ORIGINAL ARTICLE

Development and Preliminary Validation of the Lung Transplant Quality of Life (LT-QOL) Survey

Jonathan P. Singer[1], Allison Soong[1], Joan Chen[1], Pavan Shrestha[1], Hanjing Zhuo[1], Ying Gao[1], John R. Greenland[1], Steven R. Hays[1], Jasleen Kukreja[2], Jeffrey Golden[1], Steven E. Gregorich[3], and Anita L. Stewart[4]

[1]Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine, Department of Medicine, [2]Division of Cardiothoracic Surgery, [3]Department of Medicine, and [4]Institute for Health & Aging, University of California, San Francisco, San Francisco, California

ORCID ID: 0000-0003-0224-7472 (J.P.S.).

Abstract

Rationale: Although lung transplantation aims to improve health-related quality of life (HRQL), existing instruments fail to include health domains considered important in this population.

Objectives: We aimed to develop a comprehensive lung transplant–specific instrument to address this shortcoming.

Methods: We developed a pool of 126 candidate items addressing domains previously identified as important by lung transplant recipients. Through cognitive interviews conducted in 43 transplant recipients, items deemed irrelevant or redundant were dropped. The 84 remaining items were field tested in lung transplant recipients. Exploratory and confirmatory factor analyses were used to evaluate the factor structure, and scales were evaluated for internal consistency and construct validity.

Measurements and Main Results: The 84-item preliminary survey was administered to 201 lung transplant recipients with a mean age of 57.9 (±12.7) years; 46% were female. After factor analyses and internal consistency evaluation, we retained 60 items comprising the Lung Transplant Quality of Life (LT-QOL) Survey. The LT-QOL contains 10 scales that measure symptoms, health perceptions, functioning, and well-being. The confirmatory factor analysis model had good approximate fit (comparative fit index = 0.990; standardized root-mean-square residual = 0.062). Cronbach αs for the 10 scales ranged from 0.75 to 0.95. Interscale correlations were consistent with hypothesized relationships. Subjects with severe chronic lung allograft dysfunction (n = 13) reported significantly worse HRQL than subjects without chronic lung allograft dysfunction (n = 168) on 6 of the 10 LT-QOL scales.

Conclusions: The LT-QOL is a new, multidimensional instrument that characterizes and quantifies HRQL in lung transplant recipients.

Keywords: lung transplantation; disability; patient-centered outcomes; health-related quality of life

Lung transplantation aims to extend survival and improve health-related quality of life (HRQL) for adults with advanced lung disease. For lung transplant recipients, we previously identified substantial heterogeneity in the more than 20 instruments used to assess HRQL and that none were specifically developed for this population (1, 2).

HRQL reflects the effects of health, illness, and consequent medical therapy on overall quality of life (2). The theoretical health domains that comprise HRQL in a given disease drive the development of corresponding instruments (2). After lung transplantation, important health domains

(Received in original form June 29, 2018; accepted in final form October 5, 2018)

Supported by NHLBI grants K23 HL111115 and R01 HL134851 (J.P.S.), Veteran's Health Administration VA CSR&D CDA-2 Award IK2CX001034 (J.R.G.), and National Institute on Aging grant P30-AG15272 (S.E.G. and A.L.S.)

Author Contributions: All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved; J.P.S., S.E.G., and A.L.S. made substantial contributions to the conception and design of the work; J.P.S., A.S., J.C., P.S., H.Z., Y.G., S.E.G., and A.L.S. made substantial contributions to the acquisition, analysis, or interpretation of data for the work; J.P.S. wrote the first draft of the manuscript; H.Z., Y.G., J.R.G., S.R.H., J.K., J.G., S.E.G., and A.L.S. revised the manuscript for important intellectual content; all authors approved the final version of the manuscript.

Correspondence and requests for reprints should be addressed to Jonathan P. Singer, M.D., M.S., University of California, San Francisco, 505 Parnassus Avenue, M1083B, San Francisco, CA 94115. E-mail: jon.singer@ucsf.edu.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Am J Respir Crit Care Med Vol 199, Iss 8, pp 1008–1019, Apr 15, 2019

Originally Published in Press as DOI: 10.1164/rccm.201806-1198OC on October 10, 2018
Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the Subject: Although improving health-related quality of life (HRQL) is a primary clinical aim of lung transplantation, currently available instruments to measure HRQL fail to capture domains of health considered important and relevant by lung transplant recipients. Failure to capture important domains limits the validity of available instruments.

What This Study Adds to the Field: This study details the development and preliminary validation of the Lung Transplant Quality of Life survey, a novel, 60-item HRQL instrument for use in lung transplantation. This multidimensional instrument assesses 10 domains reflecting symptoms, health perceptions, functioning, and well-being. The scales exhibit strong construct validity and internal consistency, and are sensitive to differences in HRQL in patients with and without chronic lung allograft dysfunction.

include depression and anxiety (3–5), extrapulmonary and immunosuppression-related symptoms (6–9), and neurocognitive deficits (10, 11). These domains are poorly represented in existing generic or respiratory-specific instruments, limiting the content validity of those measures.

To address these limitations, based on guidelines for developing patient-reported outcomes (PROs), our first study used qualitative methods to identify relevant conceptual health domains important in lung transplantation (12, 13). We identified 11 novel domains not included in the Medical Outcomes Study Short Form (SF)-36; the most commonly used generic HRQL instrument) that were important to lung transplant recipients, such as symptoms, transplant-related health distress, cognitive limitations, and treatment burden (14).

Based on these concepts, we present herein the development and evaluation of a novel PRO measure of HRQL in lung transplantation. In Step 1: Concept and Item Development, we identify items relevant to lung transplant–specific HRQL domains and, through cognitive interviews, refined this large item pool into a preliminary survey. Step 3: Field Testing and Analysis involved administering this item pool to lung transplant recipients and conducting analyses to identify the underlying factor structure, evaluating the psychometric properties of the resulting instrument, and exploring construct validity.

Methods

Study Population

We performed this study among adult lung transplant recipients, aged 18 years or older, at the University of California, San Francisco (UCSF). Because the recruitment strategy differed by study steps, descriptions of the study populations are outlined in each step. The UCSF Committee on Human Research approved the two studies that comprise the content of this article, and written informed consent was obtained.

Step 1: Concept and Item Development

We focused on developing an HRQL instrument that could be combined with a generic instrument of an investigator's choosing. We modeled this approach on the Kidney Disease Quality of Life instrument, which combines the generic Medical Outcomes Study (MOS) RAND SF-36 instrument with 98 kidney disease-specific items (15). We aimed to reflect the health domains relevant to lung transplant recipients that we previously defined in our qualitative work (14). We searched existing validated instruments to identify candidate items and scales that met face validity by reflecting lung transplant quality-of-life domains of interest. Our criteria for scale consideration included: instruments that did not require licenses or fees for use; brevity (i.e., $<$10 items) given the multiple health domains that we intended to include in our final measure; a track record of use in more than one cohort of subjects; and that featured ordinal response options querying either frequency or intensity. Finally, after lung transplantation, pulmonary symptoms are unusual in the absence of infection, acute or chronic lung allograft rejection, and airway complications. As a result—and in the interest of instrument brevity—we focused on a limited number of items querying pulmonary symptomology.

