Measurement of Health-Related Quality of Life in the National Emphysema Treatment Trial*

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Measurement of Health-Related Quality of Life in the National Emphysema Treatment Trial*

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Purpose: **To evaluate two generic and two disease-specific measures of health-related quality of life (QOL) using prerandomization data from the National Emphysema Treatment Trial (NETT).**
Method: **The analyses used data collected from the 1,218 subjects who were randomized in the NETT. Patients completed evaluations before and after completion of the prerandomization phase of the NETT pulmonary rehabilitation program. Using data obtained prior to participation in the rehabilitation program, QOL measures were evaluated against physiologic and functional criteria using correlational analysis. The physiologic criteria included estimates of emphysema severity based on FEV_1 and measures of Pa_{O_2} obtained with the subject at rest and breathing room air. Functional measures included the 6-min walk distance (6MWD), maximum work, and hospitalizations in the prior 3 months.**
Results: **Correlation coefficients between QOL measures ranged from −0.31 to 0.70. In comparison to normative samples, scores on general QOL measures were low, suggesting that the NETT participants were quite ill. All QOL measures were modestly but significantly correlated with FEV_1, maximum work, and 6MWD. Patients who had stayed overnight in a hospital in the prior 3 months reported lower QOL on average than those who had not been hospitalized. There were significant improvements for all QOL measures following the rehabilitation program, and improvements in QOL were correlated with improvements in 6MWD.**
Comment: **The disease-specific and general QOL measures used in the NETT were correlated. Analyses suggested that these measures improved significantly following the rehabilitation phase of the NETT.** ***(CHEST 2004; 126:781–789)***

Key words: COPD; lung volume reduction surgery; outcomes assessment; quality of life

Abbreviations: ADL = activity of daily living; DLCO = diffusing capacity of the lung for carbon monoxide; LVRS = lung volume reduction surgery; MCS = mental component score; 6MWD = 6-min walk distance; NETT = National Emphysema Treatment Trial; PCS = physical component score; QOL = quality of life; QWB-SA = self-administered version of the quality-of-well-being scale; SF-36 = medical outcomes study 36-item short form; SGRQ = St. George Respiratory Questionnaire; SOBQ = shortness-of-breath questionnaire

The National Emphysema Treatment Trial (NETT) is a multicenter randomized clinical trial that is designed to compare lung volume reduction surgery (LVRS) to medical therapy.[1] Subjects with moderate-to-severe emphysema were randomly assigned to usual medical therapy alone or to usual medical therapy plus LVRS. All patients in the trial participated in pulmonary rehabilitation prior to randomization.

Although the primary outcome measures in the NETT are survival and maximum exercise capacity, quality of life (QOL) was chosen as an important secondary outcome. QOL measures have become

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common in major clinical trials. A recent PUBMED review identified > 140 articles under the headings "Quality of Life" and "COPD," and > 20 articles under the headings "Quality of Life" and "LVRS." Several studies[2–7] have suggested that there are improvements in patient QOL following LVRS. Despite the interest in QOL as an outcome in COPD clinical studies, there is still uncertainty about the optimum methods of measurement. The NETT used both disease-specific and general QOL measures. The disease-specific measures were chosen because of their direct relevance to patients with lung disease. Many authors think that these measures are necessary because they are sensitive to the effects of interventions such as pulmonary rehabilitation.[8] General measures were included because they can capture unanticipated side effects and benefits of treatment,[9] and because they are necessary for cost/utility analysis.[10] However, general measures may be less responsive to the lung disease-specific effects of interventions and may be less meaningful to clinicians.[11] Few studies have evaluated the properties of general and disease-specific measures for patients with advanced lung disease.

The purpose of this report is to evaluate four different measures of health-related QOL used in the NETT. The measures are the self-administered version of the quality-of-well-being scale (QWB-SA),[12] the medical outcomes study 36-item short form (SF-36),[13,14] the St. George Respiratory Questionnaire (SGRQ),[15] and the University of California, San Diego, shortness-of-breath questionnaire (SOBQ).[16] The NETT offers a unique opportunity to evaluate the functioning of these questionnaires, because patients with emphysema were evaluated using a large number of physiologic and clinical measures close to the time when the QOL measures were obtained. The results reported here were obtained prior to randomization.

