The Development and Validation of a Neuropathy- and Foot Ulcer–Specific Quality of Life Instrument

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OBJECTIVE — The purpose of this study was to develop a questionnaire that measures patients' perceptions of the impact of diabetic peripheral neuropathy and foot ulcers on their quality of life and to assess the psychometric properties of this instrument in a sample of patients with varying severity and symptomatology of diabetic peripheral neuropathy.

RESEARCH DESIGN AND METHODS — The neuropathy- and foot ulcer–specific quality of life instrument (NeuroQoL), generated from interviews with patients with (n = 47) and without (n = 15) diabetic peripheral neuropathy, was administered to 418 consecutive patients with diabetic peripheral neuropathy (35% with foot ulcer history) attending either U.K. (n = 290) or U.S. (n = 128) diabetes centers. Psychometric tests of NeuroQoL included factor analyses and internal consistency of scales; a series of multivariate analyses were performed to establish its criterion, construct, and incremental validity. Results were compared with those obtained using the Short Form (SF)-12 measure of health-related functioning.

RESULTS — Factor analyses of NeuroQoL revealed three physical symptom measures and two psychosocial functioning measures with good reliability (α = 0.86–0.95). NeuroQoL was more strongly associated with measures of neuropathic severity than SF-12, more fully mediated the relationship of diabetic peripheral neuropathy with overall quality of life, and significantly increased explained variance in overall quality of life over SF-12.

CONCLUSIONS — NeuroQoL reliably captures the key dimensions of the patients' experience of diabetic peripheral neuropathy and is a valid tool for studying the impact of neuropathy and foot ulceration on quality of life.

Diabetes Care 26:2549–2555, 2003

Diabetic peripheral neuropathy affects 30–50% of patients with diabetes (1). This complex disorder affects different sets of lower-limb nerve fibers and leads to a variety of clinical manifestations including pain and paresthesiae, numbness in the feet, and unsteadiness. Moreover, the gradual increase in neurological deficits, which is central to the natural history of diabetic peripheral neuropathy, is often accompanied paradoxically by improvement or even disappearance of painful symptoms (2). Lacking warning symptoms or cues to danger, this large population of relatively asymptomatic patients is at high risk of neuropathic foot ulceration. It is estimated that as many as 15% of individuals with diabetic neuropathy will experience a foot ulcer during their lifetime (3). Furthermore, foot ulcers precede 85% of all nontraumatic lower limb amputations in the U.S., resulting in high morbidity and mortality (4). Although diabetic peripheral neuropathy results in severe morbidity, few studies have assessed the quality of life of patients with diabetic peripheral neuropathy (5). The focus of those few reports has been on extreme manifestations of neuropathy such as severe unremitting pain (6,7), chronic foot ulceration (8,9), and/or amputations (10–13), and virtually no reports have addressed the full spectrum of diabetic peripheral neuropathy severity. Second, when functional status has been measured, the instruments used were generic rather than specific, e.g., the Nottingham Health Profile (14), the Sickness Impact Profile (15), the Short Form (SF)-36 (16), and the EUROQoL, EQ-5D (17). The questions in these instruments ask the individual to evaluate his/her physical, social, and mental functional status in general terms and do not ask about the functional problems specific to diabetic peripheral neuropathy, such as disturbances in balance or symptoms of reduced feeling in the feet, which are factors that may compromise quality of life for patients with diabetic peripheral neuropathy. General measures such as the SF-36 are extremely useful for comparisons of function across diseases, but they do not capture specific problems posed by diabetic peripheral neuropathy and are less useful for framing clinical interventions. Finally, although general levels of functioning in specific life domains are important, they are not direct appraisals of quality of life (18,19).

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Received for publication 7 March 2003 and accepted in revised form 30 May 2003.

Abbreviations: MCS, Mental Component Summary; NDS, Neuropathy Disability Score; NeuroQoL, neuropathy-specific quality of life instrument; PCS, Physical Component Summary; SF, Short Form; VPT, vibration perception threshold.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Individuals can report similar levels of dysfunction and differ in their subjective judgments as to the impact of these dysfunctions on their overall quality of life.

