

Chapter 6

PROMs for Systemic Lupus Erythematosus

Brian Bekker Hansen and Lise Højbjerg

Introduction and Background

Systemic Lupus Erythematosus (SLE) is a heterogeneous, inflammatory, multisystem autoimmune disease. Symptoms include joint pain and swelling, skin rash, and fatigue [1]. These symptoms impact daily and leisure activities, work productivity, emotional well-being, relationships, physical functioning, and social functioning. The symptoms of SLE appear to occur in “flares.” Subsequently, the impact of SLE can vary over time, depending on whether symptoms are present and/or more intense in severity. In addition to joint inflammation, SLE often impacts the heart, skin, lungs, blood vessels, liver, kidneys, and nervous system of patients [1]. The symptoms of SLE contribute to a substantially reduced health-related quality of life (HRQoL) [2]. A number of patient reported outcome measures (PROMs) have been used to assess the burden of SLE on patients, including measurements of fatigue, pain, emotional/psychological well-being, and work productivity. Furthermore, both SLE-specific and generic PROMs measuring HRQoL have been used.

Treatment of the more severe cases of SLE involves a balance between suppressing the signs and symptoms of the disease and minimizing the toxicities of the drugs used. With treatment, disease activity indices might improve but the patient might feel potentially worse due to the side effects of the medication. In the evaluation of patients with SLE, it is important to measure the patients’ perspective because the disease is likely to have a significant impact on physical, social, and psychological aspects impacting the patients’ HRQoL. Improvements in clinical outcome measures (e.g., lab tests, clinical evaluation) in patients with SLE may not always translate to improvements in how patients feel or function. PROMs can be used to measure all relevant and important SLE symptoms and patient-perceived abilities to function and perform daily activities.

B.B. Hansen (✉) • L. Højbjerg

Global Market Access, Novo Nordisk A/S, Søborg, Denmark

e-mail: bbkh@novonordisk.com; lhb@novonordisk.com

Conceptual Model for SLE

A conceptual model can be used to illustrate the humanistic and economic burden of key symptoms and their impact. Such models are valuable in terms of identifying key measurement concepts, which can be used to demonstrate treatment benefit, providing insight into how best to measure particular concepts, and providing a contextual basis for interpreting patient reported findings. The conceptual model (Fig. 6.1) published by Holloway et al. (2014) [3] is based on a structured literature review of qualitative and quantitative articles and can be used to assess whether available disease-specific PROMs target key symptoms and impacts of SLE. The resulting conceptual model shows the symptoms and impacts identified as key concepts related to SLE (Fig. 6.1) [3].

Fatigue and pain are two of the most important and frequent symptoms for patients with SLE [4–10]. Specifically, patients describe mental and physical symptoms of fatigue including impacts on social life [4], emotional well-being [4, 11], physical functioning [4, 12], sleep [9, 13–15], and the ability to complete daily tasks and leisure activities [16, 17]. Important cognitive symptoms include being “unable to think clearly” and memory loss [12]. Other SLE symptoms include skin rash [16, 17], weight gain [4, 16], and hair loss [5, 16]. Symptoms impact all areas of HRQoL, with detrimental consequences observed in the physical, emotional, and social functioning of

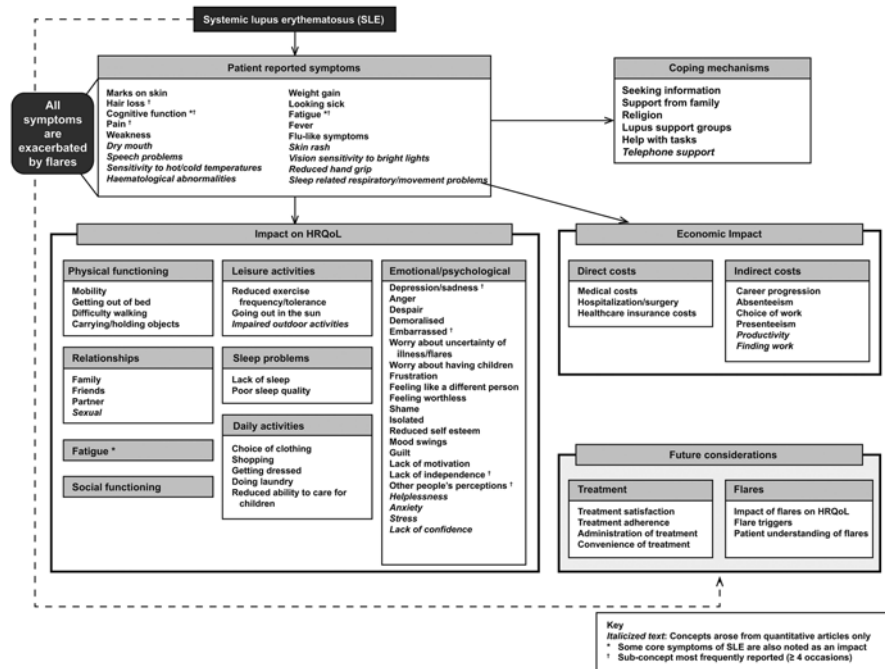


Fig. 6.1 Conceptual model [3]. Reprinted with permission from Holloway et al. [3]

SLE patients, as well as in their working life. In terms of the impact on emotional well-being, patients with SLE frequently feel sad, depressed, angry, and demoralized [4, 5, 8, 12, 18, 19]. In particular, patients feel embarrassed [4–6] or self-conscious, or they lack self-esteem, primarily because of the changes in their appearance (such as hair loss and skin manifestations) [6, 12]. Patients fear their disease worsening, and experience anxiety or stress related to the symptoms and the unpredictability of SLE [8, 16, 18, 19]. Many also experience feelings of frustration and a lack of: (1) confidence, (2) independence, (3) control over one’s life, and (4) belonging [20]. SLE has a significant negative impact on patients’ physical functioning, such as walking difficulty and other mobility problems [2, 12, 21, 22]. This affects various daily activities including opening jars and moving heavy objects [22], shopping [12], doing laundry [6], getting dressed [6], and caring for their children [4, 6]. Wider impacts on social functioning and working life are also reported [7, 20]. Specifically, patients have difficulty maintaining family and sexual relationships [4, 6, 18]. SLE also impacts negatively on patients’ career progression [5], absence from work [12], difficulty concentrating at work or study [6, 10, 12], and their choice of work [6, 16].

The conceptual model presented suggests that patients use various coping mechanisms for the unpredictability of flares, including: (1) seeking and using information, (2) seeking emotional and practical help via the Internet, (3) receiving support from hospital meetings, (4) receiving support from family, (5) attending lupus support groups, and (6) religious practice [4, 6, 16]. The conceptual model also includes concepts such as treatment satisfaction, adherence, and the impact of flares in a “future considerations” box. There was a lack of evidence pertaining to these concepts in the currently available literature.

