

# Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: National Emphysema Treatment Trial Research Group. Cost Effectiveness of Lung-Volume-Reduction Surgery for Patients with Severe Emphysema. *N Engl J Med* 2004;348:2092-102.

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 SUPPLEMENTARY APPENDIX 1.  
 COST-EFFECTIVENESS ANALYSIS
 

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**COSTS***Medical Costs*

Monthly costs for medical care were derived from Medicare-claims records and pharmacy costs. Medicare data were provided by the Centers for Medicare and Medicaid Services (CMS). Data on Medicare costs were retrieved from the data bases of inpatient, outpatient, physician, hospice, and skilled-nursing–facility claims. Claims specific to the National Emphysema Treatment Trial (NETT) were identified by CMS through an internal procedure (DemoID30) and provided in a separate data base. Monthly costs were converted to June 2002 dollars with the use of the seasonally adjusted monthly U.S.-city average Consumer Price Index (CPI) for medical care. Series Id CUSR0000SAM data extracted from the CPI Web site were used.<sup>1</sup>

Pharmacy costs were estimated for medications related to chronic obstructive pulmonary disease. The use of oral corticosteroids, inhaled corticosteroids, and bronchodilators was reported by patients at base line and at follow-up clinic visits. Patients could indicate the use of up to six different bronchodilators. Costs for each medication were assigned on the basis of the average wholesale price listed in the *Red Book*<sup>2</sup>: \$1.64 for oral corticosteroids, \$85.17 for inhaled corticosteroids, and \$44.15 for each bronchodilator. A monthly dispensing fee of \$2.50 was added for each medication. Monthly use of medication was assumed to remain constant between visits.

*Nonmedical Costs*

Nonmedical costs were estimated on the basis of costs associated with the time spent by caregivers, the time spent by the patient, and travel distance. Patients reported the weekly number of caregiver-hours at base line, at follow-up visits, and through telephone surveys. Weekly hours were multiplied by four to estimate the monthly hours of caregiver time. For monthly caregiver-hours during months without surveys, we used the average of values from the previous questionnaire and the next questionnaire.

The caregiver-hours for the month of the patient's death were prorated according to the number of days in the month that the patient was alive. Estimates of monthly costs for caregivers were generated by multiplying the number of caregiver-

hours by the median usual weekly earnings of full-time workers 20 to 64 years of age receiving wages or a salary during the third quarter of 2002 (\$626, without seasonal adjustment).<sup>3</sup> A 35-hour workweek was assumed.

The cost of the time patients spent receiving treatment was estimated on the basis of utilization data from Medicare claims. The total monthly time for each patient was estimated by adding eight hours for each day spent in the hospital, emergency room, outpatient clinic, skilled nursing facility, or hospice. Monthly costs for patients' time were then calculated by multiplying the monthly number of hours by the median usual weekly earnings of full-time workers 65 years of age or older receiving wages or a salary during the third quarter of 2002 (\$501, without seasonal adjustment).<sup>3</sup> A 35-hour workweek was assumed.

Travel costs were estimated on the basis of the number of miles traveled from the patient's home to study clinics and satellite rehabilitation centers. Patients provided their home ZIP Code at base line and at follow-up visits. Patients may have been assigned to attend additional rehabilitation sessions that took place at satellite centers. ZIP Codes were linked to a data set at SAS Institute (Cary, N.C.) that contains information on longitude and latitude for the ZIP centroid. The Great Circle Distance Formula was used to estimate the distance in miles between ZIP Codes. A cost of \$0.365, based on the federal mileage-reimbursement rate as of January 21, 2002, was accrued for each mile traveled.<sup>4</sup> Travel costs were assigned to the month in which the travel occurred. Additional rehabilitation sessions were assumed to have taken place during the first month after randomization.