In this study, diabetic peripheral neuropathy–related quality of life is conceptualized as individuals' overall, subjective assessment of their quality of life given their specific experience of diabetic peripheral neuropathy and the effects of diabetic peripheral neuropathy on their functioning in several life domains. The development and psychometric properties of a new instrument, the neuropathy-specific quality of life instrument (NeuroQoL), are herein reported and the results are compared with those obtained using a generic measure of health-related functioning, the SF-12 (20).

RESEARCH DESIGN AND METHODS

— The sequence for the development of the NeuroQoL was as follows: *1*) an item development phase that comprised a literature review, discussions with an expert panel, and semistructured interviews with patients; *2*) a pilot phase that identified and screened out items that failed to meet minimal criteria for inclusion; and *3*) a full psychometric validation phase that was conducted within an ongoing U.K. and U.S. collaborative study into the psychological determinants of preventive foot care behavior and quality of life. Permission to conduct all phases was granted by the Central Manchester Research Ethical Review Committee and, for the last phase, by Institutional Review Boards at Johns Hopkins Hospital and Pennsylvania State University. The main focus of this study is on the third, psychometric validation phase.

Item construction

Patients with established diabetic peripheral neuropathy (defined as vibration perception threshold [VPT], which is a quantitative measure of a large fiber dysfunction, ≥25 V at the hallux [21]) and diabetic control subjects with no evidence of neuropathy attending the Manchester Diabetes Center (Manchester, U.K.) were invited to participate in a series of semistructured, in-depth interviews in small (four- to six-person) focus groups. The sample comprised 15 diabetic control subjects and 47 patients with diabetic neuropathy. Patients with diabetic peripheral neuropathy were selected to cover a full range of clinical manifestations and included individuals with reduced feeling in the feet (e.g., numbness in the feet or unsteadiness), asymptomatic patients, individuals with neuropathic pain, and patients with active foot ulcers or a history of ulceration. Interviews were used to elicit domains of life important for patients' quality of life that were affected by neuropathy. Transcripts of the interviews were analyzed by four independent reviewers, and an initial 49-item draft instrument (the NeuroQoL) was generated based on the content analysis of the main themes. In addition, for each item there was a paired item that assessed either the "bother" (for physical symptoms) or the "importance" (for psychosocial function) associated with that item.

Pilot test

The 49-item NeuroQoL, was piloted on two occasions: 7–10 days apart on 38 diabetic control subjects with no evidence of neuropathy and 115 patients with diabetic peripheral neuropathy. The instrument was administered to patients attending diabetes treatment centers in both the U.K. and the U.S. Following initial statistical analyses, six items were excluded as they had low agreement (correlation) between the two time points and/or did not discriminate between the neuropathy and control groups (22). Wording changes were made to several other items to clarify their meaning.

Validation study

Subjects. In this study, a sample of 418 consecutive patients with diabetic peripheral neuropathy and either type 1 or type 2 diabetes was recruited from three sites: Manchester, U.K.; Baltimore, Maryland; and State College, Pennsylvania. In accordance with the international diagnostic guidelines for neuropathy (23), two objective tests of neurological dysfunction were used to diagnose neuropathy: the VPT (described in Item Construction section) and the Neuropathy Disability Score (NDS). The NDS, a composite, quantitative measure of both large- and small-fiber dysfunction, was derived from examination of pain sensation using a Neurotip, vibration sensation using a 128-Hz tuning fork, temperature sensation on a dorsal surface of the foot using warm and cool rods, and Achilles reflex using a tendon hammer. The sensory modalities were scored as either present (score of 0) or reduced/absent (score of 1) for each side, and reflexes as normal (score of 0), present with reinforcement (score of 1), or absent (score of 2) per side. The maximum score is 10, whereas a score of 0 represents a totally normal peripheral nervous system examination. Patients were diagnosed as having neuropathy if they had NDS ≥3 and a mean VPT ≥25 V (24). A history of foot ulcers was obtained by asking each subject: "Have you ever had a foot ulcer (an open sore on your foot)?" Those answering in the affirmative were verified by examination of medical records and careful podiatric assessment. A foot ulcer was defined as a full thickness skin break below the malleoli. Patients were excluded if they had peripheral vascular disease (defined as <1 palpable foot pulse or previous bypass surgery/angioplasty), a history of major amputation (any lower limb amputation proximal to the midfoot), or other severe chronic medical diseases or complications of diabetes (such as widespread malignant disease or renal failure/dialysis) precluding participation. Patients were also excluded if they were unable to understand sufficient English, had insufficient (corrected) vision to complete the questionnaires without assistance, or were unable to complete questionnaires for other reasons.

