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Lupus (S Keeling, Section Editor)

The Role of Patient-Reported Outcomes in Systemic Lupus Erythematosus

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Opinion statement

Purpose of review The use of patient-reported outcomes (PROs) is increasing in rheumatology and other chronic diseases, with growing evidence of its utility in complementing physical and biochemical assessments to guide management of complex conditions, such as systemic lupus erythematosus (SLE). This review describes currently utilized PROs and their use in SLE, and highlights areas of unmet need that require further attention.
Recent findings Existing PRO instruments, both generic and SLE-specific, assess a variety of health-related quality of life (HRQoL) and, to a lesser extent, non-HRQoL domains that are frequently reported health issues in SLE patients – although there remain other important aspects that are not routinely assessed, including the ability of patients to participate in social roles and relationships.
Summary PRO domains pertinent to SLE patients will continue to be identified and these areas of unmet needs will have to be addressed by novel and existing PRO instruments.

Introduction

Patient-reported outcome (PRO) measures have been designed to capture patient perceptions of their health condition, health-related quality of life (HRQOL), well-being, and other aspects [1]; PROs encompass domains such as pain, physical function, fatigue, anxiety, and depression, among many others. There are a number of benefits to using PROs in the management of rheumatic diseases as they relate to patients, healthcare providers (HCPs), regulatory agencies, and healthcare decision-makers. While physicians often focus their assessments on mainly three domains (disease activity, adverse effects to medications, and damage) [2], there is strong evidence that these domains do not correlate closely with or fully reflect HRQoL experienced by systemic lupus erythematosus (SLE) patients [3, 4, 5, 6]. This discordance between physician-obtained clinical measures and patients' perspectives can result in worsened communication, a decreased level of patient satisfaction with care, and ultimately treatment non-adherence [7–12]. Moreover, research has shown that PROs provide valuable data on treatment efficacy that are complementary to measures of disease activity and damage [13, 14]—informing time to onset of clinically important improvements, time to onset of maximum treatment efficacy, and durability of important change [14]. This supports the role PROs can play in helping to guide treatment decisions [15, 16], and provide a more holistic patient-centered approach to disease management.

Regulatory agencies and healthcare decision makers have also recognized the importance of using validated and reliable PROs to assess symptoms and treatment efficacy in chronic diseases [17, 18]. This is particularly true in rheumatology, where the use of PROs has gained an increasing amount of attention over the last two decades. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have released guidances/guidelines highlighting the importance of measuring PROs in SLE [19, 20]; and initiatives such as the Outcome Measures in Rheumatology (OMERACT) consensus effort have developed core outcome sets to be assessed in randomized controlled trials (RCTs) and longitudinal observational studies (LOS) [21–23]. In addition, the American College of Rheumatology (ACR) and the European Leagues Against Rheumatism (EULAR) have also recommended core sets of outcome measures for rheumatic diseases to be used in research and clinical practice [24]—with rheumatoid arthritis (RA) being the subject of numerous PRO studies [25, 26]. In RA, established PRO core outcome sets include physical function, pain, and patient global assessment of disease activity which are reported in virtually all RA RCTs [27]. Moreover, PROs have been shown to be at least as important as objective physical and biochemical measures when assessing disease status, treatment effects, and predicting disease outcomes [7–13, 28].

With such progress in the development of core PRO domains and instruments, recent attention by OMERACT has focused on developing translation frameworks and involving various stakeholders to promote the uptake and use of PROs in research and clinical settings [29•]. This collaborative and participatory approach to engaging stakeholders aims to involve end users in the research process, which will ultimately result in research outputs that are more relevant and useable—and therefore more likely to be implemented [30]. These different stakeholder groups include "patients and their families, the public, providers, payers/purchasers, policymakers, principal investigators (researchers and funders), and sponsors", among others [31, 32].