The initial pool of items were derived from several existing measures, including the MOS (health distress, cognitive functioning, depression, sexual problems, sleep, positive affect, loneliness/belonging scales) (16), St. George's Respiratory Questionnaire (symptom subscale) (17), Hospital Anxiety and Distress Scale/General Anxiety Disorder 7-Item Scale (18), Treatment Burden Questionnaire (19), Cystic Fibrosis Questionnaire-Revised (treatment burden subscale) (20), Pittsburgh Sleep Quality Index (21), and the Functional Assessment of Chronic Illness Therapy (FACIT) measures (General 7-Item, Bone Marrow Transplant, Leukemia, Esophageal Cancer, Lung Cancer, and Gynecologic Oncology Group–Neurotoxicity scales) (22–27). Because existing items were not designed for lung transplantation, we made minor modifications to some item stems to make them specific to lung transplant recipients. For example, we modified an item from the FACIT Bone Marrow Transplant scale from "I regret having the *bone marrow* transplant" to "I regret having the *lung* transplant." We obtained written permission to modify items from the developers of the instruments. Entirely novel items were not developed.

The product of this item development phase was 126 items (Figure 1, Part 1). Respondents were presented with five-point response scales and asked to consider their experience over the prior 4 weeks. This time frame was selected as being long enough to sample a range of symptom experiences and health perceptions, including potentially rapidly changing perceptions in the early postoperative period, yet short enough to enable accurate recall. Items asked respondents about the frequency of occurrence of symptoms (e.g., 1 = never to 5 = very often) or the extent to which a statement applied (e.g., 1 = not at all to 5 = very much).

Step 2: Pretesting and Refining Items

We next performed a series of cognitive interviews to ensure that the items were clearly understood, relevant, not redundant, and adequately reflected the conceptual domain they were intended to measure (28, 29). For this study phase, we recruited a convenience sample of lung transplant recipients who were more than 3 months

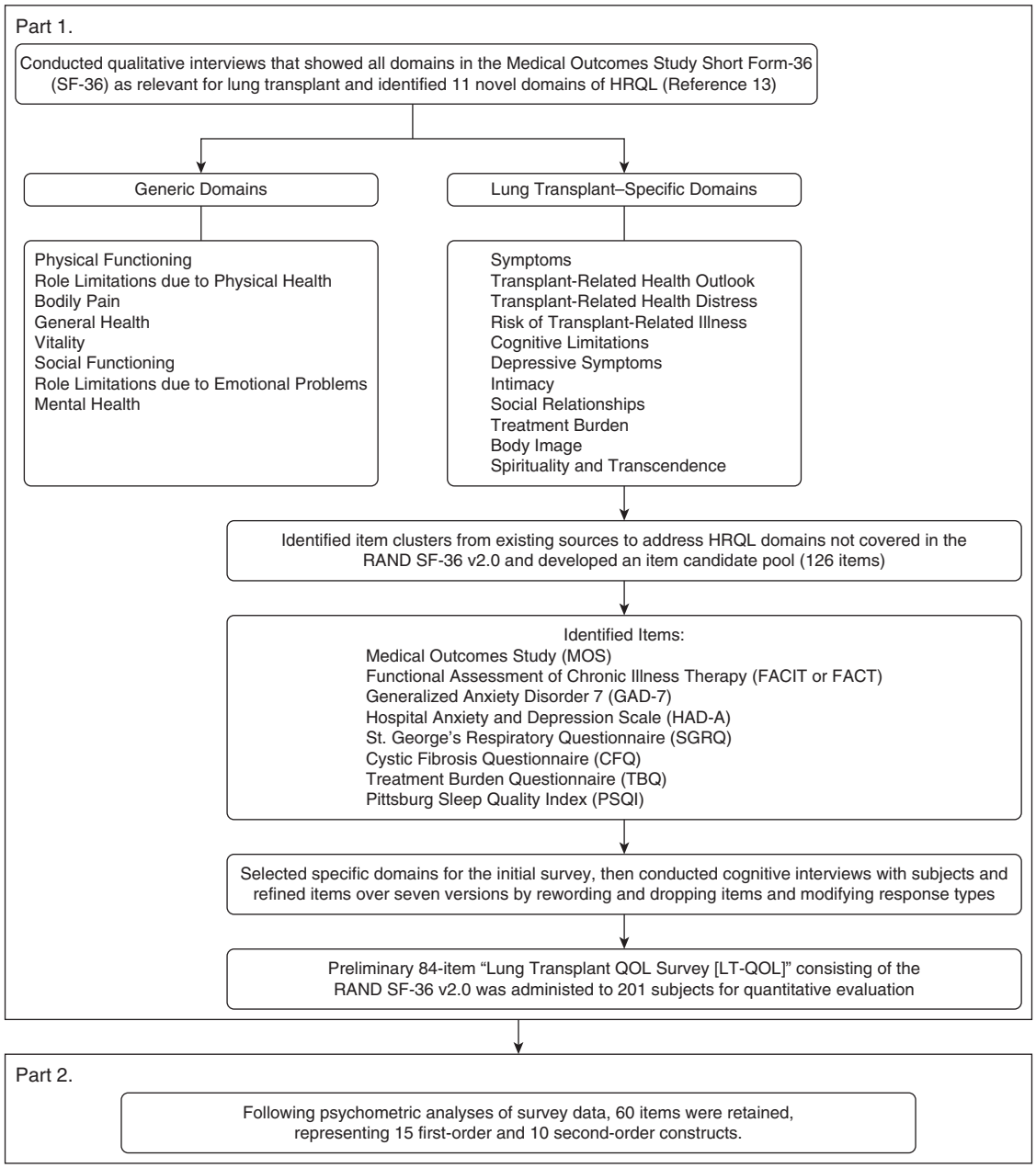

Figure 1. Steps taken to develop the Lung Transplant Quality of Life survey. HRQL = health-related quality of life; QOL = quality of life; SF-36 = Medical Outcomes Study Short Form-36.

from their transplant surgery. The principal investigator (PI; J.P.S.) and research coordinator (J.C.) identified potential participants meeting selection criteria (98% of UCSF lung transplant recipients agree to be contacted for new research studies). Before their routinely scheduled clinic visits, potential participants were telephoned to explain the study, answer questions, and, for those who were interested, establish an interview meeting time. When participants arrived at the study location, the PI or coordinator again explained the study and obtained written informed consent.

One-on-one cognitive interviews lasting approximately 1 hour were conducted in a private academic office between each participant and the PI or a research coordinator trained in qualitative interviewing (28, 29). Interviews were audio recorded and transcribed verbatim. Given the in-depth nature of the interviews, administering the entire 126 candidate item pool to each participant was not feasible. Therefore, participants were provided with a randomly selected subset of the candidate domains. For each item, we probed participants' understanding of the meaning of specific words, phrases, and overall item stems. We also asked participants to identify redundancy between items. In some cases, more than one established HRQL instrument featured item clusters relevant to a conceptual domain of interest. To optimize face validity, participants were

asked to identify which item cluster more clearly reflected their definition of HRQL. Finally, given the heterogeneity of the source instruments, response options for item clusters included both frequency and intensity options. Including heterogeneous response options in an instrument can create confusion for those completing a survey, and make scoring and interpreting scores more challenging. Thus, participants were also asked which type of response option was most relevant.

Our process for refining the candidate item pool involved transcribing and reviewing interviews in real time. Items were modified if problems were identified by more than one participant, and investigators agreed on the nature of the problem. Modifications included minor grammatical changes, eliminating redundant items, changing response scales from intensity to frequency scales, and eliminating sleep-related items. As modifications were made, subsequent participants would then review the most up-to-date version of the candidate survey. We continued performing cognitive interviews until saturation was achieved ($n = 43$). Saturation is the point at which no new information resulting in changes to items is identified through additional interviews (30). Over 7 rounds of survey refinement, 42 of the initial 126 lung transplant–specific items were dropped (*see* Table E1 in the online supplement), yielding a preliminary 84-item survey encompassing domains particularly relevant to lung transplant recipients (Figure 1, Part 1).