Instrument. The instrument consisted of 43 items assessing diabetic peripheral neuropathy–related symptoms and psychosocial functioning in several primary domains: *1*) painful symptoms and paresthesia, e.g., burning or throbbing in the feet; *2*) symptoms of reduced/lost feeling in the feet, e.g., inability to feel temperature and/or objects with the feet; *3*) diffuse sensory motor symptoms, e.g., unsteadiness while standing/walking; *4*) limitations in daily activities, e.g., inability to perform paid work or leisure activities; *5*) interpersonal problems, e.g., physical/emotional dependence on others; and 6) emotional burden, e.g., being treated differently from other people. Other domains included overall impact of neuropathy, medication side effects, and sleep disturbance. Each patient rated the neuropathic symptoms and psychosocial problems on a five-point Likert scale (all the time, most of the time, some of the time, occasionally, never).

Finally, a single item was used to measure the participant's overall quality of life. The item stated, "Overall, I would

rate my quality of life as" with responses using a five-point Likert format (excellent, very good, good, fair, poor). This response format is unlike any other item on the NeuroQoL, thereby reducing shared method variance with the neuropathy-specific items.

Procedure. Patients were screened for participation at all three sites by their usual physician or podiatrist. After explanation of the study details and an initial examination for suitability, written consent was obtained. After neurological and vascular examination, patients completed the NeuroQoL (which included items assessing symptoms and functioning specific to diabetic peripheral neuropathy), the single item presenting their overall quality of life, and the SF-12 (24). The NeuroQoL was always presented before the SF-12.

Statistical analysis

Two measures, the Physical Component Summary (PCS) and the Mental Component Summary (MCS), were derived from the SF-12 using the standard scoring algorithms (25). These were used in all analyses of the SF-12.

Psychometric analysis. To assess convergent and discriminant validity, two principle components factor analyses using equamax rotation were performed, one for physical symptoms and one for psychosocial items. Reliability (inter-item consistency) was measured by Cronbach's α. Floor effects (percentage of respondents who had the minimum possible scale score) and ceiling effects (percentage of respondents who had the maximum possible score) were assessed. Pearson correlations assessed the association between NeuroQoL physical and psychosocial measures.

Validation analysis. Two sets of multivariate linear ordinary least squares regression analyses were performed to examine the association of the NeuroQoL symptom and psychosocial function scales and the SF-12 scales with the severity of neuropathy as measured by the NDS and the presence or history of foot ulcers (criterion validity). All analyses controlled for several potential confounding factors. It was hypothesized that the criterion validity of the NeuroQoL would exceed that of the SF-12 as seen by its greater associations with neuropathy. Whereas two measures (VPT and NDS) were used to diagnose neuropathy according to recommendations (23), the NDS alone was used for criterion validation as it assesses both large- and small-fiber dysfunction and hence is a more comprehensive measure of neuropathic deficits than VPT, which only measures large-fiber dysfunction. Two sets of multivariate linear ordinary least squares regression analyses determined whether the NeuroQoL explained more variance than the SF-12 in overall quality of life and whether it added to explanatory power when combined with the SF-12 (incremental validity). The first set of analyses compared the NeuroQoL physical symptom measures with the SF-12 PCS, and the second compared NeuroQoL psychosocial functioning measures with the SF-12 MCS. Whether the NeuroQoL was more powerful than the SF-12 in mediating the relationship between quality of life and neuropathy (NDS and ulcers) was assessed by comparing the results from two sets of multivariate linear ordinary least squares regression analyses (construct validity). Mediation is demonstrated when the introduction of a potential mediator reduces the original relationship. This analysis shows which measure better captures the aspects of diabetic peripheral neuropathy that influence quality of life; more mediation (greater reduction in the size of the relationship between diabetic peripheral neuropathy and quality of life) indicates that a measure captures a greater portion of the relationship between diabetic peripheral neuropathy and quality of life. Overall quality of life was measured by the one-item measure from the NeuroQoL. The baseline model shows the relationship of neuropathy to overall quality of life, controlling for a variety of demographic and disease characteristics. It also shows (in parentheses) the β-to-enter for each of the NeuroQoL and SF-12 measures; this indicates the relationship of overall quality of life with each measure if only that single measure was added to the baseline model (this allows a comparison with the strength of each variable's independent relationship when other measures are added in models 1, 2, and 3). In model 1, SF-12 measures were added to the baseline model. In model 2, all relevant NeuroQoL measures were added to the baseline model. In model 3, both NeuroQoL and SF-12 measures were added to the baseline model. All analyses were performed using SPSS, version 10.0.7.