Materials and Methods

Subjects

The subjects were 746 men and 472 women who volunteered for the NETT. The average age of the participants was 67 years. Nearly 95% of the participants were white, and 3.4% were African-American. Participants came from all 17 NETT sites. The inclusion criteria included the following: (1) radiographic evidence of bilateral emphysema; (2) studies demonstrating severe airflow obstruction and hyperinflation; and (3) completion of a prerandomization pulmonary rehabilitation program. Exclusion criteria were formulated with the goal of excluding emphysema patients with certain characteristics, as follows: (1) characteristics that placed patients at high risk for perioperative morbidity and/or mortality; (2) emphysema that was thought to be unsuitable for LVRS; and (3) medical conditions or other circumstances that made it likely that the patient would be unable to complete the trial. The exclusionary criteria relating to cardiologic issues were based on the work of Goldman et al.[17] A more detailed description of the NETT methodology is available elsewhere.[1]

QOL Measures

In selecting measures for the NETT, it was decided to rely on questionnaires that could be self-administered by patients in a relatively short period of time. This was done for the following reasons: (1) to maximize data collection on the greatest number of patients, including those who were unable or unwilling to return for scheduled follow-up visits; (2) to minimize the time and effort required for questionnaire administration during follow-up visits, given the complexity and overall time required for the assessments; and (3) to allow for multiple questionnaires to be used.

For the general measures, the SF-36 and QWB-SA were selected. These have been widely used in health services research and can be self-completed by patients. For the disease-specific measures, the SGRQ[15] was selected because it can be completed easily by patients, and does not require structured and supervised administration. The SGRQ had been used successfully by several NETT centers. The SOBQ also was chosen because it can be completed easily by the patients, and because it provides information about breathlessness with various ADLs that can be helpful in the clinical evaluation and management of the rehabilitation program. It has been used successfully in research studies in pulmonary rehabilitation. In a study[16] comparing several strategies for measuring dyspnea in patients with COPD, it proved to be as valid and reliable as the baseline dyspnea index or the transition dyspnea index.

In a pilot test prior to their use with NETT patients, the four questionnaires (*ie*, SF-36, QWB-SA, SGRQ, and SOBQ) were self-administered to a group of patients who were similar to those eligible for the NETT. All four questionnaires were completed in an average time of < 30 min (maximum, 40 min) on the first administration with minimal instructions.

Description of Measures

The SF-36 is a 36-item general health status assessment questionnaire.[13] The SF-36 has nine separate scales, including the following: (1) physical functioning; (2) social functioning; (3) role limitations (physical); (4) role limitations (emotional); (5) emotional well-being; (6) energy/fatigue; (7) pain; (8) general health perceptions; and (9) current general health perceptions compared to 1 year ago. Data from the ninth scale are typically not reported and were excluded from these analyses. There are substantial reliability and validity data for the SF-36,[13,14,18,19] and the measure is perhaps the most common outcome-assessment instrument in use in contemporary health services research. SF-36 scores are reported as either raw scores or standardized T-scores. In this article, we report raw scores. Higher scores indicate better health status. The SF-36 has been factor-analyzed and reduced to two summary scores.[18] The physical component score (PCS) represents the four physical health scales (*ie*, physical functioning, role physical, bodily pain, and general health perceptions), while the mental component score (MCS) reflects the four mental health scales (*ie*, mental health, role emotional, vitality, and social functioning). We used both summary scores (PCS and MCS) and individual scale scores in our analysis.

The QWB-SA is a comprehensive measure of health-related QOL that includes the following five sections: acute symptoms; chronic symptoms; self-care; mobility; and social activity.[9,20–22] The observed level of function and the subjective symptomatic complaints are weighted by preference, or the utility for the state,

on a scale ranging from 0 (for dead) to 1.0 (for optimum function). The QWB-SA has been used in a wide variety of clinical and population studies[21–24] to evaluate therapeutic interventions in patients with a range of medical and surgical conditions. The average total daily score was analyzed in this report.