Step 3: Field Testing and Analysis

The preliminary survey was administered to a new convenience sample of lung transplant recipients more than 3 months from their transplant surgery to allow psychometric analyses and identify the final set of scales. We considered subjects who had consented to be contacted about new research opportunities, as well as subjects participating in a longitudinal study of the impact of lung transplant on HRQL (Breathe Again Study) (31). For Breathe Again participants, we asked them if they would be willing to complete additional survey questions during one of their regularly scheduled research visits (96% of participants approached were willing). These visits occurred at 3 and 6 months after transplantation and semiannually thereafter for up to 3 years. At these visits, participants routinely completed a 20-minute survey that included instruments to assess functional status/disability (Lung Transplant Valued Life Activities [LT-VLA] disability scale), depressive symptoms (Geriatric Depression Scale-15 [GDS-15]), respiratory-specific HRQL (Airways Questionnaire 20-Revised [AQ20-R]), generic HRQL (MOS SF-12), and health utilities (Euroqol 5D [EQ-5D] and Visual Analog Scale [VAS]) (32–36). The online supplement includes additional details on instrument properties. After obtaining informed consent, participants completed the new preliminary survey after completing the Breathe Again survey battery. Subjects were either mailed a paper survey to complete and return to the research center or, for Breathe Again participants, provided a paper survey to complete during regularly scheduled research visits.

We administered the RAND SF-36 version 2.0 (v2.0) as a generic core along with our preliminary survey (37, 38). We included the RAND SF-36 to evaluate the construct validity of our new measure and to determine whether the domains included were distinct from those included in generic measures. We also included it to simulate the experience of participants completing a larger HRQL battery that included both a generic core and lung transplant–specific items. For the participants in this field test who were part of the Breathe Again Study, we substituted the SF-36 for the SF-12.

Analysis Approach

We fit oblique principal components cluster analysis models—a form of exploratory factor analysis—to the 84 items using the PROC VARCLUS program in SAS 9.4 (SAS Institute) (39–41). Competing VARCLUS solutions with 1–35 clusters were generated and evaluated, in a largely subjective manner, to select the solution that best balanced clinical relevance, parsimony, and conceptual distinctiveness. Based upon poor fit, limited variation in response, or clinical judgement, some items and clusters were dropped. We also grouped conceptually similar remaining clusters into second-order clusters. To further explore how well this second-order cluster model fit the data, we fit a corresponding second-order confirmatory factor analysis (CFA) via maximum likelihood using LISREL 8.72 for Windows (Scientific Software International) (42). We assessed model fit by the Satorra-Bentler scaled χ^2, root mean-squared error of approximation (RMSEA), comparative fit index (CFI), and the standardized root mean-squared residual (SRMR) (43–45). Hu and Bentler (46) found that the following threshold values suggest approximate model fit: RMSEA $\leq$ 0.06; CFI $\geq$ 0.95; and SRMR $\leq$ 0.08. Before fitting all models, responses to the 84 items were transformed to normal scores (47). For CFA models, of 12,261 possible data points (201 respondents $\times$ 61 items), 183 were missing (1.5%). Only five respondents missed answering five or more items. These rare missing data were considered missing at random and multiply imputed. After imputing missing data, the asymptotic covariance matrix of item variances and covariances was estimated via bootstrap.

We next calculated first- and second-order scale scores for each participant. Scale scores were calculated as the mean response to the corresponding nonmissing items. Response choices, and therefore scale scores, had a theoretical range from 1 to 5. For all scales, higher scores indicated worse health, except for the General Quality of Life scale, in which higher scores indicated better health. This was done to convey the meaning of the original construct based on how the questions were asked. To score the eight RAND SF-36 scales, we followed guidelines for v2.0 (38), with scores ranging from 0 to 100; higher scores indicated better health.

We generated descriptive statistics for each scale, including extreme scale values indicating floor or ceiling effects. We estimated internal consistency by Cronbach α and item–scale correlation estimates for each first- and second-order scale. For each scale, the goal was to achieve a Cronbach α of greater than 0.70 and item–scale correlations corrected for overlap of greater than 0.30 (48). Scales not meeting these criteria were reviewed to determine if dropping items would improve reliability.

We performed additional assessments of construct validity. First, we examined Pearson correlations among the second-order scales. We also sought to determine if there was redundancy (correlation >0.80) between any pair of scales, including between the Lung Transplant Quality of Life (LT-QOL) scales and SF-36 scales. This value (>0.80) is close to the maximum possible association (i.e., approximating 1.0 after correcting for attenuation due to unreliability), assuming both measures have

a reliability of 0.80. Next, we examined the Pearson correlations between the LT-QOL second-order scales and measures of functioning (FEV_1% predicted and 6-minute-walk distance), patient-reported functional capacity (LT-VLA), depressive symptoms (GDS), respiratory-specific HRQL (AQ20-R), and health utility (EQ-5D and VAS). Based on the function or conceptual constructs assessed by each of these measures, we hypothesized that the strength and magnitude of their associations would differ across the individual LT-QOL scales. For example, we hypothesized that the AQ20-R would correlate most strongly with LT-QOL pulmonary symptoms and less so with gastrointestinal (GI) or neuromuscular symptoms. Additional hypotheses are detailed in the online supplement. Finally, because chronic lung allograft dysfunction (CLAD) is associated with poorer HRQL, we compared all scale scores in participants who had severe CLAD (stage 3 [$FEV_1 <$ 50% of post-transplant baseline]) to those who had no evidence of CLAD (stage 0) using the Student's *t* test (49–51). We hypothesized that participants with severe CLAD would report poorer HRQL on specific scales compared with participants without CLAD. Because few participants had severe CLAD, we did not distinguish between its obstructive and restrictive forms; we also excluded participants with CLAD stages 1 or 2 (52, 53). As a final test of construct validity, we included group comparisons of the eight RAND SF-36 scales to assess whether the strength and direction of the differences between those with and without CLAD was consistent with prior literature.

Results

A total of 201 lung transplant recipients completed the 120-item field test survey (84 lung transplant–specific items and the RAND SF-36 v2.0). Participants had a mean age of 57.9 years (SD, ±12.7 yr; range = 19.4–76.0 yr), 46% were female, 77% were white, and had a median of 2 years since lung transplant surgery (interquartile range = 1.0–4.0; range = 0.2–20.0) (Table 1). Participants needed approximately 30 minutes to complete the field test survey.

Based upon the initial VARCLUS analysis, the 15-cluster solution best balanced conceptual distinctness with parsimony, and items within each cluster had good internal consistency. During the process of selecting a final VARCLUS model, 23 of the 84 items were dropped because they were judged to share insufficient substantive content with the other items. Thus, a total of 61 items were retained, comprising 15 first-order clusters. Based on conceptual groupings, eight of the first-order clusters were grouped into three second-order clusters. The remaining seven first-order clusters were not aggregated at the second-order level (i.e., the first- and second-order clusters were identical).