The conceptual model also demonstrates the economic burden of disease, in particular the high medical costs associated with SLE compared to other chronic diseases [23]. Substantial levels of inpatient care, medication/prescriptions, and visits to healthcare professionals (HCP), which are all increased by “flares,” are the main drivers of direct costs in the treatment of SLE [24]. The conceptual model also shows that SLE is associated with high indirect costs due to lost productivity [25] resulting from unemployment and absenteeism [26], with “in-flare” patients with SLE having increased frequency and duration of time off work [27, 28].

Patient Reported Outcome Measures

Fatigue

Fatigue is one of the most important and frequent symptoms for patients with SLE. For many patients it is the most enduring complaint [15, 18]. Fatigue is described in various ways including tiredness, reduced energy, and mental fatigue, and it often impacts the HRQoL in patients with SLE [9, 20]. The lack of a clear definition of fatigue is evident in the literature and reflects the complex nature of the concept. Furthermore, there is a lack of consistent definition from patients and clinicians in terms of what

fatigue really means to patients and how it differs from other related concepts such as “normal tiredness” and “energy.” As a result, there is a notable variety and disparity in the content of the various PROMs developed to measure fatigue.

Several PROMs measuring fatigue exist. Some of the most frequently used are the Multidimensional Fatigue Inventory (MFI), Multidimensional Assessment of Fatigue (MAF), Fatigue Severity Scale (FSS), and the Functional Assessment of Chronic Illness Therapy—Fatigue scale (FACIT-Fatigue). For none of the listed fatigue PROMs the content and face validity have been established in patients with SLE using qualitative and cognitive debriefing methodologies in the development process. Of the fatigue measures, FACIT-Fatigue (Appendix 1) is currently one of the most frequently applied in recent clinical trials of belimumab [29, 30], and has been extensively validated within rheumatic diseases [31–33]. In a qualitative research study, patients with SLE perceived FACIT-Fatigue as a relevant and appropriate measure of fatigue in SLE [17].

FACIT-Fatigue is a one-dimensional 13-item PROM assessing self-reported fatigue and its impact upon functioning and daily activities. It asks patients to indicate how true each statement is on a 5-point Likert scale from 0 (*Not at all*) to 4 (*Very much*) with a 7-day recall period (see Table 6.1 and Appendix 1). The estimated completion time for the patient is 3–5 min, which limits the burden to both patient and medical staff at the clinic. The written instructions to the patient appear clear and no complex clinical terminology is included. In general the item-wording is written in a simple and understandable language for most patients.

FACIT-Fatigue has demonstrated the strong psychometric properties in terms of evidence of internal consistency, reliability, known-groups validity, concurrent validity, and ability to detect change in patients with SLE (Box 6.1) [31]. Further, test–retest reliability has been demonstrated in patients with psoriatic arthritis [32]. A minimal clinically important difference (MCID) has not been established in patients with SLE; however, in patients with rheumatoid arthritis the MCID has been estimated to be a 3–4 point change from a baseline in the score [33].

Table 6.1 Characteristics of functional assessment of chronic illness therapy—fatigue scale (FACIT-Fatigue)

Instrument characteristics	Description
Target population	Patients experiencing fatigue; no specific age range
Number of items	13
Completion time	3–5 min
Recall period	Past 7 days
Format and layout	The format and layout of the questionnaire appear simple and straightforward
Coverage	For example, fatigue, energy, tiredness, and impact on frustration and social activities
Response options	5-Point Likert scale: “Not at all”, “A little bit”, “Somewhat”, “Quite a bit”, and “Very much”
Mode of administration	Self-administered by the patient
Content validation	No patients with SLE were involved in qualitative research in the development phase

Box 6.1: Fatigue

Fatigue is one of the most frequent symptoms reported by patients with SLE.

The Functional Assessment for Chronic Illness Therapy — Fatigue scale (FACIT-Fatigue) is a well-established fatigue measure in SLE, and its psychometric properties in SLE has been established. It consists of 13 items written in a simple language without complex clinical terminology.

Pain

Pain is one of the most common complaints for patients with SLE and is described as “pain,” “hurt,” or “ache” and some patients speak specifically of “joint pain” [4–6]. Due to the subjective and variable nature of pain, it is best evaluated using patient-reported assessments.

In a review of previous studies involving SLE patients, it was reported that amongst a mean of 460 patients per study, 71–89% of patients reported experiencing pain [7]. Many publications suggest there is an association of pain with fatigue [13–15, 34] and between pain and poor sleep quality [15]. PROMs specific to pain include the McGill Pain Questionnaire (MPQ) and the Brief Pain Inventory (BPI) (Table 6.2).

The MPQ exists as both a standard form (20 items) [35] and a short form (15 items) [36]. The standard form is more comprehensive. The MPQ is a multidimensional instrument designed to measure the physical and emotional components of pain. The MPQ was developed with minimal patient input ($n=10$) and the patient group or inclusion/exclusion criteria was not specified. The instrument can be administered in any mode (e.g., self-administered or by a clinician), but the selected mode of administration should be consistent. The item and response wording is very clinical and patients with a low reading ability are likely to not understand the terminology. The recall period for assessment is “currently” or “presently.” The MPQ focuses on pain, primarily assessing descriptors of pain. Some impacts of pain are assessed including pain-related fatigue and emotional impacts. However, in the literature review for the conceptual model, it was found that SLE patients tended to discuss SLE-related pain in terms of its location—for example, muscle pain, joint pain, or headaches—rather than how it feels (i.e., aches or discomfort), which could be problematic as the MPQ does not assess where pain occurs. The recall period of current/present pain may not be appropriate for SLE, given that symptoms may arise at any time and, unless the patient is experiencing symptoms during completion, such episodes could be missed. The Brief Pain Inventory (Appendix 2) is a PROM designed to assess the intensity of pain and the extent to which pain interferes with normal function [37]. The BPI is available as a standard form and a short form. The shorter version (BPI-SF) has become the standard for use in clinical and research applications [38] and is the focus for this review (Box 6.2). The BPI-SF focuses on pain and assesses various aspects of pain including the location, severity, and the impact of pain on patients’ HRQoL. In line with the conceptual model (Fig. 6.1), the impact concepts assessed include daily activities, emotional/psycho-

Table 6.2 Characteristics of McGill Pain Questionnaire (MPQ) and Brief Pain Inventory (BPI-SF)