The SGRQ is a self-administered, standardized, 50-item instrument with three separate scales (*ie*, symptoms, activity, and impacts on daily life). A total score also can be calculated from the three component scores and is analyzed here. Specific questions carry varying weights. Lower scores on the SGRQ indicate wellness, while higher scores suggest greater disability. The questionnaire has been evaluated for reliability and validity in several studies of patients with chronic lung disease of varying severity, particularly COPD and asthma.[15]

The SOBQ is self-administered and asks subjects to rate their breathlessness for 21 various daily activities (plus 3 overall items) on a 6-point scale from none at all (0) to severe (4) to maximal or unable to do because of breathlessness (5).[16] The 21 activities of daily living (ADLs) can be grouped according to factor analysis into the following four categories: rest and light ADLs (factor 1), eight questions; moderate ADLs (factor 2), five questions; walking (factor 3), four questions; and strenuous ADLs (factor 4), four questions. In this analysis, we focus on the total score.

Physiologic Evaluation

Pulmonary function and gas exchange were assessed with spirometry, plethysmographic determination of the functional residual capacity, the single-breath diffusing capacity of the lung for carbon monoxide (DLCO) [only at the prerehabilitation evaluation], room air arterial blood gas levels measured with the patient at rest, and the maximal inspiratory and expiratory mouth pressures.[1]

Pulmonary Rehabilitation

All subjects participated in the prerandomization program, consisting of a pulmonary rehabilitation program composed of at least 16 to 20 sessions over > 6 to 10 weeks that was supervised by a NETT clinical center. Portions of the program could be carried out at a NETT-certified rehabilitation facility closer to the participant's home. Over 400 satellite centers participated in the study.

Components of the pulmonary rehabilitation program included the following: (1) a comprehensive evaluation of medical, psychosocial, and nutritional needs; (2) the setting of goals for education and exercise training; (3) exercise training (*ie*, lower extremity, flexibility, strengthening, and upper extremity); (4) education about emphysema, medical treatments, and the NETT; (5) psychosocial counseling; and (6) nutritional counseling.

Data Analysis

The data were analyzed using standard descriptive methods to estimate means and SDs and Pearson product moment correlations. The *t* test was used to compare the QOL measures for participants who had not been hospitalized in the 3 months prior to the assessment (1,039 patients) with those who had been in the hospital for ≥ 1 day (179 patients). To compare the relative performance of QOL measures in relation to the physiologic criteria, we compared the strength of the correlations. Because there were so many correlations for which pairwise comparisons of significance could be done, we used the Fisher *r*-to-Z transformation to calculate a range of values that would reach significance for the differences between any two correlations, given the minimum sample size. Using 1,218 patients as the sample size for the Fisher *r*-to-Z transformation to be conservative, we found a confidence interval of ± 0.06 for correlations in a range of differences between correlations of 0.20 to 0.40. More specifically, a correlation of 0.30 between a QOL and a physiologic measure for this sample size would be significantly different from a correlation measurement of < 0.24 or > 0.36. In addition, QOL scores obtained prior to and following rehabilitation were compared by *t* tests. Effect size for the prerehabilitation-to-postrehabilitation change was estimated by dividing the mean change by the SD of the change. A statistical software package (SPSS, version 10.0 for Macintosh; SPSS; Chicago, IL) was used to complete the calculations.

RESULTS

Table 1 summarizes the characteristics of the patients prior to completion of the NETT prerandomization rehabilitation program. Following these evaluations, all participants completed 6 to 10 weeks of comprehensive pulmonary rehabilitation. A second assessment was completed within 3 weeks prior to randomization. QOL measures were completed during the clinic visit prior to the initiation of rehabilitation, but could be completed at home following the completion of rehabilitation and returned to the clinic by mail for the second assessment.