**QUALITY OF WELL-BEING SCORES**

Quality of Well-Being scores were recorded at base line and at follow-up clinic visits. Monthly Quality of Well-Being scores were estimated on the assumption that scores remained constant between clinic visits. Missing scores for a visit were imputed as half the lowest score for all patients who filled out a form at the corresponding visit. Quality of Well-Being scores were imputed only if the patient survived beyond the end of the period during which that visit was to occur. Quality of Well-Being scores were assumed to remain constant between forms. Table A1 summarizes the monthly Quality of Well-Being scores for all patients not at high risk and among subgroups of

**Table A1. Monthly Quality of Well-Being Scores for Patients without High Risk, According to Period.\***

Variable	Surgery Group			Medical-Therapy Group			P Value
	No. of Patients	Mean ( $\pm$ SD) Score	Median Score	No. of Patients	Mean ( $\pm$ SD) Score	Median Score	
<b>All patients</b>							
0–6 Mo	531	0.576 $\pm$ 0.113	0.570	535	0.559 $\pm$ 0.112	0.550	0.01
7–12 Mo	465	0.563 $\pm$ 0.161	0.583	483	0.483 $\pm$ 0.183	0.524	<0.001
13–24 Mo	407	0.549 $\pm$ 0.179	0.571	424	0.463 $\pm$ 0.200	0.513	<0.001
25–36 Mo	277	0.530 $\pm$ 0.177	0.553	278	0.444 $\pm$ 0.192	0.497	<0.001
<b>Patients with predominantly upper-lobe emphysema and low exercise capacity</b>							
0–6 Mo	137	0.566 $\pm$ 0.119	0.551	148	0.528 $\pm$ 0.116	0.524	0.007
7–12 Mo	125	0.587 $\pm$ 0.156	0.597	127	0.441 $\pm$ 0.187	0.471	<0.001
13–24 Mo	108	0.564 $\pm$ 0.176	0.576	109	0.397 $\pm$ 0.199	0.459	<0.001
25–36 Mo	79	0.545 $\pm$ 0.172	0.554	65	0.369 $\pm$ 0.189	0.429	<0.001
<b>Patients with predominantly upper-lobe emphysema and high exercise capacity</b>							
0–6 Mo	204	0.585 $\pm$ 0.112	0.585	212	0.577 $\pm$ 0.106	0.572	0.440
7–12 Mo	182	0.572 $\pm$ 0.162	0.596	196	0.518 $\pm$ 0.165	0.553	0.002
13–24 Mo	159	0.560 $\pm$ 0.181	0.595	182	0.509 $\pm$ 0.179	0.542	0.009
25–36 Mo	102	0.548 $\pm$ 0.174	0.572	130	0.470 $\pm$ 0.186	0.517	0.001
<b>Patients with non–upper-lobe emphysema and low exercise capacity</b>							
0–6 Mo	82	0.548 $\pm$ 0.109	0.542	65	0.534 $\pm$ 0.109	0.523	0.431
7–12 Mo	69	0.508 $\pm$ 0.146	0.539	61	0.454 $\pm$ 0.188	0.509	0.070
13–24 Mo	61	0.492 $\pm$ 0.186	0.506	49	0.434 $\pm$ 0.193	0.505	0.111
25–36 Mo	40	0.485 $\pm$ 0.195	0.528	27	0.481 $\pm$ 0.156	0.501	0.929

\* Quality of Well-Being scores range from 0 to 1, with higher scores indicating a higher quality of life. The period was measured in months from randomization. High-risk patients and 12 patients with no Medicare claims were excluded from the analysis. Subgroups were defined according to characteristics at the time of randomization. The numbers of patients given are the numbers of patients who were alive at the start of the period. P values were calculated by the test for equality of means, with the use of Student's t-test with equal variances. Low exercise capacity was defined as a base-line maximal workload of 25 W or less for women and 40 W or less for men; a workload above these thresholds was considered to represent high exercise capacity.

patients not at high risk who were alive at the start of the period, according to the time after randomization.

#### INCREMENTAL COST-EFFECTIVENESS RATIOS

##### *Uncertainty in Incremental Cost-Effectiveness Ratios*

To depict uncertainty in the estimates of cost effectiveness, cost-effectiveness–acceptability curves were constructed according to the bootstrap method as applied to projected survival and the

estimates of cost and quality-adjusted life-years gained for each patient. The curve represents the probability that lung-volume–reduction surgery is associated with a cost per quality-adjusted life-year gained that is lower than the corresponding cost-effectiveness ratios (ceiling ratios) shown on the x axis. The value of the ceiling ratio at a probability of 0.5 is the median cost per quality-adjusted life-year gained for lung-volume–reduction surgery.