Instrument characteristics	Description (MPQ)	Description (BPI-SF)
Target population	Adults, all patients groups	Adults, all patients groups
Number of items	20	15
Completion time	10–15 min	5 min
Recall period	Asks patients to think about “present pain”	24 h
Format and layout	The format varies in different versions that are available online	The format of the questionnaire is clear and simple to follow
Coverage	Three sections:	1. Pain severity
	1. What does your pain feel like?	2. Extent to which pain interferes with daily life
	2. How does your pain change with time?	
	3. How strong is your pain?	
Response options	Likert scales from 2-point to 6-point scales	Twelve items ask patients to respond on a 0–10 scale. One item comprises a binary yes/no response and one item includes a diagram of a person that patients are asked to shade where they feel pain. The shading item is for informative purposes only and is not included in the scoring
Mode of administration	Self-administered or clinician administered (different version)	Self-administered by the patient
Content validation	The MPQ involved in-depth interviews with 10 patients, and health care professionals. No SLE patient input	No patients with SLE were involved in qualitative research in the development phase

logical impacts, physical functioning, relationships, and sleep problems. With a focus on pain, the BPI-SF has good concept coverage, assessing not only descriptors of pain, but also the location of pain and the impact on patients' HRQoL. Most items have an 11-point rating scale; for severity, 0=no pain and 10=pain as bad as you can imagine; and for interference, 0=does not interfere and 10=completely interferes. One item has a binary yes/no response and another asks patients to shade a diagram to show where they have pain. One item has a 0–100% scale increasing in 10% increments. The format of the questionnaire is clear and simple to follow, and thus does not appear to pose any problems for comprehension or accurate completion. BPI-SF has demonstrated strong psychometric properties in terms of internal consistency [39], test–retest reliability [37], construct [39–41] and discriminant [37, 42] validity and responsiveness [42], and a recent study confirmed the findings in an SLE population [43]. The BPI-SF appears to be the strongest measure of pain of the 2 reviewed.

Box 6.2: Pain

Pain is one of the most common complaints for patients with SLE in qualitative research and is associated with fatigue and poor sleep quality.

The **Brief Pain Inventory (BPI-SF)** can be recommended for use in patients with SLE to assess the intensity of pain and the extent to which pain interferes with normal function.

Further, qualitative research and validation of the psychometric properties of BPI are recommended to be explored in patients with SLE.

Emotional Well-Being and Depression

SLE has been shown to impact patient's emotional well-being. Changes in appearance due to the disease and side effects of treatment affect the patient's perception of their body image and sexuality, which in turn impacts their emotional well-being [8]. Patients with SLE frequently feel sad, depressed, angry, embarrassed, and have lack of self-esteem [4–6, 12]. Emotional well-being is a very broad term, and the focus of this discussion will be on anxiety and depression as it arose most frequently in the qualitative literature of patients with SLE.

Two frequently used PROMs assessing anxiety and depression are Beck's Depression Inventory (BDI) and the Hospital Anxiety and Depression Scale (HADS). Neither BDI nor HADS have been validated in patients with SLE. However, both instruments are suitable to use in clinical practice in patients with SLE who experience an impact on anxiety and depression. However, HADS could be considered over BDI, as the instructions are more detailed and straightforward and the item wording is clearer. Further, the response options in the HADS are worded simply and clearly defined, and thus should not pose any problems for patients with SLE.

HADS is a 14-item PROM assessing self-reported anxiety and depression (Box 6.3). Patients should indicate to which degree each of the 14 statements applies on a 4-point Likert-scale with a recall period of a week [44, 45] (Table 6.3). It consists of two domains (anxiety and depression) with seven items each. The estimated completion time is 2–5 min, which provides a limited burden to both patient and medical staff at clinic.

No evidence of validation of the psychometric properties of HADS has been published in patients with SLE [3]. The HADS has demonstrated strong psychometric properties in a general population and in patients with psychiatric disorders. Evidence of the ability to detect change in response to an intervention has been established in various diseases such as depression, neurotic disorder, and cancer [46].

Box 6.3: Anxiety and Depression

Anxiety and depression is frequently expressed by patients with SLE in qualitative research.

The **Hospital Anxiety and Depression Scale (HADS)** can be recommended for use in patients with SLE where the medical staff suspects that the patient's emotional well-being is impacted by anxiety or depression.

Further, qualitative research and validation of the psychometric properties of HADS are recommended to be explored in patients with SLE.

Table 6.3 Characteristics of Hospital Anxiety and Depression Scale (HADS) and Becks Depression Inventory (BDI)

Instrument characteristics	Description (HADS)	Description (BDI)
Target population	Adults	Adults
Number of items	14	21
Completion time	2–5 min	5–10 min
Recall period	Past week	Not specified
Format and layout	Acceptable format and layout; the items are fairly close together	The format is generally simple to follow
Coverage	Depression: 7 items, anxiety: 7 items	Depression total score
Response options	4-point Likert scale: (0–3 response). Response options differ depending on item	4-point Likert scale: (0–3 response). Response options differ depending on item
Mode of administration	Self-administered by the patient	Self-administered by the patient or interviewer administered
Content validation	No patients with SLE involved in qualitative research in the development phase. Developed based on clinician observations, however not specific for SLE	No patients with SLE involved in qualitative research in the development phase. Developed based on clinician observations, however not specific for SLE

Health-Related Quality of Life

HRQoL in patients with SLE is influenced by treatment, disease activity, and symptoms of fatigue, depression, pain, sleep disturbances, and cognitive dysfunction [47]. Due to the radical nature of the disease, HRQoL is an important outcome measure in patients with SLE. HRQoL can be accessed through generic or disease-specific PROMs.

Generic Assessment of HRQoL

The generic HRQoL measure selected for review is the 36-item Short Form Health Survey version 2 (SF-36v2) (Table 6.4). SF-36v2 has been validated in many different health conditions and is a widely used and accepted measure of HRQoL [40, 48]. This PROM covers many domains of importance to patients including physical function, social function, pain, vitality (fatigue and energy), and mental health, and distinguishes limitation on activities by physical and emotional factors. This is

Table 6.4 Characteristics of the short form (36 item) Health Survey version 2 (SF-36v2) and the Lupus quality of life (LupusQoL)

Instrument characteristics	Description (SF-36v2)	Description (LupusQoL)
Target population	Generic, for use in all disease populations. Adult and adolescents ≥ 14 years	SLE patients, adults
Number of items	36	34
Completion time	5–10 min	Less than 10 min
Recall period	Standard 4-week recall or Acute 1-week recall version	Last 4 weeks
Format and layout	The layout of the items is straightforward and the formatting of the instrument makes rating each item a relatively simple task	The format of the questionnaire does not appear to pose any problems for comprehension or accurate completion. However, the response options are displayed a little close, making the instrument appear slightly overcrowded
Coverage	Physical functioning, bodily pain, vitality, social functioning, mental health, general health perceptions, role limitations due to physical problems, role limitations due to emotional problems, plus an item to measure reported health transition (health compared to 1 year ago)	Physical health; pain; planning; intimate relationships; burden to others; emotional health; body image; fatigue
Response options	3 and 5-point Likert scales	5-point scale ranging from “never” to “all of the time”
Mode of administration	Self-administered by the patient as well as Interviewer/Telephone/Computer administered	Self-administered by the patient
Content validation	No patients were included in the development of the measure [52] but the SF-36 has been widely used in general health populations since its development	Items generated with input from 30 SLE patients Pilot tested with 20 SLE patients to assess face and content validity [51]

crucial in a chronic disease such as SLE where the disease, as well as the therapies used, may cause physical and emotional effects; SF-36v2 makes it possible to assess these different aspects of health status and quality of life separately.