The 61-item, second-order CFA model provided good approximate fit to the data (Satorra-Bentler scaled χ^2 [1,716] = 2,163.93; $P < 0.0001$; RMSEA = 0.036; CFI = 0.990; SRMR = 0.062; Table 2) details the first- and second-order scales and their constituent items and factor loadings. All first- and second-order factor loadings had absolute values of 0.45 or greater. The Cronbach α for the four-item, first-order scale "eating/aspiration problems" was low (0.65), because one item exhibited poor item–scale correlation ($r = 0.22$); that item was dropped resulting in 60 items in the final instrument (Figure 1, Part 2; *see* also the LT-QOL final survey in the online supplement).

Because we believe that most users of the LT-QOL will use scale scores defined at the second-order level, the remaining results report upon second-order scales. The results of the first-order scales are detailed in Tables E2 and E3. The 10 second-order lung transplant scales comprise measures of symptoms, health perceptions, functioning, and well-being. We define each one briefly here.

Table 1. Cohort Demographics and Clinical Characteristics (*n* = 201)

Characteristics	Values
Age, yr	57.9 ± 12.7
Age range, yr	19.4–76.0
Time since lung transplant, yr	
Median (IQR)	2.0 (1.0–4.0)
Range	0.2–20.0
Women, *n* (%)	92 (46)
Race/ethnicity, *n* (%)	
White, non-Hispanic	154 (77)
White, Hispanic	23 (11)
Black	10 (5)
Asian	13 (6)
American Indian	1 (1)
Diagnostic indication for transplant, *n* (%)*	
Group A (obstructive lung disease)	35 (17)
Group B (pulmonary hypertension)	12 (6)
Group C (suppurative lung disease)	19 (9)
Group D (pulmonary fibrosis)	135 (67)
FEV_1, L	2.4 ± 0.9
FEV_1% predicted	79.5 ± 24.1
FVC, L	3.1 ± 1.0
FVC % predicted	77.5 ± 19.7

Definition of abbreviation: IQR = interquartile range.
Data are presented as *n* (%) or mean ± SD.
*Diagnostic categories used for the Lung Allocation Score (64).

Symptoms

- *Pulmonary*: shortness of breath (tightness in chest, respiratory problems) and coughing (phlegm, wheezing).
- *GI*: eating/aspiration (trouble swallowing), lack of interest in eating, upper GI (stomach pain or cramps) and lower GI (diarrhea).
- *Neuromuscular*: discomfort/numbness in hands or feet, shaky hands, weak muscles.

Health Perceptions

- *Worry about future health*: worry about infections, uncertainty about future health, and difficulty planning for the future.
- *Treatment burden*: treatment (including medications) makes daily life difficult.

Functioning

- *Cognitive limitations*: became confused, reacted slowly to things, difficulty reasoning, forgetful, trouble keeping attention, and difficulty concentrating.

Table 2. Factor Loadings for Lung Transplant Quality of Life Items

Item	No. of Items	Second-Order Factor Loading	First-Order Factor Loading
Symptoms			
Pulmonary symptoms	**7**		
Shortness of breath	3	0.98	
I had shortness of breath			0.90
I feel tightness in my chest			0.66
How many good days with few respiratory problems have you had?			0.57
Cough	4	0.72	
I have coughed			0.73
I brought up phlegm (sputum)			0.72
I have had episodes of wheezing			0.60
During the last 3 mo, how many severe or very unpleasant episodes of lung/respiratory problems have you had?			0.45
GI symptoms	**11**		
Eating/aspiration problems	3	0.62	
I had trouble swallowing food			0.76
I had difficulty swallowing liquids			0.80
I have choked when I swallowed			0.65
I have been able to swallow naturally and easily*			−0.48
Lack of interest in eating	3	0.81	
I have been bothered by changes in the way food tastes			0.55
I had a poor appetite			0.67
I had nausea			0.71
Upper GI symptoms	3	0.82	
I had discomfort or pain in my stomach area			0.93
I had swelling or cramps in my stomach area			0.85
I had constipation			0.54
Lower GI symptoms	2	0.70	
I had diarrhea			0.85
I have been afraid to be far from a toilet			0.77
Neuromuscular symptoms†	4		
I had shaky hands			0.54
My leg muscles felt weak			0.82
I had numbness and tingling in my hands or feet			0.62
I feel discomfort in my hands or feet (pain, cramping, burning, etc.)			0.58
Health perceptions			
Worry about future health†	5		
I worry that the transplant will not work or that I will get rejection			0.61
I worry about getting infections			0.58
Because of the lung transplant, I have difficulty planning for the future			0.65
I worry that my health will get worse			0.91
I feel uncertain about my future health			0.88
Treatment burden†	3		
The effects of the treatment have been worse than I had imagined			0.69
To what extent did your treatments (including medications) make your daily life more difficult?			0.86
How difficult was it for you to do your treatments (including medications) each day?			0.72
Functioning			
Cognitive limitations†	6		
How much of the time, during the past month, did you have difficulty reasoning and solving problems; for example, making plans, making decisions, or learning new things?			0.84
During the past month, how much of the time did you have difficulty doing activities involving concentration and thinking?			0.90
During the past month, how much of the time did you become confused and start several actions at a time?			0.77

(Continued)

Table 2. (*Continued*)

Item	No. of Items	Second-Order Factor Loading	First-Order Factor Loading
During the past month, how much of the time did you forget, for example, things that happened recently, where you put things, or appointments?			0.75
How much of the time, during the past month, did you have trouble keeping your attention on any activity for long?			0.83
How much of the time, during the past month, did you react slowly to things that were said or done?			0.78
Sexual problems†	3		
Lack of sexual interest?			0.86
Unable to relax and enjoy sex?			0.90
Difficulty in becoming sexually aroused?			0.94
Well-being			
Anxiety/depression	**13**		
Anxiety	7	0.90	
Feeling nervous, anxious, or on edge			0.80
Not being able to stop or control worrying			0.88
Worrying too much about different things			0.89
Trouble relaxing			0.82
Being so restless that it is hard to sit still			0.67
Becoming easily annoyed or irritable			0.65
Feeling afraid as if something awful might happen			0.70
Depression	6	0.88	
During the past month, how often has feeling depressed interfered with what you usually do?			0.84
During the past month, how much of the time did you feel depressed?			0.93
During the past month, how much of the time have you been moody or brooded about things?			0.76
During the past month, how much of the time have you been in low or very low spirits?			0.86
How much of the time during the past 4 wk did you feel downhearted and depressed?			0.91
During the past month, how depressed (at its worst) have you felt?			0.91
Health distress†	6		
How often in the past 4 wk were you frustrated about your health?			0.84
How often in the past 4 wk did you feel weighed down by your health problems?			0.93
How often in the past 4 wk were you discouraged by your health problems?			0.92
How often in the past 4 wk did you feel despair over your health problems?			0.79
How often in the past 4 wk were you afraid because of your health?			0.75
How often in the past 4 wk was your health a worry in your life?			0.76
General quality of life†	**2**		
I am able to enjoy life			0.90
I am content with the quality of my life right now			0.83

Definition of abbreviation: GI = gastrointestinal.
Bold scale names and numbers of items are for second-order factors; italic scale names are for first-order factors.
*This item was dropped from the final scale because it resulted in lowered reliability.
†First- and second-order factors are one and the same.

- *Sexual problems*: lack of sexual interest, unable to enjoy sex, difficulty becoming aroused.

Well-Being

- *Anxiety/depression*: feelings of anxiety (nervous, anxious, worry, restless) and depression (low spirits, depressed, moody).
- *Health distress*: feeling distressed about health (e.g., discouraged, worried, afraid because of health).
- *General quality of life*: overall enjoyment of life, contentment with quality of life.

