the alternative to surgery is MT. Since MT is considered the best alternative for patients with emphysema, it is also an appropriate choice for the economic analysis. In the clinical trial, two LVRS surgical approaches are being compared: median sternotomy and video-assisted thoracoscopy. Although power calculations indicate that the number of subjects planned for this trial are sufficient to evaluate the overall cost-effectiveness of LVRS, there may be insufficient numbers to evaluate the cost-effectiveness of each surgical approach compared to MT. Because person-to-person variation in costs is usually much greater than variation in effects, the number of patients required to establish cost-effectiveness is usually greater than the number needed to establish clinical efficacy alone [14].

All subjects enrolled in the NETT will undergo a pulmonary rehabilitation program prior to randomization into the surgical or medical therapy arms. Although evidence exists that pulmonary rehabilitation may improve outcomes for patients with emphysema, it has not traditionally been part of standard therapy for this condition in the United States [15, 16]. Thus, it would be appropriate to test the efficacy and cost-effectiveness of either LVRS or pulmonary rehabilitation alone in comparison to MT for patients with emphysema. Because pulmonary rehabilitation is integrated into the trial as a required preliminary intervention for all trial participants, however, it will not be possible to estimate the incremental cost-effectiveness of rehabilitation (although its impact on quality of life will be assessed).
Identification and Valuation of Measures of Effectiveness and Costs

MEASURES OF EFFECTIVENESS. The measure of effectiveness for this cost-effectiveness analysis is quality-adjusted life years (QALYs), a measure of life expectancy, modified by patient-derived estimates of quality of life over this time period. Measures of health-related quality of life, when they reflect individual preferences for particular states of health, are known as utilities. Utilities are measured on a scale from 0 (death) to 1 (optimal health). The utility values (called weights) are obtained by interviewing patients using standardized survey techniques at regular intervals over time. Average utility weights for the treatment and control groups are multiplied by the percent surviving each period (those who have died have a utility of 0) to obtain a QALY estimate for each group. The difference in the QALY estimates for each group, which can be shown graphically (Fig 2) is the gain in quality-adjusted life expectancy afforded by the treatment. This is reflected by the difference under the quality-adjusted survival curves. For example, if subjects in the LVRS arm lived an average of 2 years after their operation and had an average utility score of 0.7 over this time period, then they would be assigned 1.4 QALYs. The NETT clinical protocol calls for measurement of health-related quality of life using several measures of general health status and emphysema-specific health status. The quality of life survey instrument that is most salient to the cost-utility analysis is the Quality of Well Being (QWB) questionnaire, a validated general health status measure that contains several domains, such as mobility, physical activity, and social activity [11] (Table 2). The QWB has been used in studies of chronic obstructive pulmonary disease (COPD) patients for about 20 years, and has been shown to be valid, reliable, and responsive to changes in health status for individuals with this condition [17, 18]. A methodology has been developed to translate the responses from the QWB into utility weights that may be used to derive QALYs [11]. The QWB questionnaire will be administered at enrollment and at months 6, 12, 24, 36, 48, and 60 from the point of randomization. Survival estimates for patients in each trial arm for each time period postrandomization will be multiplied by utility weights for those time periods and summed to determine total QALYs for LVRS and MT.

COSTS. Costs are derived by identifying resources that are consumed during the course of care, and then assigning values or prices to each resource. When taking the perspective of society, it is important to consider all costs