Table 1—*Demographic and disease characteristics of the study population*

Variable	U.K.	U.S.	Total
n	290	128	418
Sex (men) (%)	72.4	67.2	70.8
Age (years)*	61.05 ± 11.82	63.39 ± 9.34	61.76 ± 11.17
Education (%)*			
Primary	3.2	1.6	2.7
Secondary	59.5	43.1	54.5
Some college	25.0	14.6	21.9
College graduate	7.4	21.1	11.5
Postgraduate	4.9	19.5	9.3
Marital status (living alone)	33.2	26.8	31.2
Diabetes type (type 2)*	66.6	87.4	72.9
Diabetes duration (years)	17.31 ± 11.34	16.75 ± 9.85	17.14 ± 10.89
Diabetes complications	1.56 ± 1.05	1.57 ± 1.20	1.56 ± 1.10
Concomitant disorders*	0.76 ± 0.89	1.51 ± 1.29	0.99 ± 1.08
VPT (V)*	39.43 ± 9.48	45.54 ± 8.52	41.29 ± 9.61
NDS*	7.21 ± 2.26	7.67 ± 2.09	7.35 ± 2.22
Foot ulcer history (%)			
Ever*	28.3	50.8	35.3
Current	25.5	17.9	24.3

Data are means ± SD. *Differences between countries significant ($P < 0.05$) based on χ^2 statistic (for percentage) or *t* test (for means).

RESULTS — Demographic and disease characteristics of the subjects are presented in Table 1. There were significant differences between the U.K. and U.S. participants. Specifically, U.S. patients

were older and had higher levels of college/postgraduate education. More of them had type 2 diabetes and concomitant disorders. Concomitant disorders include all self-reported medical conditions other than diabetes and its complications. These conditions were included in the analyses to control for their impact on quality of life. Complications of diabetes include retinopathy ($n = 181$), nephropathy ($n = 66$), and cardiovascular disease ($n = 200$). With respect to neuropathy, U.S. patients had greater deficits on objective testing (NDS, VPT), and a greater proportion had a foot ulcer history. Because of these differences, all bivariate and multivariate analyses controlled for country; multivariate analyses also controlled for all demographic and diabetes factors listed in Table 1.

Psychometric analyses

Preliminary analysis of the 43 NeuroQoL items indicated that four items relating to medication side effects and sleep disturbance did not relate to the measures of diabetic peripheral neuropathy, and those were eliminated from further analysis. Three items did not cluster with the hypothesized dimensions, and another was judged to be redundant; all four were eliminated from further analysis. Seven items measuring subjects' attributions of the impact of diabetic peripheral neuropathy on quality of life were eliminated from the analysis because they comprised an alternative scheme for measuring impact of diabetic peripheral neuropathy. Finally, preliminary psychometric and validation analysis (paralleling the analyses reported below) indicated that the versions of the scales where items were weighted by the level of "bother" or "importance" had no better reliability or validity than the unweighted versions, so no further analysis was performed on the weighted data. The remaining analyses used the 28 items included in the final instrument.

Factor analysis (1 for the 13 physical symptoms and 1 for the 14 psychosocial functioning items) showed good convergent and discriminant validity, and all of the items in each analysis loaded above 0.60 on the hypothesized factor and less on the other factors (Table 2). As hypothesized, the three resulting factors for physical symptoms were: *1*) painful symptoms, 2) reduced feeling, and 3) diffuse sensory motor symptoms. The two resulting factors for psychosocial functioning were: *1*) disruption of daily activities and 2) interpersonal-emotional burden. Two domains (interpersonal and emotional) formed a single factor.