The SF-36v2 has 36-items; 26 are rated on a 5-point scale and 10 are rated on a 3-point scale. These items and response options are generally clear and easy to understand, and the instructions are simple and straightforward to follow. In terms of the recall period of the questionnaire, both a 4-week recall and an acute 1-week recall version exist. A recall period of the past 7 days may be more appropriate, given the fluctuating nature of the condition—patient's symptoms and limitations may vary significantly from day to day. SF-36v2 has demonstrated good psychometric properties in terms of internal consistency, reliability, and test–retest reliability, construct validity, and concurrent validity in the general population [48, 49]. More importantly, in an SLE population, the SF-36v2 has demonstrated evidence of internal consistency reliability, concurrent validity, and known groups validity [50]. Of note, the SF36v2 is able to detect change in many conditions [48, 51] and distribution and anchor-based estimates suggest Minimal Clinically Important Differences (MCIDs) of approximately 3–6 points in an SLE population [50]. SF-36v2 is able to discriminate between levels of disease severity, which is important for assessing change. Patients were not involved in the initial development, but the SF-36v2 has been widely used in general health populations since its development.

SLE-Specific Assessment of HRQoL

Several disease-specific instruments have been designed to assess HRQoL in SLE: Lupus Quality of Life (LupusQoL), L-QoL, SLE-QoL, and Lupus-PRO. The LupusQoL is the strongest of the disease-specific HRQoL measures in terms of development, conceptual coverage, and validation and will be the focus for this review. The LupusQoL (Appendix 3, Table 6.4) is a 34-item questionnaire designed to assess SLE patients' HRQoL (Box 6.4). Concept elicitation interviews were conducted with 30 SLE patients to gather information regarding concepts that are relevant to patients [52]. The LupusQoL comprises 8 domains: physical health, pain, planning, intimate relationships, burden to others, emotional health, body image, and fatigue [52]. It emphasizes areas such as sleep, body image, and sexual health, which are not specifically queried in SF-36v2. LupusQoL has demonstrated good internal consistency, test–retest reliability, and concurrent validity with the generic SF-36v2 [52].

The response options are clearly worded and appear to be easy for patients to understand. The item wording is clear and simple to understand, however the response options may be somewhat skewed toward the higher end of the severity spectrum and some options could be difficult to differentiate between. Patients are required to think over the past 4 weeks. This is a fairly long period and may elicit inaccurate responses, as some patients may forget the impact that their illness had over this time. LupusQoL has good psychometric properties in terms of reliability, construct validity, discriminant validity, and concurrent/convergent validity [52]. No evidence is available on ability to detect change.

Box 6.4: Health-Related Quality of Life

Health-Related Quality of Life (HRQoL) in patients with SLE is influenced by treatment, disease activity, and symptoms of fatigue, depression, pain, sleep disturbances, and cognitive dysfunction.

The **Short Form Health Survey (SF-36v2)** can be recommended to assess different aspects of general health status and quality of life.

The **LupusQoL** can be used to assess the impact that SLE has upon patients' HRQoL and it emphasizes areas such as sleep, body image, and sexual health, which are not specifically queried in SF-36v2.

Reflections and Considerations for the Future

To understand the value of therapies for SLE from the patient perspective, PROMs should be included in clinical practice in conjunction with well-established clinical assessments. The selection of suitable measures to assess SLE-related symptoms and impacts in clinical practice requires careful consideration [53, 54]. This chapter therefore presented a conceptual model of the key symptoms and impacts associated with SLE. The key patient-reported concepts identified within the model were fatigue, pain, cognition, daily activities, emotional well-being, physical/social functioning, and work productivity. The subjective nature of many SLE symptoms and impacts requires accurate and reliable measurement of these symptoms based on patient self-report. In light of this, it is important to also review and evaluate the content validity and psychometric properties of PROMs that may be appropriate for use in an SLE population.

The FACIT-Fatigue, LupusQoL, BPI, SF-36v2, and LupusQoL appear to be the strongest PROMs as measures of the key concepts identified in the conceptual model and all had evidence of the psychometric validity. In addition, the generic SF-36v2 is widely used in randomized clinical trials with patients with SLE and is recognized and accepted by clinical, patient, regulatory, reimbursement, and academic communities. FACIT-Fatigue has proven to be a valid measure of fatigue through a qualitative study [17] and the psychometric properties in an SLE population are well documented [31]. Of the PROMs reviewed, only the LupusQoL has documented evidence of qualitative input from patients with SLE in the development process.

In clinical standard practice it could be advantageous if all of the key symptoms and impacts were covered in one single PROM. Some PROMs have recently been developed for this purpose such as the Multi-Dimensional Questionnaire for Patient Reported Outcome Measures-SLE (MDPROMs SLE) [55] and Lupus Impact Tracker (LIT) [56]. Further research and experience with the use of multidimensional measures in clinical practice are needed.

It is important to acknowledge that patients with SLE may experience many symptom-free days, followed by a severe flare. Flares are likely to impact patients'

HRQoL [2, 57]. Therefore, further research in developing PROMs that capture the impact of flares should be considered in the future. SLE often involves day-to-day symptom fluctuations due to these flares, thus the recall period of the measurement instrument is also an important consideration. PROs with shorter recall periods may underestimate symptom burden and may place undue demand on patients; however, longer recall period may not allow for reliable symptom and impact reporting.

The recommended PROMs in this chapter have been selected on the basis of identification of key SLE symptoms and impacts in the conceptual model. PROMs of other symptoms of SLE not reported in the conceptual model were thus de-prioritized and therefore not included. Appropriate and validated PROMs for some key concepts identified in the model (e.g., skin manifestations of the disease, impact of flares, and treatment satisfaction) were not identified, or no PROMs have been used to measure these concepts in patients with SLE. This represents a gap in knowledge that may benefit from further research. PROMs are in this context considered complementary to more objective measures and should be incorporated into clinical practice.

Conclusion

SLE is a condition associated with high unmet need and considerable burden to patients, as demonstrated by the conceptual model presented in this chapter. This review highlights some of the existing PROMs of SLE signs and symptoms and HRQoL that demonstrate appropriate content validity and are psychometrically adequate for a population of patients with SLE, and as a result such measures may be suitable for use in clinical practice for patients with SLE.