**Table 2. Quality of Well-Being/General Health Policy Model: Domains and Step Definitions**

<table>
<thead>
<tr>
<th>Step No.</th>
<th>Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobility Scale (MOB)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>No limitations for health reasons</td>
</tr>
<tr>
<td>4</td>
<td>Did not drive a car, health related; did not ride in a car as usual for age (younger than 15 y), health related, or did not use public transportation, health related; or had or would have used more help than usual for age to use public transportation, health related</td>
</tr>
<tr>
<td>2</td>
<td>In hospital, health related</td>
</tr>
<tr>
<td>Physical Activity Scale (FAC)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>No limitations for health reasons</td>
</tr>
<tr>
<td>3</td>
<td>In wheelchair, moved or controlled movement of wheelchair without help from someone else; or had trouble or did not try to lift, stoop, bend over, or use stairs or inclines, health related; or limped, used a cane, crutches, or walker, health related; or had any other physical limitation in walking, or did not try to walk as far as or as fast as other the same age are able, health related</td>
</tr>
<tr>
<td>1</td>
<td>In wheelchair, did not move or control the movement of wheelchair without help from someone, or in bed, chair, or couch for most or all of the day, health related</td>
</tr>
<tr>
<td>Social Activity Scale (SAC)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>No limitations for health reasons</td>
</tr>
<tr>
<td>4</td>
<td>Limited in other (eg, recreational) role activity, health related</td>
</tr>
<tr>
<td>3</td>
<td>Limited in major (primary) role activity, health related</td>
</tr>
<tr>
<td>2</td>
<td>Performed no major role activity, health related, but did perform self-care activities</td>
</tr>
<tr>
<td>1</td>
<td>Performed no major role activity, health related, and did not perform or had more help than usual in performance of one or more self-care activities, health related</td>
</tr>
</tbody>
</table>
stemming from a therapy. These include the costs of: (1) direct medical care (including preoperative evaluation, the operation, and all emphysema-related care after surgery); (2) nonmedical care related to the treatment (such as the cost of traveling to and from the clinic); (3) the value of time that family and friends spend caring for the patient; and (4) the value of the patient's time in treatment (Table 3).

As mentioned above, health insurers would generally not consider costs other than direct medical care. In addition, although direct medical care costs would also include the cost of nursing home care, the Medicare program provides limited coverage of this service. We will account for the Medicare perspective by omitting nonmedical costs and including only the cost of the first 100 days of nursing home care covered by Medicare.

Since the great majority of patients in this study will be enrolled in the Medicare program, the values assigned to each resource will be the reimbursement amounts that Medicare provides for the services. Since Medicare reimbursements for hospital, outpatient, and physician services are often lower than what private health insurers will pay for the same service, the total costs of care that will be estimated for each treatment arm in this study might be considered conservative in this respect.

### Accounting for Time Preference When Valuing Future Costs and Effects

In general, people prefer to receive health benefits today and incur the costs sometime in the future, all other things being equal. From an economic point of view, this phenomenon involves trade-offs between current costs and future benefits. The costs may be purely psychic, such as the loss of pleasure from passing up a rich dessert. They may involve time, such as that used to undertake exercise programs, or they may involve financial and nonfinancial resources. Health benefits typically take the form of reductions in the probability of mortality or morbidity from disease sometime in the future. The acceptance of a current cost for a future benefit constitutes an investment, and individuals and health payers differ in their willingness or ability to undertake investments. That is, they have different time preferences.

For example, most people faced with the question, "Would you rather have $100 now, or $103 in 1 year?" will prefer to take the money today rather than wait 1 year for the extra $3. Time preference applies to both health care costs and benefits, including survival. To account for this characteristic of human nature, health economists use a mathematical procedure to decrease the future value of costs and benefits associated with a particular intervention, a practice known as discounting. Some have criticized the practice of discounting health benefits on the grounds that future health and life is not a "commodity" like other goods and services. In defense, economists note that discounting costs but not benefits can lead to a situation where a health intervention will become more and more cost-effective as the program is delayed farther and farther into the future. In addition, evidence exists that individuals internally "discount" future health benefits at the same rate as costs. Because of these issues, most health economists take the position that discounting is necessary. In the economic analysis of the NETT, the base "discount rate" for future costs and benefits will be 3% [12], but this value will ultimately be varied between 0% and 10% in separate analyses.