Descriptive statistics for the second-order lung transplant scales are detailed in Table 3. Cronbach αs for the LT-QOL scales ranged from 0.75 to 0.95; all but one were 0.80 or greater, indicating excellent internal consistency. The scale scores had a possible range from 1 to 5. Mean (±SD) scores on the scales for which higher scores represent worse health ranged from a low of 1.69 (±0.65) on the GI symptoms scale to a high of 2.51 (±1.08) on the neuromuscular

Table 3. Descriptive Statistics for 10 Lung Transplant Quality of Life Second-Order Scales and the RAND Medical Outcomes Study Short Form-36 Scales

Second-Order Scales*	No. of Items	Mean	SD	% Floor	% Ceiling	α	Item–Scale Correlations
Symptoms							
Pulmonary symptoms	7	1.87	0.74	11	0	0.80	0.39–0.73
Gastrointestinal symptoms	11	1.69	0.65	13	0	0.84	0.38–0.70
Neuromuscular symptoms	4	2.51	1.08	8	3	0.75	0.39–0.61
Health perceptions							
Treatment burden	3	1.76	0.84	33	0	0.80	0.56–0.74
Worry about future health	5	2.01	0.89	11	1	0.85	0.57–0.81
Functioning							
Cognitive limitations	6	1.94	0.94	22	1	0.92	0.73–0.86
Sexual problems	3	2.37	1.35	32	10	0.92	0.81–0.88
Well-being							
Anxiety/depression	13	1.77	0.76	18	0	0.95	0.61–0.86
Health distress	6	1.86	0.93	24	2	0.94	0.77–0.89
General quality of life	2	4.12	0.93	1	38	0.85	0.74
RAND SF-36 scales							
Physical functioning	10	71.18	25.65	1	7	0.93	0.54–0.83
Role functioning–physical	4	67.97	27.10	1	24	0.94	0.83–0.90
Pain (absence of)	2	71.36	25.29	1	24	0.87	0.77
General health perceptions	5	57.79	20.92	1	1	0.76	0.28–0.70
Emotional well-being	5	79.53	16.72	0	12	0.85	0.60–0.73
Role functioning–emotional	3	84.38	21.78	1	52	0.91	0.74–0.87
Social function	2	77.30	24.78	1	41	0.88	0.78
Energy/fatigue	4	63.56	21.77	1	6	0.89	0.75–0.77

Definition of abbreviation: SF-36 = Medical Outcomes Study Short Form-36.
*Lung Transplant Quality of Life scales range from 1 to 5. Higher scores denote worse heath status except for the general quality-of-life scale, in which higher scores denote better quality of life. RAND SF-36 scales range from 0 to 100. Higher scores denote better health status.

symptoms scale. Only three of these scales had a mean value greater than 2.0. The general quality of life scale (for which higher is better) mean was 4.12 (±0.93). Participant HRQL across the second-order scales was generally fairly high.

Correlations among the 10 second-order scales were consistent with our conceptual model and supported scale construct validity (Table 4; Table E3). First, the correlations between all of the scales generally were moderate; of the 45 coefficients, only two were >0.70. These involved *health distress* with *worry about the future* ($r = 0.75$) and with *anxiety/depression* ($r = 0.73$). We found weak correlations between conceptually distinct scales (e.g., the *sexual problems* scale correlated weakly with *treatment burden* ($r = 0.23$), *neuromuscular symptoms* ($r = 0.29$), and *general quality of life* ($r = -0.24$)).

The correlations between the 10 second-order LT-QOL scales and the 8 SF-36 scales were generally weak to moderate, demonstrating that the LT-QOL measures domains distinct from those in the SF-36 (Table E4). Coefficients were greater than 0.60 for only 6 of the 80 comparisons. The strength and direction of the correlations between the 10 second-order LT-QOL scales and measures of functioning (FEV_1, 6-minute-walk distance, LT-VLA), depressive symptoms (GDS), respiratory-specific HRQL (AQ20-R), and health utility (VAS and EQ-5D) were generally as hypothesized (Table 5).

Finally, the LT-QOL and RAND SF-36 scale scores for those with and without severe CLAD are presented in Table 6 and Table E5. Subjects with CLAD ($n = 13$) reported worse quality of life across 6 of the 10 LT-QOL scales compared with subjects without CLAD ($n = 168$). For example, subjects with CLAD had worse *pulmonary symptoms* scale scores of (mean 3.1 ± 1.0) compared with those without CLAD (1.8 ± 0.6) ($P < 0.0001$). Similarly, those with CLAD had more *worry about future health* (2.7 ± 1.2) than those without (1.9 ± 0.8) ($P = 0.002$). In contrast, there was no difference in the *treatment burden* scale ($P = 0.155$), consistent with expectations, because those with CLAD are not prescribed substantially more medical therapies than those without CLAD. On the SF-36, those with CLAD had worse *quality of life* on seven of the eight scales.

Discussion

The multidimensional LT-QOL is a novel instrument specific for lung transplantation, with excellent evidence of content and construct validity and internal consistency. The domains included in this instrument reflect the perspectives of lung transplant recipients derived from our qualitative work (14). These domains also align closely with research highlighting the importance of symptom burden, worry about the future, depression, cognitive impairments, and others in lung transplantation (3, 5, 6, 9–11, 54–57). The LT-QOL scales are distinct from each other, have strong construct validity, and are sensitive to differences between patients with and without CLAD. In contrast, pre-existing measures of HRQL were not developed specifically for use in lung transplantation. Although some instruments satisfy certain properties of construct validity in lung transplant recipients, all fail to some extent to measure relevant health domains important in this population (8, 14, 54, 58, 59).

The development of the LT-QOL adhered to recommendations from government agencies and industry on the development of PROs (12). We employed qualitative methods

Table 4. Pearson Correlations among 10 Lung Transplant Quality of Life Second-Order Scales

		1	2	3	4	5	6	7	8	9
	Symptoms									
1	Pulmonary symptoms	—	—	—	—	—	—	—	—	—
2	Gastrointestinal symptoms	0.46 (<0.0001)	—	—	—	—	—	—	—	—
3	Neuromuscular symptoms	0.40 (<0.0001)	0.43 (<0.0001)	—	—	—	—	—	—	—
	Health perceptions									
4	Treatment burden	0.32 (<0.0001)	0.48 (<0.0001)	0.34 (<0.0001)	—	—	—	—	—	—
5	Worry about future health	0.46 (<0.0001)	0.34 (<0.0001)	0.41 (<0.0001)	0.48 (<0.0001)	—	—	—	—	—
	Functioning									
6	Cognitive limitations	0.41 (<0.0001)	0.49 (<0.0001)	0.52 (<0.0001)	0.40 (<0.0001)	0.51 (<0.0001)	—	—	—	—
7	Sexual problems	0.41 (<0.0001)	0.38 (<0.0001)	0.29 (<0.0001)	0.23 (0.0019)	0.33 (<0.0001)	0.36 (<0.0001)	—	—	—
	Well-being									
8	Anxiety/depression	0.40 (<0.0001)	0.43 (<0.0001)	0.42 (<0.0001)	0.40 (<0.0001)	0.69 (<0.0001)	0.63 (<0.0001)	0.37 (<0.0001)	—	—
9	Health distress	0.47 (<0.0001)	0.48 (<0.0001)	0.42 (<0.0001)	0.56 (<0.0001)	0.75 (<0.0001)	0.54 (<0.0001)	0.41 (<0.0001)	0.73 (<0.0001)	—
10	General quality of life	−0.33 (<0.0001)	−0.44 (<0.0001)	−0.36 (<0.0001)	−0.49 (<0.0001)	−0.49 (<0.0001)	−0.38 (<0.0001)	−0.24 (0.0012)	−0.53 (<0.0001)	−0.55 (<0.0001)

Data are presented as Pearson correlation (*P* value). The numbers in the column heads correspond to the numbers listed in the first column.