Both generic and disease-specific PROMs were reviewed. Those PROMs included HRQoL, measures of fatigue, pain, and depression/anxiety. The Functional Assessment for Chronic Illness Therapy Fatigue scale (FACIT-fatigue) is the strongest fatigue measure in terms of psychometric properties and conceptual coverage. The Brief Pain Inventory (BPI-SF) is the strongest pain instrument in terms of content validity. However, qualitative research in patients with SLE is needed to ensure the applicability of the items and the appropriateness of the recall period. The Hospital Anxiety and Depression Scale (HADS) is the recommended PROM for measurement of anxiety and depression as the instructions and response options are straightforward and clearly defined. The LupusQoL is the strongest HRQoL measure in terms of the development, conceptual coverage, and validation. It might be favorable in standard clinical practice to consider including 1 cohesive PROM for the assessment of patient reported key symptoms and impacts in SLE. However, further research and validation studies as well as experience with the use of these “all-in-one” PROMs in clinical practice are needed.

Appendix 1: FACIT-Fatigue is presented with permission from the copyright holder. Potential users

Potential users should go to <http://www.facit.org/FACITOrg> and contact copyright holder for permission before using FACIT-Fatigue in studies and clinical practice.

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless (<i>washed out</i>)	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <i>starting</i> things because I am tired	0	1	2	3	4
An4	I have trouble <i>finishing</i> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

Appendix 2: Brief Pain Inventory—Short Form

BPI-SF is presented with permission from the copyright holder. Potential users should go to www.mdanderson.org/departments/prg and contact copyright holder for permission before using BPI-SF in studies and clinical practice.

STUDY ID #: _____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Brief Pain Inventory (Short Form)

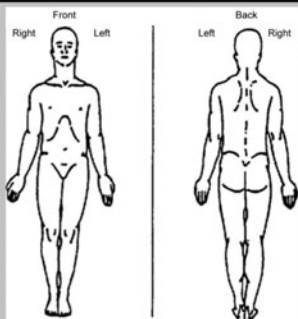
Date: ____ / ____ / ____ Time: _____

Name: _____
 Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
 No Pain Pain as bad as you can imagine

STUDY ID #: _____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Date: ____/____/____ Time: _____
 Name: _____
 Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

- A. General Activity**
 0 1 2 3 4 5 6 7 8 9 10
 Does not Completely
 Interfere Interferes
- B. Mood**
 0 1 2 3 4 5 6 7 8 9 10
 Does not Completely
 Interfere Interferes
- C. Walking Ability**
 0 1 2 3 4 5 6 7 8 9 10
 Does not Completely
 Interfere Interferes
- D. Normal Work (includes both work outside the home and housework)**
 0 1 2 3 4 5 6 7 8 9 10
 Does not Completely
 Interfere Interferes
- E. Relations with other people**
 0 1 2 3 4 5 6 7 8 9 10
 Does not Completely
 Interfere Interferes
- F. Sleep**
 0 1 2 3 4 5 6 7 8 9 10
 Does not Completely
 Interfere Interferes
- G. Enjoyment of life**
 0 1 2 3 4 5 6 7 8 9 10
 Does not Completely
 Interfere Interferes

Copyright 1991 Charles S. Cleeland, PhD
 Pain Research Group
 All rights reserved

Appendix 3: LupusQoL

LupusQoL is presented with permission from the copyright holders. Anyone running a commercially funded study must obtain a license for the LupusQoL and pay the license fee. Use is free for noncommercially funded studies but copyright holders requires that researchers contact the licensors for permission before using to ensure that researchers use the professionally developed and validated translations only.

Potential users should go to www.lupusqol.com for more information on using LupusQoL in studies and clinical practice.

LupusQoL©

LupusQoL Questionnaire

The following questionnaire is designed to find out how SLE affects your life. Read each statement and then circle the response, which is closest to how you feel. Please try to answer all the questions as honestly as you can.

How often over the last 4 weeks

1. Because of my Lupus I need help to do heavy physical jobs such as digging the garden, painting and/or decorating, moving furniture

All of the time most of the time a good bit of the time occasionally never

2. Because of my Lupus I need help to do moderate physical jobs such as vacuuming, ironing, shopping, cleaning the bathroom

All of the time most of the time a good bit of the time occasionally never

3. Because of my Lupus I need help to do light physical jobs such as cooking/preparing meals, opening jars, dusting, combing my hair or attending to personal hygiene

All of the time most of the time a good bit of the time occasionally never

4. Because of my Lupus I am unable to perform everyday tasks such as my job, childcare, housework as well as I would like to

All of the time most of the time a good bit of the time occasionally never

5. Because of my Lupus I have difficulty climbing stairs

All of the time most of the time a good bit of the time occasionally never

6. Because of my Lupus I have lost some independence and am reliant on others

All of the time most of the time a good bit of the time occasionally never

7. I have to do things at a slower pace because of my Lupus

All of the time most of the time a good bit of the time occasionally never

8. Because of my Lupus my sleep pattern is disturbed

All of the time most of the time a good bit of the time occasionally never

How often over the last 4 weeks

9. I am prevented from performing activities the way I would like to because of pain due to Lupus

All of the time most of the time a good bit of the time occasionally never

LupusQoL©

10. Because of my Lupus, the pain I experience interferes with the quality of my sleep

All of the time most of the time a good bit of the time occasionally never

11. The pain due to my Lupus is so severe that it limits my mobility

All of the time most of the time a good bit of the time occasionally never

12. Because of my Lupus I avoid planning to attend events in the future

All of the time most of the time a good bit of the time occasionally never

13. Because of the unpredictability of my Lupus I am unable to organise my life efficiently

All of the time most of the time a good bit of the time occasionally never

14. My Lupus varies from day to day which makes it difficult for me to commit myself to social arrangements

All of the time most of the time a good bit of the time occasionally never

15. Because of the pain I experience due to Lupus I am less interested in a sexual relationship

All of the time most of the time a good bit of the time occasionally never not applicable

16. Because of my Lupus I am not interested in sex

All of the time most of the time a good bit of the time occasionally never not applicable