The correlations among the QOL measures are shown in Table 2. The SF-36 MCS and PCS scores were originally derived from factor analysis, and were expected to be uncorrelated. With this exception, all other correlations in Table 2 are statistically significant, with values ranging from −0.31 to 0.70. Some of the correlations in Table 2 are negative. This occurs because good health on the SOBQ and SGRQ is associated with lower scores, while better health is associated with higher scores for the SF-36 and QWB-SA. Figure 1 places the means for the general QOL measures in context by showing the mean scores in relation to normative populations matched for age and gender. QWB-SA scores were multiplied by 100 to place them on approximately the same scale as the SF-36. For the QWB-SA and the SF-36 scales, the normative sample was older adults selected from the general population in Beaver Dam, WI.[25] Patients in the Beaver Dam sample had a mean age of 64.1 years. Since the Beaver Dam sample did not include PCS and MCS scores, we compared the NETT participants against general population norms for the US population in the age category 55 to 64 years, as reported by Ware.[13] These summary measures suggest that the participants in the NETT were quite ill. With the exception of SF-36 scores for bodily pain, all other measures show NETT participants to be well below the population norms. Considering the SF-36 summary scores, NETT patients had significant deficits as evaluated

Table 1—*Minimum Scores, Maximum Scores, Means, and SDs of Variables Prior to Completion of Rehabilitation

Variables	Minimum Score	Maximum Score	Mean Score	SD
Physiologic measures				
Pre-BD FEV_1, L	0.29	1.58	0.68	0.22
Pre-BD FVC, L	0.71	5.19	2.14	0.72
DLCO†	0.30	21.40	8.03	3.15
Maximum work, W	0	111	36.0	21.07
QOL measures				
SF-36				
Physical functioning	0	100	22.1	16.8
Role physical	0	100	20.9	30.8
Role emotional	0	100	68.5	41.0
Energy/fatigue	0	95	43.8	19.6
Emotional well-being	0	100	74.6	17.5
Social functioning	0	100	61.8	27.7
Bodily pain	0	100	75.8	23.7
General health perceptions	0	100	37.6	20.2
Physical health summary index	8.3	55.5	28.3	7.4
Mental health summary index	11.7	72.9	53.2	10.9
SGRQ total score	19.6	100	56.5	13.0
SOBQ total score	8	120	65.6	19.0
QWB-SA average score	0.09	1.00	0.54	0.12

*BD = bronchodilator. No. of participants varies from 1,204 to 1,218 due to missing data.
†DLCO values are unadjusted for hemoglobin.

by Z tests (in relation to population norms[26]) on the PCS ($p < 0.01$) but were comparable to those of the normative population.

Correlations between the QOL measures and physiologic parameters are shown in Table 3. Maximum work was significantly correlated ($p < 0.001$) with each QOL measure. FEV_1 was correlated with each QOL measure using at least a $p < 0.05$ criterion. In every case evaluated, the SOBQ was more highly correlated with the physiologic measures than with the other health-related QOL measures. Although statistically significant, the correlations among pulmonary function measures (*ie*, FEV_1 and FVC) and QOL measures (*ie*, MCS and QWB-SA) tended to be low. The relationships were slightly stronger among FEV_1, FVC, and the disease-specific SOBQ. For example, the correlation between SOBQ and FVC was −0.18, and the correlation between SOBQ and FEV_1 was −0.23. Using confidence intervals from the Fisher *r*-to-Z transformation, the correlations between disease-specific QOL measures and physiologic parameters were determined to be significantly higher than those between general QOL measures and physiologic parameters. The only nonsignificant relationships shown in Table 3 are between PCS with FVC and PCS with DLCO. The disease-specific and generic QOL measures were moderately correlated with one another (Table 2).

Table 2—*Pearson Correlations Between QOL Measures at Postrehabilitation Baseline

Variables	SF-36 PCS	SF-36 MCS	SOBQ	QWB-SA	SGRQ Total
SF-36					
PCS	1.0	0.01	−0.54	0.423	−0.57
MCS		1.0	−0.31	0.35	−0.43
SOBQ			1.0	−0.44	0.70
QWB-SA				1.0	−0.52
SGRQ total					1.0

*With exception of SF-36 physical and SF-36 mental, all other correlations are statistically significant ($p < 0.01$).