### Allowance for Uncertainty in the Estimates

Two important sources of uncertainty must be addressed in the CEA of the NETT. The first source is primarily a statistical issue: With what degree of confidence can we say that the cost-effectiveness ratio we derive from the trial is the true incremental cost-effectiveness of LVRS? As is routinely done for the clinical portion of random-
ized trials, this can be accomplished by creating a confidence interval around the estimate of incremental cost effectiveness. Creating the interval is technically difficult, and economists have only recently devised methods for estimating these intervals [19]. These intervals can be used to present the data in ways that are helpful for decision-makers; for example, by stating that there is a 90% probability that the incremental cost-effectiveness of LVRS is at, or below, a certain threshold value.

The second source of uncertainty is how closely the cost-effectiveness estimates derived in the artificial situation of a clinical trial will represent cost-effectiveness in the "real world" setting. Here, there are several issues to consider. One issue of concern to trial investigators is that some patients who are randomized to the medical therapy arm may obtain surgery outside the clinical trial. Including these patients as originally randomized for analysis (an "intent-to-treat" analysis) would bias both the final cost and outcome estimates. If a substantial proportion of patients in the medical therapy arm obtain surgery outside the trial, the analysis will need to be rerun excluding such patients and then comparing the results to an intent-to-treat analysis. If the differences are great, both results may have to be presented. A second issue is that patient selection criteria for the trial have been made with limited knowledge. If it is possible to reliably identify patients who are going to have a particularly poor or good outcome prior to surgery, then guidelines might be established recommending against or for surgery in these subgroups. In this case, performing a separate cost-effectiveness analysis for study patients who meet guidelines would be appropriate. Finally, as with other carefully designed and monitored clinical trials, outcomes are likely to be better for both LVRS and MT patients than is typical for community practice. Thus, commonly stated concerns about the external validity of clinical trials also translate to the cost-effectiveness analysis. Health economists address this issue with a technique called sensitivity analysis. Here, one examines the sensitivity of the primary cost-effectiveness estimate to alternative scenarios that might more closely reflect "real world" uses and outcomes for LVRS.

Several analytic steps will be performed to attempt to identify outcomes and costs that are likely to reflect typical clinical use of LVRS. First, the cost-effectiveness of LVRS will be estimated after removing research protocol-induced costs. To identify these elements, principal investigators from the participating NETT centers will be polled to identify resources that are unlikely to be utilized outside the clinical trial setting. Second, cost-effectiveness ratios will be calculated using data for subgroups of trial enrollees (eg, upper and lower bounds of the eligible age range, pulmonary function parameters, and QWB score at entry). These analyses may help predict the cost-effectiveness when LVRS is applied to patients that fall somewhat outside the eligibility criteria established in the NETT protocol. Finally, the cost-effectiveness ratio for LVRS will be reanalyzed after varying the values of key input parameters (for example, the cost of the surgery itself), both individually (one-way sensitivity analysis) and simultaneously (two and n-way sensitivity analysis). Worst- and best-case cost-effectiveness ratios will then be calculated using the upper and lower bounds of 95% confidence intervals derived for the input parameters that were used to calculate the baseline cost-effectiveness ratio. This analysis will be used to account for trends that occur over the course of the NETT trial. For example, it is possible that average postoperative hospital length of stay will fall over the course of the trial as trial participants gain experience with managing these patients. Using a simple average of hospitalization costs obtained throughout the trial might produce an overestimate of the true costs of hospital care that can be expected following the trial. To address trending over time, time-series analysis regression techniques will be used. For parameters where a trend is found, the cost-effectiveness ratio will be estimated using: (1) average values for inputs obtained during the last year of observation; (2) predicted input parameters for the end of the period of observation from the time-series model.