Table 5. Pearson Correlations between 10 Lung Transplant Quality of Life Second-Order Scales and Measures of Functioning and Other Patient-reported Outcomes

		FEV_1% Predicted	6MWD	LT-VLA	GDS	AQ20-R	EQVAS	EQ5D
	Symptoms							
1	Pulmonary symptoms	−0.39 (<0.0001)	−0.21 (0.0759)	0.50 (<0.0001)	0.37 (0.0004)	0.61 (<0.0001)	−0.34 (0.0016)	−0.42 (<0.0001)
2	Gastrointestinal symptoms	−0.23 (0.0012)	−0.15 (0.2108)	0.49 (<0.0001)	0.37 (0.0004)	0.38 (0.0002)	−0.32 (0.0024)	−0.45 (<0.0001)
3	Neuromuscular symptoms	−0.17 (0.0149)	−0.16 (0.1748)	0.38 (<0.0001)	0.34 (0.0012)	0.31 (0.0028)	−0.23 (0.0354)	−0.41 (<0.0001)
	Health perceptions							
4	Treatment burden	−0.16 (0.0237)	−0.33 (0.0060)	0.42 (<0.0001)	0.49 (<0.0001)	0.48 (<0.0001)	−0.36 (0.0006)	−0.39 (<0.0001)
5	Worry about future health	−0.20 (0.0047)	−0.32 (0.0068)	0.39 (<0.0001)	0.52 (<0.0001)	0.35 (0.0007)	−0.31 (0.0034)	−0.45 (<0.0001)
	Functioning							
6	Cognitive limitations	−0.15 (0.0298)	−0.30 (0.0116)	0.36 (<0.0001)	0.45 (<0.0001)	0.35 (0.0007)	−0.46 (<0.0001)	−0.41 (<0.0001)
7	Sexual problems	−0.22 (0.0029)	−0.30 (0.0210)	0.28 (0.0001)	0.19 (0.0924)	0.32 (0.0040)	−0.28 (0.0133)	−0.39 (<0.0001)
	Well-being							
8	Anxiety/depression	−0.15 (0.0313)	−0.26 (0.0280)	0.42 (<0.0001)	0.68 (<0.0001)	0.40 (0.0001)	−0.44 (<0.0001)	−0.54 (<0.0001)
9	Health distress	−0.18 (0.0135)	−0.52 (<0.0001)	0.51 (<0.0001)	0.60 (<0.0001)	0.42 (<0.0001)	−0.53 (<0.0001)	−0.60 (<0.0001)
10	General quality of life	0.13 (0.0668)	0.29 (0.0140)	−0.53 (<0.0001)	−0.61 (<0.0001)	−0.36 (0.0006)	0.37 (0.0004)	0.48 (<0.0001)

Definition of abbreviations: 6MWD = 6-minute-walk distance; AQ20-R = Airway Questionnaire 20-Revised (a measure of respiratory-specific health-related quality of life [HRQL]; higher scores denote worse HRQL); EQ5D = Euroqol 5D; EQVAS = Euroqol Visual Analog Scale (measures of health utility; higher scores denote better health utility); GDS = Geriatric Depression Scale (a measure of depressive symptoms; higher scores denote more depressive symptoms); LT-VLA = Lung Transplant Valued Life Activities (a measure of patient-reported functional capacity/disability; higher scores denote more disability).

Data are presented as Pearson correlation (*P* value). Lung transplant scales range from 1 to 5. Higher scores denote worse heath status except for "general quality of life" scale, in which higher scores denote better quality of life.

Table 6. Scale-Specific Lung Transplant Quality of Life and RAND Medical Outcomes Study Short Form-36 Version 2.0 Scores for Subjects with Severe Chronic Lung Allograft Rejection and Subjects without Chronic Lung Allograft Dysfunction

	Severe CLAD (*n* = *13*)	No CLAD (*n* = *168*)	*P* Value
Symptoms*			
Pulmonary symptoms	3.1 (1.0)	1.8 (0.6)	<0.0001
GI symptoms	2.2 (0.7)	1.7 (0.7)	0.0063
Neuromuscular symptoms	3.0 (1.2)	2.5 (1.1)	0.1314
Health perceptions*			
Treatment burden	2.1 (1.0)	1.7 (0.8)	0.1545
Worry about future health	2.7 (1.2)	1.9 (0.8)	0.0015
Functioning*			
Cognitive limitations	2.6 (1.3)	1.9 (0.9)	0.0140
Sexual problems	3.1 (1.5)	2.3 (1.3)	0.0420
Well-being*			
Anxiety/depression	2.0 (0.8)	1.7 (0.7)	0.1348
Health distress	2.5 (1.1)	1.8 (0.9)	0.0055
General quality of life	3.7 (0.9)	4.2 (0.9)	0.0596
RAND SF-36 scales*			
Physical functioning	39.6 (26.8)	73.5 (24.6)	<0.0001
Role functioning–physical	38.5 (23.4)	70.4 (26.3)	<0.0001
Pain (absence of)	52.3 (21.4)	72.9 (25.3)	0.0047
General health perceptions	38.1 (23.6)	59.8 (19.8)	0.0002
Emotional well-being	76.2 (14.3)	80.2 (16.8)	0.3973
Role functioning–emotional	73.7 (22.0)	86.3 (20.8)	0.0378
Social function	53.8 (23.6)	78.8 (24.6)	0.0005
Energy/fatigue	48.1 (24.5)	65.1 (21.6)	0.0075

Definition of abbreviations: CLAD = chronic lung allograft dysfunction; GI = gastrointestinal; SF-36 = Medical Outcomes Study Short Form-36.
Data are presented as mean (SD).
*Lung Transplant Quality of Life scales range from 1 to 5. Higher scores denote worse heath status except for the general quality of life scale, in which higher scores denote better quality of life. RAND SF-36 scales range from 0 to 100. Higher scores denote better health status.

to identify health domains that were relevant and important to lung transplant recipients (14). Based on these domains, we identified item clusters from validated instruments that reflected these domains. We refined and eliminated items through a series of cognitive interviews and then administered a final candidate item pool to a large cohort of lung transplant recipients. Finally, we subjected patient data on this item pool to psychometric evaluation to identify and validate a final set of items and corresponding scales comprising a multidimensional lung transplant–specific measure, the LT-QOL.

As survival after lung transplant improves, the role of PROs as a metric of transplant efficacy is becoming increasingly relevant (60–62). The LT-QOL addresses a pressing clinical and regulatory need for validated, disease-specific PROs in lung transplantation, of which there are currently only two (9, 58). By design, we anticipate that the LT-QOL will be paired with a generic HRQL measure in a modular fashion. Including both generic and a broader range of lung transplant–specific health domains captured in the LT-QOL will leverage the advantages of both generic and disease-specific HRQL measures, while offsetting their disadvantages (1, 63). For example, the LT-QOL may identify high-yield areas for intervention, and may also be more responsive to interventions aimed at improving problems in lung transplant recipients. This is especially relevant for PROs, as, to properly evaluate interventions, we require PRO measures that are specifically aligned with the targets of those interventions.