Although the range of hospital days for the 3 months prior to study enrollment was 0 through 44, most participants (1,039 patients) had not been hospitalized. The *t* tests comparing QOL for those who had been hospitalized and for those who had not showed a significant difference for the PCS and MCS components of the SF-36, the QWB-SA, the disease-specific SGRQ total score, and the SOBQ. For all comparisons, differences were statistically significant at the 0.001 level (Table 4). Effect size was calculated by dividing the difference between those who had been hospitalized and those who had not been in the hospital by the SD of those who had been hospitalized. The observed effect size ranged from 0.28 (for the SF-36 PCS) to 0.46 (for the SGRQ). In detecting the effect of hospitalization, the disease-specific measures performed only slightly better than the generic measures.

The prerehabilitation-to-postrehabilitation changes showed significant improvements on all QOL measures (Table 5). The largest effect size was observed for the SGRQ followed by the generic QWB-SA. Overall, the

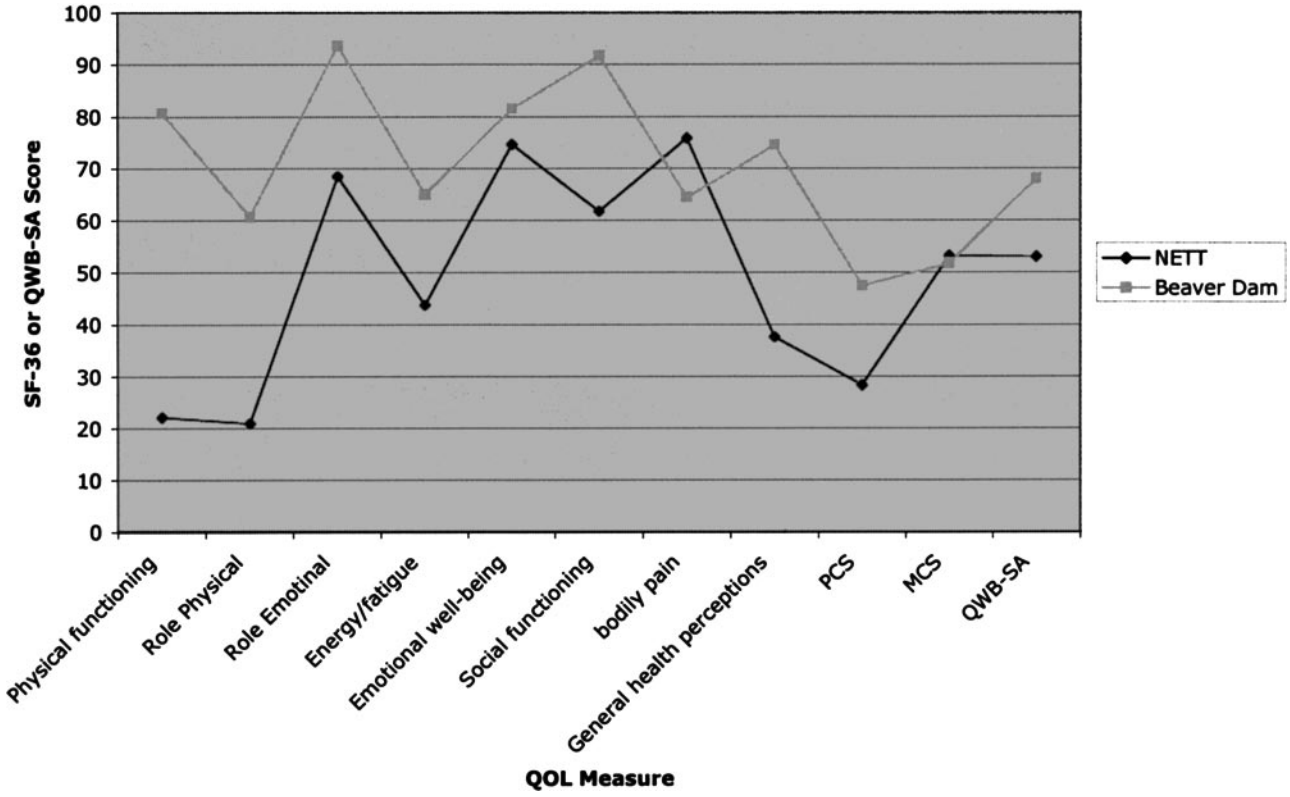

FIGURE 1. Comparison of QOL scores for NETT and normative samples. QWB-SA and SF-36 scale scores are from the 1-year normative sample of the Beaver Dam eye study for subjects with a mean age of 64 years.[25] MCS and PCS norms from the US general population are for the age group 55 to 64 years, as reported by Ware.[13] QWB-SA scores have been multiplied by 100 to place them in units similar to SF-36 scores.

effect sizes were comparable across the measures. The correlations among the changes in QOL measures and the change in the 6-min walk distance (6MWD) from baseline to the completion of rehabilitation are shown in Table 6. Although the magnitude of the correlations is small, all relationships were statistically significant.

Table 3—*Correlations Between Prerehabilitation Physiologic and QOL Measures

Variables	SF-36 PCS	SF-36 MCS	SGRQ Total Score	SOBQ Total Score	QWB-SA Average Score
Maximum work, W	0.18†	0.14†	−0.23†	−0.34†	0.19†
Pre-BD					
FVC, L	0.05	0.11†	−0.10†	−0.18†	0.09†
FEV_1, L	0.06‡	0.09†	−0.13†	−0.23†	0.07‡
DLCO§	0.05	0.06‡	−0.06‡	−0.19†	0.08†
Best 6MWD	0.19†	0.17†	−0.26†	−0.37†	0.24†

*See Table 1 for abbreviation not used in the text.
†Correlation is significant at the 0.01 level (two-tailed).
‡Correlation is significant at the 0.05 level (two-tailed).
§DLCO values are unadjusted for hemoglobin.