**Interpretation and Application of the Results**

If patient outcomes were so improved after LVRS compared to MT that the initial cost of surgery was more than offset by savings from reduced emphysema-related care in the years following surgery, LVRS would dominate MT (quadrant C, Fig 1). Likewise, if outcomes were worse and lifetime costs were higher for LVRS patients, MT would dominate LVRS. Many experts associated with the NETT, however, expect an outcome where LVRS is both more expensive and more effective than standard medical therapy for emphysema (quadrant A in Fig 1). Even if we assume that this will be the case, the magnitude of the difference in costs and benefits remains a critically important issue. In today’s budget-driven health care system, it is not unreasonable to argue that the relative cost-effectiveness or cost-ineffectiveness of LVRS may ultimately determine the degree to which it is adopted by the health care system at large.

We are seeking to determine whether LVRS is “cost-effective” compared to MT. This of course begs the question of whether there is a widely agreed upon threshold value for cost-effectiveness. A commonly cited manuscript suggests that interventions with an incremental cost-effectiveness ratios of $27,000 per QALY (1997 US dollars) or less had “strong evidence” of cost-effectiveness, while those ratios between $27,000 and $125,000 per QALY had “moderate evidence of cost-effectiveness” [20]. Still, decision-makers are more likely to evaluate the cost-effectiveness of LVRS relative to the cost-effectiveness of other common health care interventions than by whether it exceeds a reference value. Table 4 lists cost-effectiveness ratios for several common medical interventions. Cost-effectiveness studies have not been major factors in decisions to adopt or not adopt new technologies in the United States. Still, if LVRS is shown to have marginal effectiveness and a very high cost compared to other common therapies, it is likely that health insurers will erect barriers to limit their reim-
Table 4. Cost-Effectiveness Ratios for Selected Health Care Interventions (1995$)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Comparator</th>
<th>Target Population</th>
<th>$ per QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTCA</td>
<td>No intervention</td>
<td>Patients with severe angina and 1-vessel coronary disease</td>
<td>7,700-10,000</td>
</tr>
<tr>
<td>Annual FOBT screen for colorectal cancer</td>
<td>No screening</td>
<td>Population ages 50–75</td>
<td>18,000</td>
</tr>
<tr>
<td>Coronary angioplasty and revascularization if indicated</td>
<td>Medication only</td>
<td>AMI patients, 45–74, positive exercise test or angina, and prior MI</td>
<td>17,500-45,000</td>
</tr>
<tr>
<td>Vinorelbine + cisplatin chemotherapy</td>
<td>Vindesine + cisplatin chemotherapy</td>
<td>Patients with non-small cell lung cancer</td>
<td>26,000</td>
</tr>
<tr>
<td>Autologous bone marrow transplantation</td>
<td>Standard chemotherapy, cyclophosphamide, methotrexate, fluorouracil</td>
<td>Women, 45, with metastatic breast cancer</td>
<td>110,000</td>
</tr>
<tr>
<td>Lung-transplantation</td>
<td>Medical therapy</td>
<td>Patients with end-stage lung disease</td>
<td>100,200–177,000</td>
</tr>
<tr>
<td>Perioperative autologous blood donation to prevent HBV, HCV, and HIV</td>
<td>No autologous blood donation</td>
<td>Patients undergoing hip or knee replacement</td>
<td>180,000</td>
</tr>
</tbody>
</table>

AMI = acute myocardial infarction; FOBT = fecal occult blood test; HBC = hepatitis C virus; HBV = hepatitis B virus; HIV = human immunodeficiency virus; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; QALY = quality adjusted life years.

Conclusion

In today's cost-conscious health care environment, obtaining accurate economic information regarding new medical technologies has become extremely important. If LVRS is shown to be beneficial for patients with severe emphysema, the economic impact of widespread adoption of LVRS will be substantial. The results of the analysis—which is one of the largest clinical trials to include a cost-effectiveness analysis—will provide high-quality economic evidence to guide medical decision-making. This study will employ standardized and accepted methods for conducting and presenting economic analyses, which will facilitate the usefulness of the results for policymaking and comparing the economic outcomes for LVRS to other advanced technologies for the treatment of chronic illness.

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