Several features of the LT-QOL permit flexibility for end users. Like the Kidney Disease–QOL instrument, the LT-QOL can be paired with a generic instrument. In this study, we used the RAND SF-36 v2.0 as our generic core and the 60-item LT-QOL spanning 15 domains relevant to lung transplant recipients (15). For studies focused on in-depth evaluations of HRQL, we would recommend using the SF-36; for studies with more limited capacity, shorter versions (i.e., SF-12, -10, or -6) or other generic measures may be substituted without compromising the depth and breadth of the lung-transplant QOL evaluation. Furthermore, the reporting of results from the LT-QOL can be simplified by reporting the 10 second-order scales, rather than the 15 first-order scales.

Despite following rigorous recommendations on the development of PROs, our study has limitations. Our patient sample was drawn from a single center in the western United States, and excluded retransplant recipients. It is possible that the items and scales included in the final instrument or the results of our construct validity testing would have differed if the study had been performed elsewhere or if retransplant recipients had been included. In addition, we balanced the desire to develop an instrument that comprehensively reflected HRQL in lung transplantation with the need for brevity—a lengthy instrument is unlikely to be widely adopted. A consequence of brevity, however, is reduced scale diversity. This may be particularly notable in the setting of CLAD in which respiratory-specific measures will more comprehensively reflect respiratory-specific HRQL impairments. Further, because participants were administered the 120-item field test survey, we do not have data on the time needed to complete the final 60-item survey. Because most adults can complete three to five simple survey items per minute, we estimate that the LT-QOL will require 15–20 minutes to complete. In addition, although our cohort was the largest used for PRO development in lung transplantation, our sample size and diversity prevented us from generating clinically derived minimally important differences. Finally, the factor structure of the LT-QOL should be considered as provisional until confirmatory analyses in new samples are conducted.

In summary, the LT-QOL is a novel, relatively brief, modular instrument to quantify HRQL in lung transplantation. With the growing number of lung transplant recipients, many of whom are living longer, the LT-QOL represents a new tool to better measure the outcomes that matter most to patients. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors greatly appreciate the hundreds of patients who participated in this study.

References

1. Singer JP, Chen J, Blanc PD, Leard LE, Kukreja J, Chen H. A thematic analysis of quality of life in lung transplant: the existing evidence and implications for future directions. *Am J Transplant* 2013;13:839–850.
2. McDowell I. Measuring health: a guide to rating scales and questionnaires. New York: Oxford University Press; 2006.
3. Dew MA, DiMartini AF, DeVito Dabbs AJ, Fox KR, Myaskovsky L, Posluszny DM, *et al*. Onset and risk factors for anxiety and depression during the first 2 years after lung transplantation. *Gen Hosp Psychiatry* 2012;34:127–138.
4. Dew MA, DiMartini AF. Psychological disorders and distress after adult cardiothoracic transplantation. *J Cardiovasc Nurs* 2005;20(5 suppl): S51–S66.
5. Courtwright AM, Salomon S, Lehmann LS, Wolfe DJ, Goldberg HJ. The effect of pretransplant depression and anxiety on survival following lung transplant: a meta-analysis. *Psychosomatics* 2016;57:238–245.
6. Kugler C, Fischer S, Gottlieb J, Tegtbur U, Welte T, Goerler H, *et al*. Symptom experience after lung transplantation: impact on quality of life and adherence. *Clin Transplant* 2007;21:590–596.
7. Kugler C, Geyer S, Gottlieb J, Simon A, Haverich A, Dracup K. Symptom experience after solid organ transplantation. *J Psychosom Res* 2009; 66:101–110.
8. De Vito Dabbs A, Dew MA, Stilley CS, Manzetti J, Zullo T, McCurry KR, *et al*. Psychosocial vulnerability, physical symptoms and physical impairment after lung and heart-lung transplantation. *J Heart Lung Transplant* 2003;22:1268–1275.
9. Dobbels F, Moons P, Abraham I, Larsen CP, Dupont L, De Geest S. Measuring symptom experience of side-effects of immunosuppressive drugs: the Modified Transplant Symptom Occurrence and Distress Scale. *Transpl Int* 2008;21:764–773.
10. Hoffman BM, Blumenthal JA, Carney RC, O'Hayer CV, Freedland K, Smith PJ, *et al*. Changes in neurocognitive functioning following lung transplantation. *Am J Transplant* 2012;12:2519–2525.
11. Smith PJ, Rivelli S, Waters A, Reynolds J, Hoyle A, Flowers M, *et al*. Neurocognitive changes after lung transplantation. *Ann Am Thorac Soc* 2014;11:1520–1527.
12. U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research; U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research; U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health Qual Life Outcomes* 2006;4:79.
13. Brod M, Tesler LE, Christensen TL. Qualitative research and content validity: developing best practices based on science and experience. *Qual Life Res* 2009;18:1263–1278.
14. Singer JP, Chen J, Katz PP, Blanc PD, Kagawa-Singer M, Stewart AL. Defining novel health-related quality of life domains in lung transplantation: a qualitative analysis. *Qual Life Res* 2015;24:1521–1533.
15. Hays RD, Kallich JD, Mapes DL, Coons SJ, Carter WB. Development of the kidney disease quality of life (KDQOL) instrument. *Qual Life Res* 1994;3:329–338.
16. Stewart AL, Ware JE Jr. Measuring functioning and well-being: the Medical Outcomes Study approach. Durham, NC: Duke University Press; 1992.
17. Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992; 145:1321–1327.
18. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006;166:1092–1097.
19. Tran VT, Montori VM, Eton DT, Baruch D, Falissard B, Ravaud P. Development and description of measurement properties of an instrument to assess treatment burden among patients with multiple chronic conditions. *BMC Med* 2012;10:68.
20. Quittner AL, Buu A, Messer MA, Modi AC, Watrous M. Development and validation of the Cystic Fibrosis Questionnaire in the United States: a health-related quality-of-life measure for cystic fibrosis. *Chest* 2005;128:2347–2354.
21. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
22. Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy– Lung (FACT-L) quality of life instrument. *Lung Cancer* 1995;12:199–220.
23. McQuellon RP, Russell GB, Cella DF, Craven BL, Brady M, Bonomi A, *et al*. Quality of life measurement in bone marrow transplantation: development of the Functional Assessment of Cancer Therapy–Bone Marrow Transplant (FACT-BMT) scale. *Bone Marrow Transplant* 1997;19:357–368.
24. Calhoun EA, Welshman EE, Chang CH, Lurain JR, Fishman DA, Hunt TL, *et al*. Psychometric evaluation of the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity (Fact/GOG-Ntx) questionnaire for patients receiving systemic chemotherapy. *Int J Gynecol Cancer* 2003;13:741–748.
25. Darling G, Eton DT, Sulman J, Casson AG, Celia D. Validation of the functional assessment of cancer therapy esophageal cancer subscale. *Cancer* 2006;107:854–863.
26. Cella D, Jensen SE, Webster K, Hongyan D, Lai JS, Rosen S, *et al*. Measuring health-related quality of life in leukemia: the Functional Assessment of Cancer Therapy–Leukemia (FACT-Leu) questionnaire. *Value Health* 2012;15:1051–1058.
27. Yanez B, Pearman T, Lis CG, Beaumont JL, Cella D. The FACT-G7: a rapid version of the Functional Assessment of Cancer Therapy–General (FACT-G) for monitoring symptoms and concerns in oncology practice and research. *Ann Oncol* 2013;24:1073–1078.
28. Willis GB. Cognitive interviewing: a "how-to" guide. American Statistical Association: Research Triangle Institute; 1999 [accessed 2018 Sep 5]. Available from: http://www.chime.ucla.edu/publications/docs/cognitive%20interviewing%20guide.pdf.
29. Willis GB. Cognitive interviewing: a tool for improving questionnaire design. Thousand Oaks, CA: Sage Publications; 2005.
30. Strauss AL, Corbin JM. Basics of qualitative research: grounded theory procedures and techniques. Newbury Park, CA: Sage Publications; 1990.
31. Singer JP, Katz PP, Soong A, Shrestha P, Huang D, Ho J, *et al*. Effect of lung transplantation on health-related quality of life in the era of the lung allocation score: a U.S. prospective cohort study. *Am J Transplant* 2017;17:1334–1345.
32. Ware J Jr, Kosinski M, Keller SDA. A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220–233.
33. Chen H, Eisner MD, Katz PP, Yelin EH, Blanc PD. Measuring disease-specific quality of life in obstructive airway disease: validation of a modified version of the airways questionnaire 20. *Chest* 2006;129: 1644–1652.
34. Group E; EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.
35. Bass DS, Attix DK, Phillips-Bute B, Monk TG. An efficient screening tool for preoperative depression: the Geriatric Depression Scale-Short Form. *Anesth Analg* 2008;106:805–809. [Table of Contents.]
36. Singer JP, Blanc PD, Dean YM, Hays S, Leard L, Kukreja J, *et al*. Development and validation of a lung transplant–specific disability questionnaire. *Thorax* 2014;69:437–442.
37. Hays RD, Sherbourne CD, Mazel RM. The RAND 36-Item Health Survey 1.0. *Health Econ* 1993;2:217–227.
38. Daigl M. SF36V2: Stata module to score Short-Form 36 version 2: statistical software components S457212. Boston College Department of Economics; 2010 [revised 2011 Oct 4; accessed 2017 Feb 1]. Available from: https://ideas.repec.org/c/boc/bocode/s457212.html.
39. Huang AJ, Gregorich SE, Kuppermann M, Nakagawa S, Van Den Eeden SK, Brown JS, *et al*. Day-to-Day Impact of Vaginal Aging questionnaire: a multidimensional measure of the impact of vaginal symptoms on functioning and well-being in postmenopausal women. *Menopause* 2015;22:144–154.
40. Mehling WE, Price C, Daubenmier JJ, Acree M, Bartmess E, Stewart A. The Multidimensional Assessment of Interoceptive Awareness (MAIA). *PLoS One* 2012;7:e48230.
41. Walker KO, Stewart AL, Grumbach K. Development of a survey instrument to measure patient experience of integrated care. *BMC Health Serv Res* 2016;16:193.