Reliability of the scales ranged from 0.86 to 0.95. Scale scores were computed by taking the mean of the items loading on each factor. Floor effects were modest (14.4–28.4% of respondents had the minimum possible scale score), and there was less evidence of ceiling effects (0.5–19.0% of respondents had the maximum possible scale score). NeuroQoL physical and psychosocial scales were moderately correlated with one another ($r = 0.39$–0.67).

Validation analyses

Criterion validity. Results (Table 3) indicated that the NeuroQoL physical symptom scales and the SF-12 PCS were significantly associated with the NDS, and the NeuroQoL scale assessing symptoms of reduced feeling showed the strongest associations ($\beta = 0.40$, $P < 0.001$). Both the NeuroQoL physical symptom measure and SF-12 PCS were less strongly associated with ulcers than with the NDS scores, with the NeuroQoL scale of reduced feeling in the feet showing the greatest association with ulcers ($\beta = 0.24$, $P < 0.001$). NeuroQoL scales of interpersonal-emotional burden were significantly associated with both ulcers ($\beta = 0.27$, $P < 0.001$) and the NDS ($\beta = 0.29$, $P < 0.001$). The SF-12 MCS was associated with neither the NDS nor ulcers. Thus, as expected, the NeuroQoL subscales were more strongly associated than the SF-12 measures with both criteria of neuropathic severity.

Incremental validity. The NeuroQoL and the SF-12 were similar in their ability to predict overall quality of life (Table 4). NeuroQoL physical symptom measures accounted for more variance in overall quality of life than the SF-12 PCS in analyses including both NDS and ulcers ($r^2 = 0.287$ and 0.295 vs. 0.257 and 0.260). In contrast, NeuroQoL psychosocial functioning measures accounted for less variance in overall quality of life than the SF-12 MCS in analyses including both NDS and ulcers ($r^2 = 0.350$ and 0.350 vs. 0.374 and 0.372). At least one NeuroQoL measure was significant in every model that included SF-12 PCS or MCS, demonstrating that they were independent predictors of overall quality of life.

Construct validity. The degree of mediation can be observed by comparing the coefficient of the neuropathy measure in the baseline model with that in other models incorporating NeuroQoL and SF-12 measures (Table 4). The NeuroQoL physical symptom measures and the SF-12 PCS both mediated the relationship of NDS scores with overall quality of life (both measures reduced the relationship between overall quality of life and neuropathy severity). The SF-12 PCS was superior in mediating the relationship of ulcers with overall quality of life (entering the NeuroQoL measures did not reduce the relationship to nonsignificance). The NeuroQoL psychosocial functioning measures were superior to the SF-12 MCS in mediating the relationship of NDS and ulcers with overall quality of life (MCS did not reduce either of the relationships to nonsignificance, whereas the NeuroQoL measures reduced both to nonsignificance).

CONCLUSIONS — NeuroQoL is a reliable and valid measure that allows insight into the effects of diabetic peripheral neuropathy and its sequelae on an individual's quality of life. The NeuroQoL physical symptom and psychosocial functioning scales proved their validity by demonstrating stronger associations than the SF-12 with the clinical indicators of neuropathic severity, by mediating more fully the relationship of neuropathy to overall quality of life, and by explaining additional variance beyond that accounted for by the SF-12 measures.

The regression analyses produced a number of clinically meaningful results, for example, whereas all NeuroQoL physical symptom scales were significantly associated with the NDS, the associations with ulcers were either weaker or absent (for painful symptoms), and these symptoms did not mediate the relationship between ulcers and overall quality of life. These findings are in keeping with clinical practice where ulcers occur in more advanced neuropathy, often with symptoms of sensory loss but in the absence of pain, and suggest that ulcers have independent effects on quality of life beyond symptoms of sensory loss or pain.