17. I am concerned that my Lupus is stressful for those who are close to me

All of the time most of the time a good bit of the time occasionally never

18. Because of my Lupus I am concerned that I cause worry to those who are close to me.

All of the time most of the time a good bit of the time occasionally never

19. Because of my Lupus I feel that I am a burden to my friends and/or family

All of the time most of the time a good bit of the time occasionally never

Over the past 4 weeks I have found my Lupus makes me feel**20. Resentful**

All of the time most of the time a good bit of the time occasionally never

21. So fed up nothing can cheer me up

All of the time most of the time a good bit of the time occasionally never

LupusQoL©

22. Sad

All of the time most of the time a good bit of the time occasionally never

23. Anxious

All of the time most of the time a good bit of the time occasionally never

24. Worried

All of the time most of the time a good bit of the time occasionally never

25. Lacking in self-confidence

All of the time most of the time a good bit of the time occasionally never

How often over the past 4 weeks

26 My physical appearance due to Lupus interferes with my enjoyment of life

All of the time most of the time a good bit of the time occasionally never

27. Because of my Lupus, my appearance (e.g. rash, weight gain/loss) makes me avoid social situations

All of the time most of the time a good bit of the time occasionally never not applicable

28. Lupus related skin rashes make me feel less attractive

All of the time most of the time a good bit of the time occasionally never not applicable

How often over the past 4 weeks

29. The hair loss I have experienced because of my Lupus makes me feel less attractive

All of the time most of the time a good bit of the time occasionally never not applicable

30. The weight gain I have experienced because of my Lupus treatment makes me feel less attractive

All of the time most of the time a good bit of the time occasionally never not applicable

31. Because of my Lupus I cannot concentrate for long periods of time

All of the time most of the time a good bit of the time occasionally never

LupusQoL©

32. Because of my Lupus I feel worn out and sluggish

All of the time most of the time a good bit of the time occasionally never

33. Because of my Lupus I need to have early nights

All of the time most of the time a good bit of the time occasionally never

34. Because of my Lupus I am often exhausted in the morning

All of the time most of the time a good bit of the time occasionally never

Please feel free to make any additional comments.

Please check that you have answered each question

Thank you, for completing this questionnaire

© 2006. University of Central Lancashire & East Lancashire Hospitals NHS Trust. All rights reserved. Not to be reproduced in whole or in part without the permission of the copyright holder.

Appendix 4: Multidimensional Questionnaire for Patient Reported Outcome Measures—SLE

Multi-Dimensional Questionnaire for Patient Reported Outcome Measures – SLE

This questionnaire includes information not available from blood tests, X-rays, or any source other than you. Please try to answer each question. There is **no right or wrong answer**. Please answer exactly as **YOU** think or feel.

1. We are interested in learning how your illness affects your ability to function in daily life. Please tick (✓) the ONE best answer that describes your usual abilities OVER THE PAST WEEK:

Over the LAST WEEK were you able to	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	Unable TO DO	
1. Get on and off the toilet?	Fn. Dis.
2. Use your grip strength; eg, open previously opened jars Or lift a saucepan during cooking?	
3. Dress yourself, including tying shoelaces & doing buttons?	
4. Stand up from a chair without arms?	
5. Wait in a line for 15 minutes?	
6. Reach and get down a 5-pound object (such as a bag of sugar) from just above your head?	
7. Walk outdoors on flat ground?	
8. Go up 2 or more flights of stairs?	
9. Do housework/DIY jobs around the house?	
10. Move heavy objects?	
					Not Applicable
1. Get a good night's sleep?	QoL
2. Deal with the usual stresses of daily life?	
3. Cope with social/family activities?	
4. Deal with feelings of anxiety or being nervous?	
5. Deal with feelings of low self-esteem or feeling blue?	
6. Get going in the morning?	
7. Do your work as you used to do?	
8. Deal with any worries about your future?	
9. Continue doing things you used to do, despite tiredness?	
10. Continue your relationship with your partner (husband/wife)?	

2. How much PAIN or body ache have you had because of Lupus disease OVER THE PAST WEEK? Please put a circle around the number that best indicates your level of pain:

3. Considering all the ways Lupus may be affecting you AT THIS TIME, Please put a circle around the number that best indicates how well you are doing:

4. How much of a problem has UNUSUAL FATIGUE or tiredness been for you OVER THE PAST WEEK? (Please put a circle around the number that best indicates your fatigue)

5. OVER THE LAST WEEK when you awakened in the morning, did you feel stiff?

YES: Please indicate the number of minutes or hours until you are as limber as you will be for the day.

NO:

MS

El Miedany et al. EULAR 2014

6. Please place an (X) in the appropriate box to indicate in which of your joints you feel painful **TODAY**.

Alternatively you can put a figure 1, 2, or 3 to describe the severity of the pain you feel in any joint as follows:

1 = mild pain
2 = moderate pain
3 = severe pain

Tender Joint count

Tender Joint count	
Pt.	Phys.

7. Please tick (✓) if you have experienced any of the following **OVER THE LAST 10 DAYS**:

Fits/seizures	Tender finger nodules	Gynecological problem	Cardiovascular Risk Assessment
Hallucinations	Muscle pain	Short plans for having a baby	Age > 50 years old
Illogical thinking	Muscle weakness	Miscarriage	High blood pressure
Bizarre/disorganized behavior	New/recurrent skin rash	Sexual relationship problems	High cholesterol
Difficulty to focus	Patchy of diffuse loss of hair	Problems with passing water	Current smoker
Altered speech	Mouth ulcers	Dark/reddish urine/kidney problem	Ischemic heart disease
Insomnia	Wheezing/asthma	I worry about my appearance	Stroke
Daytime drowsiness	Cough/shortness of breath	Lost height	Irregular heart beats
Visual disturbance	Chest pain	Had a recent fracture	Diabetes mellitus
Double vision/squint	Feeling sickly/Nausea	Falls Risk Assessment	The section below is for official use. Please do not tick
Change in the look of your face	Dry eye	Loss of your balance	
Problems with hearing	Dry mouth	Problems with your sight	
Persistent headache	Fever	Weakness of your grip strength	
Migraine	Pulmonary embolism/DVT	> I fall in the last year	ESR: CRP:
Finger ulcers/gangrene/dark spots	Diagnosed to have cancer	Change in gait/Slow walking speed	WCC: Plt:
			SLEDAL: BMI:
			B/P: Chol:

8. The statements below concern your personal beliefs. Please circle the number that best describes how you feel about the statement. 0 = Not at all; 10 = Strongly Agree

mRAI

1. My condition is controlling my life.	0 1 2 3 4 5 6 7 8 9 10
2. I would feel helpless if I could not rely on other people for help with my condition.	0 1 2 3 4 5 6 7 8 9 10
3. I am concerned that medicines cannot help me.	0 1 2 3 4 5 6 7 8 9 10
4. I've concerns regarding side effects of medications used to treat my condition.	0 1 2 3 4 5 6 7 8 9 10
5. I often do not take my medicines as directed.	0 1 2 3 4 5 6 7 8 9 10
6. No matter what I do, or how hard I try, I just cannot seem to get relief from my symptoms.	0 1 2 3 4 5 6 7 8 9 10
7. I am not coping effectively with my condition.	0 1 2 3 4 5 6 7 8 9 10
8. Sometimes I feel my condition is beyond both my and my doctor's control.	0 1 2 3 4 5 6 7 8 9 10
9. Sometimes my condition makes me feel like giving up.	0 1 2 3 4 5 6 7 8 9 10
10. Due to my condition, sometimes I feel I am a burden to those close to me.	0 1 2 3 4 5 6 7 8 9 10

Date: / /201_

I consent to my clinical data being used for research/audit.