The correlations were slightly, but nonsignificantly, higher for the disease-specific measures. Prior to rehabilitation, the mean FEV_1 value obtained before bronchodilator therapy was 0.68 ± 0.22 L. FEV_1 improved slightly (1,215 codes in the analysis) following rehabilitation (mean, 0.69 ± 0.22 L; $p = 0.04$). Although this difference was statistically significant, it was very small (*ie*, < 0.007 L).

DISCUSSION

There are very few published studies that have evaluated QOL measures for patients with advanced lung disease. Similarly, there are limited data on the impact of interventions on various lung-related QOL parameters. The NETT has provided the opportunity to study a large number of emphysema patients in a detailed manner. Disease-specific and general measures were included to elucidate any possible effect of surgery and pulmonary rehabilitation.

The disease-specific and general QOL measures used in the NETT are modestly correlated. These findings confirm those of previous reports[27] identifying relationships among QOL measures. Preliminary evi-

Table 4—*Comparison of Postrehabilitation QOL Scores for Those Admitted and Not Admitted to a Hospital in the 3 Months Prior to NETT Initial Interview

Measure	Admitted to Hospital (n = 179)	Not Admitted to Hospital (n = 1,039)	p Value	Effect Size
SF-36				
PCS	27.8 (7.3)	30.0 (7.8)	0.001	0.28
MCS	52.9 (9.6)	55.7 (9.2)	0.001	0.30
SGRQ total score	57.9 (13.3)	52.2 (12.4)	0.001	0.46
SOBQ total score	68.4 (18.1)	61.5 (18.2)	0.001	0.38
QWB-SA average score	0.537 (0.132)	0.577 (0.111)	0.001	0.35

*Values given as mean (SD), unless otherwise specified.

dence from the NETT has suggested that QOL measures improve following pulmonary rehabilitation. Although the QOL changes following rehabilitation were small, they may be clinically meaningful. A change in the QWB-SA of 0.04 U, for example, if maintained for 1 year, would produce the equivalent of about 1 year of life for every 25 patients treated. Although some studies[28] have failed to find changes in QOL measures following rehabilitation, other studies[29,30] have confirmed improvements in QOL measures following pulmonary rehabilitation. The generic measures used in this study had low, but statistically significant, correlations with physiologic and functional measures. Other studies[31] have shown that disease-specific measures are more highly correlated with FEV_1. In terms of responsiveness to clinical change, the disease-specific measures performed only slightly better than the generic measures.