Similar to RA, SLE has also followed a similar trend as it pertains to the increasing use of PROs in disease management [33]. As a heterogeneous disease, SLE also requires a number of different PROs to assess its various manifestations and disease impact. Since SLE affects a predominantly younger age group, improved survival has translated to a longer disease duration and a significant accrual of disease damage burden [34–37], which include fatigue, pain, sleep disturbances, musculoskeletal, renal, internal organ, and skin problems, as well as neurologic/psychiatric conditions (e.g., anxiety, depression, headaches, motor/sensory deficits, and cognitive impairment) [38]. Due to the disease's variable multi-system involvement, treatment can impact many aspects of patients' lives, including their overall well-being and HRQoL [34–36]. OMERACT has defined a core set of outcome measures for SLE to be used in RCTs and LOS—that include disease activity, damage, HRQoL, economic costs, and adverse events [22, 39]. However, there remains a lack of consensus regarding a core set of PRO instruments to be used for assessing HRQoL in SLE. Thus, an important area of future investigation is the identification of

those PROs to be assessed in clinical practice, LOS, and RCTs in SLE.

In Table 1, we have referenced a framework by the World Health Organization (WHO) that aims to list various PRO domains that can be used in RCTs and LOS in the general population as well as in chronic rheumatic diseases. PRO categories can include Physical Health (which covers fatigue, pain, sleep, etc), Mental Health (encompassing self-concept, anxiety and depression, cognitive function, etc), and Social Health (which

Table 1. World Health Organization quality of life domains QOL. The following framework by the WHO represents a thorough list of possible PRO domains. This framework can be used as a checklist of PRO's that are currently measured in SLE, as well as opportunities to fill potential content gaps in SLE. Not all domains will be relevant to SLE

- Overall quality of life and general health
  - Physical Health
    - Energy and fatigue
    - Pain and discomfort
    - Sleep and rest
  - Psychological
    - Bodily image and appearance
    - Negative feelings
    - Positive feelings
    - Self-esteem
    - Thinking, learning, memory, and concentration
  - Level of Independence
    - Mobility
    - Activities of daily living
    - Dependence on medicinal substances and medical aids
    - Work capacity
  - Social Relations
    - Personal relationships
    - Social support
    - Sexual activity
  - Environment
    - Financial resources
    - Freedom, physical safety and security
    - Health and social care: accessibility and quality
    - Home environment
    - Opportunities for acquiring new information and skills
    - Participation in and opportunities for recreation/leisure
    - Physical environment (pollution/noise/traffic/climate)
    - Transport
  - Spirituality/religion/personal beliefs
    - Religion/spirituality/personal beliefs (single facet)

include social relationships and the ability to participate in social roles and activities) [40]; Fig. 1 lists domains with their corresponding categories which are further elaborated in Table 1.

Physical health domains

Under physical health, the WHO framework includes symptoms of fatigue, pain, physical function and sleep function, among others. In this review, we will focus on the most commonly reported physical health issues reported by SLE patients [41]; e.g., fatigue and pain have been consistently identified as two of the most important and frequent symptoms affecting patients with SLE [41–43].

Fatigue has been reported to be present in up to 90% of SLE patients with a significant effect on patients' ability to function [44, 45]. OMERACT has recommended the assessment of fatigue in SLE RCTs [23], and the ACR published a systematic review regarding instruments used to measure the effects, severity, and frequency of fatigue affecting patients' functioning [46]. The instruments listed in the ACR review include domains of generic HRQOL questionnaires such the Medical Outcomes Study Short Form 36 (SF-36) that measure energy level and fatigue, as well as portions of SLE-specific questionnaires such as LupusQoL [47] and LupusPRO [48] that focus on fatigue. However, there are also dedicated fatigue questionnaires such as The Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue), which has demonstrated high reliability, consistency, and ability to detect change in SLE patients over

Fig. 1. PRO domains in SLE. This figure reflects different PRO domains along with their categories (mental, physical, and social health). PROs have been assessed in SLE by HRQoL generic questionnaires (e.g. SF-36 and EQ-5D) as well as SLE-specific questionnaires (e.g. LupusQoL and Lupus PRO).

time [49, 50]. In a study by Strand et al., patients treated with belimumab reported significant improvements in FACIT-Fatigue scores—associated with similar changes in the SF-36 vitality domain [50, 51]. The Multidimensional Fatigue Inventory (MFI), Multidimensional Assessment of Fatigue (MAF), and Fatigue Severity Scale (FSS) are examples of other dedicated fatigue assessments that have been used in SLE, although each have limitations [52, 53]. Moreover, the FSS which was originally developed by Krupp et al. for use in SLE and MS patients has since been used to measure fatigue severity in a variety of medical conditions [54].