Signature of the patient: _____

Patient:

D.O.B:

References

- Manson JJ, Rahman A. Systemic lupus erythematosus. Orphanet J Rare Dis. 2006;1:6.
- Jolly M, Pickard AS, Wilke C, Mikolaitis RA, Teh LS, McElhone K, Fogg L, Block J. Lupus-specific health outcome measure for US patients: the LupusQoL-US version. Ann Rheum Dis. 2010;69:29-33.

3. Holloway L, Humphrey L, Heron L, Pilling C, Kitchen H, Højbjerg L, Strandberg-Larsen M, Bekker Hansen B. Patient-reported outcome measures for systemic lupus erythematosus clinical trials: a review of content validity, face validity and psychometric performance. *Health Qual Life Outcomes*. 2014;12:116.
4. Beckerman NL. Living with lupus: a qualitative report. *Soc Work Health Care*. 2011;50:330–43.
5. McElhone K, Abbott J, Gray J, Williams A, Teh LS. Patient perspective of systemic lupus erythematosus in relation to health-related quality of life concepts: a qualitative study. *Lupus*. 2010;19:1640–7.
6. Robinson J, Aguilar D, Schoenwetter M, Dubois R, Russak S, Ramsey-Goldman R, Navarra S, Hsu B, Revicki D, Cella D, Rapaport MH, Renahan K, Ress R, Wallace D, Weisman M. Impact of systemic lupus erythematosus on health, family, and work: the patient perspective. *Arthritis Care Res*. 2010;62:266–73.
7. Schneider M, Schmeding A, Carnarius H, Ager M, McWade V. Systemic lupus erythematosus (SLE): understanding the burden. *Value Health*. 2010;13:A470.
8. Yee CS, McElhone K, Teh LS, Gordon C. Assessment of disease activity and quality of life in systemic lupus erythematosus—new aspects. *Best Pract Res Clin Rheumatol*. 2009;23:457–67.
9. Aberer E. Epidemiologic, socioeconomic and psychosocial aspects in lupus erythematosus. *Lupus*. 2010;19:1118–24.
10. Strand V, Galateanu C, Pushparajah DS, Nikai E, Sayers J, Wood R, van Vollenhoven RF. Limitations of current treatments for systemic lupus erythematosus: a patient and physician survey. *Lupus*. 2013;22:819–26.
11. Pettersson S, Lovgren M, Eriksson LE, Moberg C, Svenungsson E, Gunnarsson I, Henriksson EW. An exploration of patient-reported symptoms in systemic lupus erythematosus and the relationship to health-related quality of life. *Scand J Rheumatol*. 2012;41:383–90.
12. Gallop K, Nixon A, Swinburn P, Sterling KL, Naegeli AN, Silk ME. Development of a conceptual model of health-related quality of life for systemic lupus erythematosus (SLE) from the patients' perspective. *Lupus*. 2012;21:934–43.
13. Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria for Fatigue. Measurement of fatigue in systemic lupus erythematosus: a systematic review. *Arthritis Care Res*. 2007;57:1348–57.
14. Cleathous S, Tyagi M, Isenberg DA, Newman SP. What do we know about self-reported fatigue in systemic lupus erythematosus? *Lupus*. 2012;21:465–76.
15. Ramsey-Goldman R, Rothrock N. Fatigue in systemic lupus erythematosus and rheumatoid arthritis. *PM R*. 2010;2:384–92.
16. Mattsson M, Moller B, Stamm T, Gard G, Bostrom C. Uncertainty and opportunities in patients with established systemic Lupus Erythematosus: a qualitative study. *Musculoskeletal Care*. 2012;10:1–12.
17. Kosinski M, Gajria K, Fernandes AW, Cella D. Qualitative validation of the FACIT-fatigue scale in systemic lupus erythematosus. *Lupus*. 2013;22:422–30.
18. Danoff-Burg S, Friedberg F. Unmet needs of patients with systemic lupus erythematosus. *Behav Med*. 2009;35:5–13.
19. Yazdany J, Yelin E. Health-related quality of life and employment among persons with systemic Lupus Erythematosus. *Rheum Dis Clin North Am*. 2010;36:15–32.
20. Doward LC, McKenna SP, Whalley D, Tennant A, Griffiths B, Emery P, Veale DJ. The development of the L-QoL: a quality-of-life instrument specific to systemic lupus erythematosus. *Ann Rheum Dis*. 2009;68:196–200.
21. Robinson M, Sheets CS, Currie LM. Systemic lupus erythematosus: a genetic review for advanced practice nurses. *J Am Acad Nurse Pract*. 2011;23:629–37.
22. Johnsson PM, Sandqvist G, Bengtsson A, Nived O. Hand function and performance of daily activities in systemic lupus erythematosus. *Arthritis Rheum*. 2008;59:1432–8.
23. Carls G, Li T, Panopalis P, Wang S, Mell AG, Gibson TB, Goetzel RZ. Direct and indirect costs to employers of patients with systemic lupus erythematosus with and without nephritis. *J Occup Environ Med*. 2009;51:66–79.