Interestingly, the generic SF-12 MCS was neither associated with the severity of neuropathy nor mediated the effects of NDS or ulcers on overall quality of life. In contrast, a specific measure of interper-

Table 2—*Factor loadings and descriptive statistics of NeuroQoL*

Item	Factors for physical symptoms			Factors for psychosocial symptoms	
	Factor 1 (pain)	Factor 2 (reduced feeling)	Factor 3 (diffuse sensory motor)	Factor 1 (interpersonal/ emotional burden)	Factor 2 (activity limitations)
Burning in your legs or feet	0.75				
Excessive heat or cold in your legs or feet	0.63				
Pins and needles in your legs or feet	0.75				
Shooting or stabbing pain in your legs or feet	0.76				
Throbbing in your legs and feet	0.78				
Sensations in your legs or feet that make them jump	0.72				
Irritation of the skin caused by something touching your feet	0.60				
Numbness in your feet		0.79			
Inability to feel the difference between hot and cold with your feet		0.91			
Inability to feel objects with your feet		0.92			
Weakness in your hands			0.65		
Problems with balance or unsteadiness while walking			0.90		
Problems with balance or unsteadiness while standing			0.88		
As a result of foot problems:					
Your self-confidence has been affected				0.81	
You feel older than your years				0.80	
Your life is a struggle				0.79	
You feel frustrated				0.79	
You feel embarrassed				0.78	
You feel depressed				0.72	
Foot problems interfere with close relationships				0.72	0.44
As a result of foot problems:					
You feel more physically dependent				0.67	0.56
You feel more emotionally dependent				0.70	0.44
Your role in family changed				0.66	0.50
You are treated differently				0.65	
Foot problems interfere with:					
Ability to perform paid work					0.73
Ability to perform daily tasks					0.76
Ability to take part in leisure activities					0.76
Eingenvalue	6.12	1.86	1.07	8.84	1.26
Percentage of variance explained	47.11	14.28	8.21	58.95	8.38
Valid *N*	416	416	412	409	416
Scale mean	1.98	2.88	2.28	2.52	2.31
Scale SD	0.89	1.50	1.19	1.38	1.19
Percentage minimum score	14.4	20.4	25.5	28.4	20.70
Percentage maximum score	0.5	19.0	4.4	8.3	1.0
Cronbach's α	0.88	0.90	0.86	0.90	0.95

Note: factor analyses were performed separately on physical and psychosocial items. All loadings ≥0.40 are shown.

sonal-emotional burden from the NeuroQoL was strongly associated with markers of neuropathic severity and was an important mediator of the effects of neuropathy on quality of life. This points to the need for assessing specific rather than generic emotional burden when studying disease-related quality of life. On the other hand, the mental functioning scale of the SF-12 accounted for more variance in quality of life than the NeuroQoL psychosocial functioning scale. This indicates the ability of the generic measure to account for variance in quality of life, which is not specific to the condition that is the focus of the study.

The NeuroQoL contrasts with other approaches to quality of life used in studies of diabetic peripheral neuropathy. First, it represents a patient-centered, neuropathy-specific method to quality of life assessment as the content of the domains included in this instrument was derived directly from interviews with patients affected by neuropathy and foot ulcers. In comparison, an examination of the item content of the SF-12 PCS suggests that its predictive power, unlike that of the NeuroQoL, benefits from confounding of psychological and somatic items, e.g., "how much did pain interfere with your normal work (including work both outside the home and housework)?"

Table 3—*Criterion validity: the associations of NeuroQoL and SF-12 scales with neuropathy*

NeuroQoL and SF-12 scale criterion variables	Predictors	
	NDS	Ulcer
Painful symptoms	0.165*	−0.095
Symptoms of reduced feeling	0.395*	0.237*
Diffuse sensory motor symptoms	0.283*	0.105†
SF-12 PCS	−0.268*	−0.135‡
Activity limitations	0.234*	0.270*
Interpersonal-emotional burden	0.294*	0.270*
SF-12 MCS	−0.085	−0.014

Note: cell entries are standardized regression (β) coefficients, controlling for country, age, sex, education, marital status, type of diabetes, duration of diabetes, sequelae of diabetes, and concomitant diseases. Each cell represents a separate analysis of the listed outcome using the predictor indicated. *$P < 0.001$; †$P < 0.05$; ‡$P < 0.01$.