As for *pain*, SLE patients report a range of manifestations including headaches, arthralgias/arthritis and/or myalgias, or generalized body pain [41]. The result of this pain can affect a number of different health domains, including sleep, anxiety, depression, and physical function [41]. The majority of SLE patients report being affected in their activities of daily living, including carrying groceries or even getting dressed—as the pain and joint swelling can make these a difficult challenge [43]. Currently, pain and physical function in SLE are assessed by the generic SF-36 and EuroQoL-5 Dimensions (EQ-5D), as well as the disease-specific LupusQoL [47] and LupusPRO [48] questionnaires. A recent review also demonstrated the reliability and responsiveness of dedicated pain questionnaires such as the Brief Pain Inventory-Short Form (BPI-SF) and the McGill Pain Questionnaire (MPQ), though neither have been used extensively in SLE [52]. For instruments assessing physical function, there exists the Health Assessment Questionnaire (HAQ) and the Arthritis Impact Measurement Scale (AIMS) [55]; neither of which have been commonly utilized in SLE, although HAQ has been validated in SLE patients [56].

Mental health domains

Mental health domains encompass a wide variety of emotional measures such as anxiety, depression, self-concept, cognitive function, and substance abuse, among many others. These outcome measures are closely linked with the physical health domains since SLE symptoms of pain, fatigue, and body changes (e.g., weight gain and hair loss) impact patients' emotional well-being [42]. SLE patients have frequently reported feelings of depression, anxiety, anger, and stress due to the unpredictable nature of the disease, its associated flares, and accrued damage [42, 43, 57–59]. In addition, patients have also reported feelings of embarrassment and negative *self-image* due to changes in their appearance related to their SLE skin manifestations, hair loss, and weight gain secondary to glucocorticoids [41–43, 58, 60]. This negative self-image can be assessed by LupusQoL and LupusPRO—although recent SLE studies have also demonstrated the utility of more focused questionnaires such as the Body Image Quality of Life Inventory (BIQLI) and the Body Image Disturbance Questionnaire (BIDQ) [61, 62]. In this study by Jolly, Pickard et al., BIQLI scores were significantly decreased among SLE patients, and inversely correlated with overall disease damage, cutaneous damage, and alopecia. [61]. With demonstrated associations with depression [63], risky sexual behaviors [64], and poorer health outcomes [65], it is clear that body image is an important domain to be assessed by HCPs when managing SLE patients—especially those exhibiting cutaneous manifestations of SLE or adverse events to glucocorticoids.

Cognitive impairment is another important mental health domain to assess in SLE patients, as it has a significantly negative impact on a patient's HRQOL and participation—including their ability to fulfill their roles in a workplace setting [66]. Prevalence ranges from 20–80% depending on the metric being used, and on the presence or absence of neuropsychiatric SLE symptoms [67]. In a recent systematic review by Al Rayes et al., the pooled prevalence of cognitive impairment detected by cognitive battery assessment was 34% [68]. Other PRO instruments that have been used to measure cognitive impairment in SLE patients include the Cognitive Failures Questionnaire (CFQ), the Cognitive Symptom Inventory (CSI), Multiple Assessment Questionnaire (MAQ), Perceived Deficits Questionnaire (PDQ), and Patient Assessment of Own Functioning (PAOFI) [68].

Depression and *anxiety* represent mental health domains that have also been frequently reported in SLE patients, and may be linked to cognitive impairment [69, 70]. A systematic review by Moustafa et al., reported a pooled prevalence for depression of 35.2% based on data from 70 studies in 23,399 patients, and a pooled prevalence for anxiety of 24.2% based on data from 39 studies in 4495 patients—a prevalence much higher than in the general population [71]. Currently, screening for anxiety and depression in SLE utilizes self-administered questionnaires, including generic instruments such as SF36 and EQ5-D, as well as SLE-specific LupusQoL and LupusPRO. More focused questionnaires for depression and anxiety have also been used in SLE studies, including the Beck Depression/Anxiety Inventory (BDI/BAI), the Center of Epidemiological Studies Depression Scale (CES-D), and the Hospital Anxiety and Depression Scale (HADS), among many others [69, 71]. In a study by Julian et al., CES-D was found to be a useful screening measure to identify depression in SLE patients exhibiting a wide range of disease activity. Moreover, their results also suggested a different SLE-specific CES-D cutoff point for classifying depression in lupus patients [16].