*Extrapolation to Estimate Incremental Cost-Effectiveness Ratios to 10 Years*

Incremental cost-effectiveness ratios were extrapolated out to 10 years with the use of assumptions about survival, accrual of costs, and future Quality of Well-Being scores. Models were fitted to observed trends in these variables and then used to predict the results at 10 years of follow-up.

*Analysis of Trends in Survival*

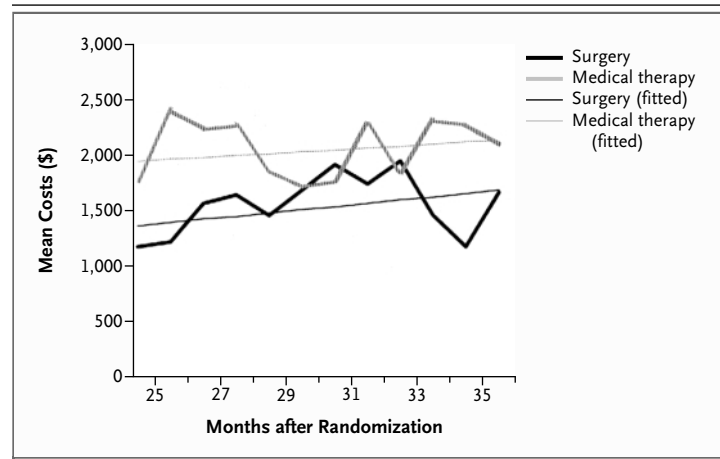
In an effort to estimate long-term survival more accurately, the log-logistic model was fitted to survival data from only those patients who survived for at least one year. Several models were tried; the log-logistic model provided the best fit to the observed data, according to expert opinion. Regression analysis was used to determine the relation between survival and censoring information for survivors and treatment-group assignment in order to derive estimates of the parameters to be used in the model. Monthly survival data were extrapolated beyond three years with the use of the intercept and regression parameters for the log-logistic model.

Because in some subgroups there was a survival advantage for lung-volume-reduction surgery as compared with medical therapy at three years, several models were constructed for all groups to predict outcomes under alternative assumptions of the duration of the relative survival benefit. In the base case, point estimates for the relative survival advantage were first set at observed levels for year 3 (for example, the relative risk of death among all patients, excluding the high-risk subgroup, was 0.89 [P=0.31]). In separate models, the relative hazard of death was then assumed to change to 1.0 (no benefit) at years 3, 5, and 10. Changes in the relative hazard over time were modeled as a linear function, starting from 3 years after randomization and continuing until the date specified (3, 5, or 10 years). Future costs and quality-adjusted life-years were discounted by 3 percent per year.

*Analysis of Trends in Mean Costs and Quality of Well-Being Scores*

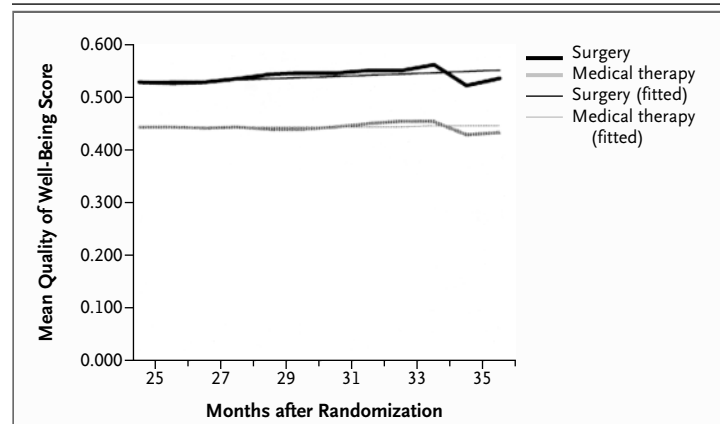
A least-squares linear-regression model was used to estimate the mean costs and Quality of Well-Being scores. The model analyzed the mean costs and Quality of Well-Being scores, with time (in months after randomization) as the predictor. Mean costs and Quality of Well-Being scores from year 3 were used for the regression analysis. Re-

gression parameters were estimated separately for the surgery group and the medical-therapy group. The regression estimates for the intercept and time from randomization for mean costs were \$635.74 and \$28.87 (P=0.22) for the surgery group and \$1,515.23 and \$17.05 (P=0.48) for the medical-therapy group. The regression estimates for the intercept and time from randomization for mean Quality of Well-Being scores were 0.478 and 0.002 (P=0.11) for the surgery group and 0.440 and 0.000 (P=0.69) for the medical-therapy group. Figures A1 and A2 show mean costs and



**Figure A1.** Mean Costs and Fitted Linear-Regression Curves for 25 to 36 Months after Randomization in the Surgery Group and the Medical-Therapy Group.