Second, because the NeuroQoL differentiates among the specific symptomatic expressions of neuropathy, unlike the global approach to symptoms of the SF-12 PCS, it provides both the clinical investigator and the treating clinician with specific points for interventions. Behavioral interventions can be more tuned to the nature of the underlying pathology, and the outcome expectations surrounding pharmacological treatment can be more precise. Most importantly, if evaluations of quality of care are to represent accurately the effectiveness of treatment systems, then they need to incorporate disease-specific measures of quality of life that identify competence in the management of specific diseases (26). Generic assessments have a role to play in quality assurance, but their failure to detect disease-specific outcomes is an inherent limitation. Therefore, it is important to use disease-specific instruments such as the NeuroQoL when studying or treating populations that share a common disease state.

Table 4—*Incremental and construct validity: NeuroQoL and SF-12 measures as predictors of overall quality of life*

Predictors	Baseline model	Model 1 (SF-12 only)	Model 2 (NeuroQoL only)	Model 3 (SF-12 and NeuroQoL)
NDS	−0.15*	−0.05	−0.02	0.02
Painful symptoms	(−0.37)†	NA	−0.22†	−0.16*
Symptoms of reduced feeling	(−0.33)†	NA	−0.12	−0.11
Sensory motor symptoms	(−0.38)†	NA	−0.21*	−0.14‡
SF-12 PCS	(0.41)†	0.41†	NA	0.25†
r^2	0.121	0.257	0.287	0.322
Ulcer	−0.13‡	−0.08	−0.10‡	−0.08
Painful symptoms	(−0.41)†	NA	−0.25†	−0.19*
Symptoms of reduced feeling	(−0.33)†	NA	−0.09	−0.07
Sensory motor symptoms	(−0.39)†	NA	−0.20†	−0.14‡
SF-12 PCS	(0.42)†	0.42†	NA	−0.23†
r^2	0.112	0.260	0.295	0.327
NDS	−0.15*	−0.11‡	−0.00	−0.04
Activity limitations	(−0.38)†	NA	−0.09	−0.12‡
Interpersonal-emotional burden	(−0.53)†	NA	−0.47†	−0.22*
SF-12 MCS	(0.52)†	0.52†	NA	0.36†
r^2	0.118	0.374	0.350	0.429
Ulcer	−0.13‡	−0.12‡	0.02	−0.03
Activity limitations	(−0.39)†	NA	−0.10	−0.12‡
Interpersonal-emotional burden	(−0.53)†	NA	−0.46†	−0.22*
SF-12 MCS	(0.52)†	0.52†	NA	0.36†
r^2	0.110	0.372	0.350	0.427

Note: cell entries are standardized regression (β) coefficients, controlling for country, age, sex, education, marital status, type of diabetes, duration of diabetes, sequelae of diabetes, and concomitant diseases. Baseline model shows β coefficient for NDS or ulcer and in parentheses the β-to-enter (β if only that one scale were added to the baseline model) for NeuroQoL and SF-12 measures; r^2 for the baseline model does not include any NeuroQoL or SF-12 measures. Models 1–3 show coefficients for NDS/ulcer and all NeuroQoL and SF-12 measures in that model; variables not included are designated. *$P < 0.01$; †$P < 0.001$; ‡$P < 0.05$. NA, not applicable.

Acknowledgments— Part of this research was supported by Park Davis (Ann Arbor, MI). We also acknowledge funding support from both Diabetes U.K. and the American Diabetes Association.

We particularly thank Howard Foyt, MD, for encouragement. In addition, we are grateful to all our collaborators (A. Findlow, C. Waterman, A. Garrow, R. Chandrasekaran, N. Scheffler, M. Becker, J.S. Ulbrecht, and P.R. Cavanagh) and to the patients who took part. Copies of the instrument are available from the corresponding author.