This analysis confirms the findings of previous studies[32] suggesting that there are QOL benefits for pulmonary rehabilitation. In the NETT study, FEV_1 changed only very slightly during the rehabilitation phase (about 0.01 L). The results are also consistent with studies that have failed to show changes in pulmonary function measures following rehabilitation[28] and with studies that have found low, but statistically significant, correlations between QOL and physiologic measures.[33]

Although the QOL measures in the NETT were modestly correlated with one another, each has a specific purpose. Disease-specific measures, such as the SOBQ and SGRQ, may be more sensitive to clinical improvement following pulmonary rehabilitation. However, evidence from the NETT indicates that general measures also detect significant clinical change following rehabilitation. Thus, we did not find clear evidence that disease-specific measures were significantly more responsive to clinical change. General measures have some advantages because they allow comparisons with other benchmarks. For example, the impact of COPD can be compared with the impact of other chronic diseases. Patients in the NETT, for example, had lower QWB scores than patients in other clinical trials of rehabilitation. NETT patients were comparable to patients with macular degeneration in terms of QOL.[34] Their QOL was higher than patients with Alzheimer disease.[21] These comparisons cannot be made with disease-specific measures. Further, utility-based QOL measures are required for analyzing the cost-effectiveness of complex treatments.[35] Because a utility-based measure was used in the NETT, it was possible to show that LVRS produces a quality-adjusted life-year for $190,000, when considered at 3 years, and $98,000 for a subgroup with predominantly upper lobe emphysema and lower exercise

Table 5—*QOL Outcomes Before and After Pulmonary Rehabilitation (1,209 to 1,216 pairs)*

Variable	Pulmonary Rehabilitation		p Value	Effect Size
	Before	After		
SF-36				
PCS	28.3	29.7	< 0.001	0.19
MCS	53.2	55.3	< 0.001	0.21
SGRQ	56.5	53.1	< 0.001	0.35
SOBQ	66.7	62.5	< 0.001	0.24
QWB-SA	0.537	0.571	< 0.001	0.29

Table 6—*Correlations Between Changes in the 6MWD and Changes in QOL

Variables	6MWD	SF-36		SGRQ	SOBQ	QWB-SA
		PCS	MCS			
6MWD	1.00	0.10	0.10	−0.15	−0.13	0.11
SF36						
PCS		1.00	−0.26	−0.31	−0.26	0.18
MCS			1.00	−0.25	−0.13	0.18
SGRQ				1.00	0.40	−0.26
SOBQ					1.00	−0.20
QWB-SA						1.00

*All correlations are significant at the 0.01 level (two-tailed). No. of participants varies from 1,209 to 1,217 due to missing data.

capacity at baseline.[10,36] These results contributed to the Centers for Medicare and Medicaid Services decision to reimburse selected centers for LVRS. Finally, generic measures may capture unanticipated negative consequences of treatment.

In summary, the NETT offers an unusual opportunity to evaluate outcomes for patients with COPD. Evidence from the prerandomization phase of the trial suggests that the measurement of QOL is feasible, and that generic and disease-specific measures are associated with each other and with clinical changes following pulmonary rehabilitation. Furthermore, there are modest associations among QOL measures and measures of disease severity such as FEV_1 and 6MWD. We concluded that QOL measures are meaningful indicators of outcome in clinical trials for patients with COPD. Disease-specific measures may be slightly more sensitive to clinical change, although the responsiveness of the generic measures was comparable in these analyses. On the basis of these evaluations, we recommend either the SGRQ or the SOBQ as COPD-specific outcome measures. The SF-36 is the preferred generic measure for studies requiring a profile of health outcomes, while the QWB-SA is recommended for studies considering companion cost-effectiveness.

Appendix: Members of the NETT Research Group

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