24. Zhu TY, Tam LS, Li EK. The socioeconomic burden of systemic lupus erythematosus: state-of-the-art and prospects. *Expert Rev Pharmacoecon Outcomes Res.* 2012;12:53–69.
25. Zhu TY, Tam LS, Li EK. Cost-of-illness studies in systemic lupus erythematosus: a systematic review. *Arthritis Care Res (Hoboken).* 2011;63:751–60.
26. Yelin E, Katz P. Introduction to special section: cost and social and psychological impact of rheumatic diseases. *Arthritis Rheum.* 2008;59:457.
27. Zhu TY, Tam LS, Lee VWY, Lee KKC, Li EK. The impact of flare on disease costs of patients with systemic lupus erythematosus. *Arthritis Rheum.* 2009;61:1159–67.
28. Aghdassi E, Zhang W, St. Pierre Y, Clarke AE, Morrison S, Peeva V, Landolt-Marticorena C, Su J, Reich H, Scholey J, Herzenberg A, Pope JE, Peschken C, Lunnet Canios I, Wither JE, Fortin PR. Healthcare cost and loss of productivity in a Canadian population of patients with and without lupus nephritis. *J Rheumatol.* 2011;38:658–66.
29. Strand V, Chu AD. Measuring outcomes in systemic lupus erythematosus clinical trials. *Expert Rev Pharmacoecon Outcomes Res.* 2011;11:455–68.
30. Furie R, Petri MA, Strand V, Gladman DD, Zhong ZJ, Freimuth WW. Clinical, laboratory and health-related quality of life correlates of Systemic Lupus Erythematosus Responder Index response: a post hoc analysis of the phase 3 belimumab trials. *Lupus Sci Med.* 2014;1, e000031.
31. Lai JS, Beaumont JL, Ogale S, Brunetta P, Cella D. Validation of the functional assessment of chronic illness therapy-fatigue scale in patients with moderately to severely active systemic lupus erythematosus, participating in a clinical trial. *J Rheumatol.* 2011;38:672–9.
32. Chandran V, Bhella S, Schentag C, Gladman DD. Functional assessment of chronic illness therapy-fatigue scale is valid in patients with psoriatic arthritis. *Ann Rheum Dis.* 2007;66:936–9.
33. Cella D, Yount S, Sorensen M, Chartash E, Sengupta N, Grober J. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. *J Rheumatol.* 2005;32:811–9.
34. Ozel F, Argon G. The effects of fatigue and pain on daily life activities in systemic lupus erythematosus. *European J Internal Med.* 2011;22:S70.
35. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain.* 1975;1(3):277–99.
36. Melzack R. The short-form McGill Pain Questionnaire. *Pain.* 1987;30(2):191–7.
37. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore.* 1994;23(2):129–38.
38. Cleeland CS. The brief pain inventory: user guide. 2009. 63 p. http://www.mdanderson.org/education-and-research/departments-programs-andlabs/departments-and-divisions/symptom-research/symptom-assessmenttools/BPI_UserGuide.pdf.
39. Cleeland CS, Gonin R, Hatfield AK, Edmonson JH, Blum RH, Stewart JA, Pandya KJ. Pain and its treatment in outpatients with metastatic cancer. *N Engl J Med.* 1994;330(9):592–6.
40. Food and Drug Administration. Guidance for industry: patient-reported outcome measures: use in medical product development to support labelling claims. Silver Spring, MD: Food and Drug Administration; 2009.
41. Atkinson TM, Rosenfeld BD, Sit L, Mendoza TR, Fruscione M, Lavene D, Shaw M, Li Y, Hay J, Cleeland CS, Scher HI, Breitbart WS, Basch E. Using confirmatory factor analysis to evaluate construct validity of the Brief Pain Inventory (BPI). *J Pain Symptom Manage.* 2011;41(3):558–65.
42. Daut RL, Cleeland CS, Flannery RC. Development of the Wisconsin Brief Pain Questionnaire to assess pain in cancer and other diseases. *Pain.* 1983;17(2):197–210.
43. Naegeli AN, Tomaszewski EL, Al Sawah S. Psychometric validation of the Brief Pain Inventory-Short Form in patients with systemic lupus erythematosus in the United States. *Lupus.* 2015;24:1377–83.
44. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983;67:361–70.
45. Snaith RP. The hospital anxiety and depression scale. *Health Qual Life Outcomes.* 2002;1:29.

46. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale-A review of validation data and clinical results. *J Psychosom Res.* 1997;42:17–41.
47. Garris CP, Oglesby AK. Assessment of health care resource utilization by level of flare severity in patients with systemic lupus erythematosus (SLE) in the managed care setting. *J Manag Care Pharm.* 2011;17:552.
48. QualityMetric Inc. User’s manual for the SF-36v2 health survey. 3rd ed. **2011.** <http://www.qualitymetric.com/WhatWeDo/ManualsUserGuides/UsersManualfortheSF36v2HealthSurvey/tabid/328/Default.aspx>.
49. Brazier JE, Harper R, Jones NM, O’Cathain A, Thomas KJ, Usherwood T, Westlake L. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *BMJ.* 1992;305(6846):160–4.
50. Beaumont JLLJ, Cella D, Brunetta P, Ogale S. Validation of the SF-36 in patients with systemic lupus erythematosus (SLE). *Arthritis Rheum.* 2009;60:296.
51. Busija L, Pausenberger E, Haines TP, Haymes S, Buchbinder R, Osborne RH. Adult measures of general health and health-related quality of life: Medical Outcomes Study Short Form 36-Item (SF-36) and Short Form 12-Item (SF-12) Health Surveys, Nottingham Health Profile (NHP), Sickness Impact Profile (SIP), Medical Outcomes Study Short Form 6D (SF-6D), Health Utilities Index Mark 3 (HUI3), Quality of Well-Being Scale (QWB), and Assessment of Quality of Life (AQOL) [abstract]. *Arthritis Care Res.* 2011;63:S383–412.
52. McElhone K, Abbott J, Shelmerdine J, Bruce IN, Ahmad Y, Gordon C, Peers K, Isenberg D, Ferenkeh-Koroma A, Griffiths B, Akil M, Maddison P, Teh L-S. Development and validation of a disease-specific health-related quality of life measure, the LupusQoL, for adults with systemic lupus erythematosus. *Arthritis Care Res.* 2007;57:972–9.
53. Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992;30(6):473–83.
54. Food and Drug Administration. Guidance for industry: systemic lupus erythematosus—developing medical products for treatment. 2010. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072063.pdf>.
55. European Medicines Agency. Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus, cutaneous lupus and lupus nephritis (draft). 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139615.pdf.
56. El Miedany Y, El Gaafary M, El Yassaki A, Ahmed I, Youssef S, Hegazi MO, Palmer D. Incorporating patient reported outcome measures in clinical practice: development and validation of a PROMs questionnaire for SLE. *Ann Rheum Dis.* 2013;72 Suppl 3:484.
57. Jolly M, Garris CP, Mikolaitis RA, Jhingran PM, Dennis G, Wallace DJ, Clarke A, Dooley MA, Parke A, Strand V, Alárcon GS, Kosinski M. Development and validation of the Lupus Impact Tracker: a patient-completed tool for clinical practice to assess and monitor the impact of systemic lupus erythematosus. *Arthritis Care Res (Hoboken).* 2014;66(10):1542–50.
58. Ruperto N, Hanrahan LM, Alarcon GS, Belmont HM, Brey RL, Brunetta P, Buyon JP, Costner MI, Cronin ME, Dooley MA, Filocamo G, Fiorentino D, Fortin PR, Franks Jr AG, Gilkeson G, Ginzler E, Gordon C, Grossman J, Hahn B, Isenberg DA, Kalunian KC, Petri M, Sammaritano L, Sánchez-Guerrero J, Sontheimer RD, Strand V, Urowitz M, von Feldt JM, Werth VP, Merrill JT. International consensus for a definition of disease flare in lupus. *Lupus.* 2011;20:453–62.