References

1. Shaw JE, Zimmet PZ: The epidemiology of diabetic neuropathy. *Diabetes Rev* 7:245–252, 1999
2. Boulton AJM, Malik RA: Diabetes mellitus: neuropathy. In *Endocrinology*. 4th ed. DeGroot LJ, Jameson JL, Eds. Philadelphia, WB Saunders Co, 2000, p. 868–878
3. Reiber GE: Epidemiology of foot ulcers and amputations in the diabetic foot. In *The Diabetic Foot*. 6th ed. Bowker JH, Pfeifer MA, Eds. St. Louis, MO, Mosby, 2001, p. 13–32
4. Pecoraro RE, Reiber GE, Burgess EM: Pathways to diabetic limb amputation: basis for prevention. *Diabetes Care* 13: 513–521, 1990
5. Vileikyte L: Psychological aspects of diabetic peripheral neuropathy. *Diabetes Rev* 7:387–394, 1999
6. Benbow SJ, Wallymahmed ME, Macfarlane IA: Diabetic peripheral neuropathy and quality of life. *Q J Med* 91:733–737, 1998
7. Galer BS, Gianas A, Jensen MP: Painful diabetic polyneuropathy: epidemiology, pain description, and quality of life. *Diabetes Res Clin Pract* 47:123–128, 2000
8. Brod M: Quality of life issues in patients with diabetes and lower extremity ulcers: patients and care givers. *Qual Life Res* 7:365–372, 1998

9. Meijer JW, Trip J, Jaegers SM, Links TP, Smits AJ, Groothoff JW, Eisma WH: Quality of life in patients with diabetic foot ulcers. *Disabil Rehabil* 23:336–340, 2001
10. Carrington A, Mawdsley SKV, Morley M, Kincey J, Boulton AJM: Psychological status of diabetic people with or without lower limb disability. *Diabetes Res Clin Pract* 32:19–25, 1996
11. Peters EJG, Childs MR, Wunderlich RP, Harkless LB, Armstrong DG, Lavery LA: Functional status of persons with diabetes-related lower-extremity amputations. *Diabetes Care* 24:1799–1804, 2001
12. Ahroni JH, Boyko EJ: Responsiveness of the SF-36 among veterans with diabetes mellitus. *J Diabetes Complications* 14:31–39, 2000
13. Tennvall GR, Apelqvist J: Health-related quality of life in patients with diabetes mellitus and foot ulcers. *J Diabetes Complications* 14:235–241, 2000
14. Hunt SM, McKenna SP, McEwen J, Williams J, Papp E: The Nottingham health profile: subjective health status and medical consultations. *Soc Sci Med* 15:221–229, 1981
15. Bergner M, Bobbitt RA, Carter WB, Gilson BS: The sickness impact profile: development and final revision of a health status measure. *Med Care* 19:78–86, 1981
16. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36) I: conceptual framework and item selection. *Med Care* 30:473–483, 1992
17. Busschbach JJ, McDonnell J, Essink-Bot ML, van Hout BA: Estimating parametric relationships between health description and health valuation with an application to the EuroQol EQ-5D. *J Health Econ* 18: 551–571, 1999
18. Bradley C: Importance of differentiating health status from quality of life (Letter). *Lancet* 357:7–8, 2001
19. Leventhal H, Colman S: Quality of life: a process view. *Psychol Health* 12:753–767, 1997
20. Ware Jr JE, Kosinski M, Keller S: A 12-item short-form health survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 34:220–233, 1996
21. Abbott CA, Vileikyte L, Williamson S, Carrington AL, Boulton AJM: Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic foot ulceration. *Diabetes Care* 21:1071–1074, 1998
22. Vileikyte L, Bundy CE, Shaw JE, Walsh T, Tomenson B, Boulton AJM: The first neuropathy-specific quality of life instrument: construction of scales and preliminary results of reliability and validity (Abstract). *Diabetes* 47 (Suppl. 1):A44, 1998
23. Dyck PJ, Karnes JL, Daube J, O'Brien P, Service FJ: Clinical and neuropathological criteria for the diagnosis and staging of diabetic polyneuropathy. *Brain* 108:861–880, 1985
24. Young MJ, Boulton AJM, Macleod AF, Williams DRR, Sonksen PH: A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. *Diabetologia* 36:150–154, 1993
25. Ware JE, Kosinski M, Keller SD: *How to Score the SF-12 Physical and Mental Health Summary Scales*. 2nd ed. Boston, MA, The Health Institute, New England Medical Center, 1995
26. Donaldson MS (Ed.): *Measuring the Quality of Health Care*. Washington, DC, National Academy Press, 1999, p. 1–24