42. Joreskog KG, Sorbom D. Lisrel 8.7 for Windows [computer software]. Lincolnwood ISSI, Inc., editor. 2004.
43. Satorra A, Bentler PM. Corrections to test statistics and standard errors in covariance structure analysis. Latent variables analysis: applications for developmental research. Thousand Oaks, CA: Sage Publications, Inc.; 1994. pp. 399–419.
44. Steiger JH. Statistically based tests for the number of common factors. Presented at the 1980 Annual Meeting of the Psychometric Society. May 1980, Iowa City, IA.
45. Bentler PM. Comparative fit indexes in structural models. *Psychol Bull* 1990;107:238–246.
46. Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. *Struct Equ Modeling* 1999;6:1–55.
47. Blom G. Statistical estimates and transformed beta-variables. New York: Wiley; 1958.
48. Stewart AL, Hays RD, Ware JE. Methods of constructing health measures. In: Stewart AL, Ware JE, editors. Measuring functioning and well-being: the Medical Outcomes Study Approach. Durham, NC: Duke University Press; 1992. pp. 67-85.
49. Künsebeck HW, Kugler C, Fischer S, Simon AR, Gottlieb J, Welte T, *et al*. Quality of life and bronchiolitis obliterans syndrome in patients after lung transplantation. *Prog Transplant* 2007;17:136–141.
50. Smeritschnig B, Jaksch P, Kocher A, Seebacher G, Aigner C, Mazhar S, *et al*. Quality of life after lung transplantation: a cross-sectional study. *J Heart Lung Transplant* 2005;24:474–480.
51. Gerbase MW, Soccal PM, Spiliopoulos A, Nicod LP, Rochat T. Long-term health-related quality of life and walking capacity of lung recipients with and without bronchiolitis obliterans syndrome. *J Heart Lung Transplant* 2008;27:898–904.
52. Todd JL, Jain R, Pavlisko EN, Finlen Copeland CA, Reynolds JM, Snyder LD, *et al*. Impact of forced vital capacity loss on survival after the onset of chronic lung allograft dysfunction. *Am J Respir Crit Care Med* 2014;189:159–166.
53. Estenne M, Maurer JR, Boehler A, Egan JJ, Frost A, Hertz M, *et al*. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. *J Heart Lung Transplant* 2002;21:297–310.
54. Lanuza DM, Lefaiver CA, Brown R, Muehrer R, Murray M, Yelle M, *et al*. A longitudinal study of patients' symptoms before and during the first year after lung transplantation. *Clin Transplant* 2012;26: E576–E589.
55. Dew MA, Rosenberger EM, Myaskovsky L, DiMartini AF, DeVito Dabbs AJ, Posluszny DM, *et al*. Depression and anxiety as risk factors for morbidity and mortality after organ transplantation: a systematic review and meta-analysis. *Transplantation* 2015;100: 988–1003.
56. Cohen DG, Christie JD, Anderson BJ, Diamond JM, Judy RP, Shah RJ, *et al*. Cognitive function, mental health, and health-related quality of life after lung transplantation. *Ann Am Thorac Soc* 2014;11: 522–530.
57. Smith PJ, Blumenthal JA, Trulock EP, Freedland KE, Carney RM, Davis RD, *et al*. Psychosocial predictors of mortality following lung transplantation. *Am J Transplant* 2016;16:271–277.
58. Hoffman BM, Stonerock GL, Smith PJ, O'Hayer CV, Palmer S, Davis RD, *et al*. Development and psychometric properties of the Pulmonary-Specific Quality-of-Life Scale in lung transplant patients. *J Heart Lung Transplant* 2015;34:1058–1065.
59. Song MK, Devito Dabbs AJ, Studer SM, Arnold RM, Pilewski JM. Exploring the meaning of chronic rejection after lung transplantation and its impact on clinical management and caregiving. *J Pain Symptom Manage* 2010;40:246–255.
60. Yusen RD. Technology and outcomes assessment in lung transplantation. *Proc Am Thorac Soc* 2009;6:128–136.
61. Yusen RD. Lung transplantation outcomes: the importance and inadequacies of assessing survival. *Am J Transplant* 2009;9: 1493–1494.
62. Abecassis M, Bridges ND, Clancy CJ, Dew MA, Eldadah B, Englesbe MJ, *et al*. Solid-organ transplantation in older adults: current status and future research. *Am J Transplant* 2012;12:2608–2622.
63. Singer JP, Singer LG. Quality of life in lung transplantation. *Semin Respir Crit Care Med* 2013;34:421–430.
64. Egan TM, Murray S, Bustami RT, Shearon TH, McCullough KP, Edwards LB, *et al*. Development of the new lung allocation system in the United States. *Am J Transplant* 2006;6:1212–1227.