The high-risk subgroup and 12 patients with no Medicare claims were excluded from the analysis.



**Figure A2.** Mean Quality of Well-Being Scores and Fitted Linear-Regression Curves for 25 to 36 Months after Randomization in the Surgery Group and the Medical-Therapy Group.

The high-risk subgroup and 12 patients with no Medicare claims were excluded from the analysis.

**Table A2. Cost-Effectiveness Ratios for Lung-Volume-Reduction Surgery as Compared with Medical Therapy, under Alternative Time Horizons and Assumptions Regarding Duration of Survival Benefit from Surgery.\***

Survival-Benefit Assumption	5 Years			10 Years		
	Mean No. of Quality-Adjusted Life-Years	Mean Total Costs	Incremental Cost-Effectiveness Ratio for Surgery	Mean No. of Quality-Adjusted Life-Years	Mean Total Costs	Incremental Cost-Effectiveness Ratio for Surgery
			\$			\$
Relative hazard of death=1.0 after 3 yr						
Surgery	2.17	128,879	88,000	3.30	194,502	53,000
Medical therapy	1.77	94,013		2.49	150,925	
Relative hazard of death=1.0 after 5 yr						
Surgery	2.18	129,218	87,000	3.33	195,887	54,000
Medical therapy	1.77	94,013		2.49	150,925	
Relative hazard of death=1.0 after 10 yr						
Surgery	2.18	129,367	86,000	3.37	198,129	54,000
Medical therapy	1.77	94,013		2.49	150,925	

\* Future costs and benefits were discounted by 3 percent per year. The duration of the relative survival benefit from surgery was modeled as a linear function, from 3 years after randomization to the date specified (3, 5, or 10 years). Survival in the medical-therapy group was modeled with the use of a log-logistic distribution.

Quality of Well-Being scores and their fitted linear-regression curves, respectively.

*Alternative Assumptions Regarding Duration of Survival Benefit*

Increasing the duration of the relative survival benefit from surgery to 5 years and then to 10 years had very little effect on the incremental 10-year cost-effectiveness ratio for surgery as compared with medical therapy (Table A2).

*Sensitivity Analysis of the Discount Rate*

The effect of varying the discount rate applied to costs and quality-adjusted life-years gained on the 10-year incremental cost-effectiveness ratios was examined with a sensitivity analysis. Discount rates are applied per year. Discount rates of 0, 3, 5, and 10 percent were analyzed. Table A3 reports the 10-year cost-effectiveness ratios at the different discount rates, assuming a relative hazard of death of 1.0 at year 3 as the base case.

**Table A3. Ten-Year Cost-Effectiveness Ratios with Discount Rates Applied.\***

Discount Rate	10-Yr Incremental Cost-Effectiveness Ratio for Surgery
<b>All patients</b>	\$
0.00	49,000
0.03	53,000
0.05	57,000
0.10	65,000
<b>Patients with predominantly upper-lobe emphysema and low exercise capacity</b>	
0.00	16,000
0.03	21,000
0.05	25,000
0.10	34,000
<b>Patients with predominantly upper-lobe emphysema and high exercise capacity</b>	
0.00	51,000
0.03	54,000
0.05	56,000
0.10	61,000

**Table A3. Continued.**

Discount Rate	10-Yr Incremental Cost-Effectiveness Ratio for Surgery
<b>Patients with non–upper-lobe emphysema and low exercise capacity</b>	
0.00	–46,000
0.03	–38,000
0.05	–31,000
0.10	–14,000

\* High-risk patients and 12 patients with no Medicare claims were excluded from the analysis. Subgroups were defined according to characteristics at the time of randomization. Low exercise capacity was defined as a baseline maximal workload of 25 W or less for women and 40 W or less for men; a workload above these thresholds was considered to represent high exercise capacity. In this case, a negative cost-effectiveness ratio indicates that the cost of surgery per quality-adjusted life-year gained was lower than the cost of medical therapy per quality-adjusted life-year gained.

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