Social health domains

Social health is another important category, which includes domains related to social roles, social relationships, as well as work productivity. Due to the aforementioned effects of SLE on physical and emotional domains, this can result in a significantly negative impact on patients' *social functioning* [41]—including their ability to maintain family/social and sexual relationships, and carry out their roles in a workplace setting [41, 42, 57]. Particularly, the unpredictable and relapsing nature of SLE can manifest in repeated work absences, reduced productivity, and altered career choice [72]. Further, cognitive symptoms of SLE affecting patients' memory and ability to concentrate, can influence their capability to find or hold a job [41, 43, 58, 59, 69]. In a study by Dhanhani et al., one third of their sample size of 362 SLE patients reported difficulties with physical, cognitive, and energy work activities [73]. Moreover, 70% of the same cohort of SLE patients reported the need for job accommodations—including sick leave days, permanent changes to work tasks, and assistive devices, among others [74]. To assess the impact of rheumatic diseases on work productivity, OMERACT has recommended the following measures: WALS (Workplace Activity Limitations Scale), WLQ PDmod (Work Limitations Questionnaire with

modified physical demands scale), WAI (Work Ability Index), WPS (Arthritis-specific Work Productivity Survey), and WPAI (Work Productivity and Activity Impairment Questionnaire) [75]. Other instruments that have been used to measure work productivity in SLE include Work Productivity and Activity Impairment Questionnaire: Lupus (WPAI:Lupus), The WHO Health and Work Performance Questionnaire (HPQ) and the workplace activity limitations scale (WALS) [73]. The WPAI questionnaire has been validated in a number of diseases [76, 77], with the WPAI:Lupus version specifically designed for SLE patients. In addition to these specific questionnaires, commonly used HRQoL PRO questionnaires such as SF-36, EQ-5D, LupusQoL, and LupusPRO also assess social aspects of health in SLE patients [78].

Assessment of HRQoL in SLE

HRQoL is one of the five OMERACT defined core outcome sets to be measured in SLE [23]. As a result, it is important to understand that, in the literature, the term HRQoL is very inclusive and has been utilized to describe health-related physical, emotional, psychological, and social well-being—as well as the impact the disease and/or its treatments affect these [79]. HRQoL in SLE is measured by generic (e.g. SF-36 [80] and EQ-5D [81, 82]) and SLE-specific questionnaires (e.g. LupusQol and LupusPRO) [83]. The SF-36 is one of the most widely studied PRO questionnaires in SLE [33] and captures eight separate HRQoL domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, emotional role, and mental health. Originally validated in SLE patients from the UK, SF-36 has since been shown to be responsive to changes in several reports, including studies in Canadian and French SLE patients [5, 84]. SF-36 continues to be one of the most common questionnaires included in clinical research studies [85, 86], RCTs [6, 50, 52, 84, 85, 87–97], and in psychometric studies focusing on the validation of new SLE-specific PRO questionnaires [21, 47, 48, 98]. However, the SF-36 has also faced criticisms pertaining to its inability to differentiate between patients of varying disease activity, and its lack of sensitivity to change in longitudinal disease activity [99]—a finding that has been confirmed by other studies [100, 101]. This may partly be explained by the administration of the survey on an annual or bi-annual basis. Due to rapid fluctuations in SLE disease activity, it is conceivable that changes may not have been fully captured by annual or bi-annual measures—resulting in a perceived lack of change in disease score. There is evidence for this theory as SF-36 scores have been shown to change with disease activity when the questionnaire is administered on a monthly basis or frequently in RCTs following initiation of treatment [5, 6].

The other commonly used generic PRO in SLE is the EQ-5D, which measures five areas of disability, including: mobility, self-care, usual activities (e.g. work, study, housework, family, or leisure activities), pain/discomfort, and anxiety/depression. In addition, EQ-5D also includes an additional PRO measure for overall health on a single visual analog scale (thermometer). Currently, EQ-5D has been used in LOS and RCTs, with one particular study utilizing EQ-5D to assess the effects of belimumab treatment plus standard of care SLE therapy on HRQoL in patients with active, autoantibody-positive SLE [50]. Both SF-36 and EQ-5D have demonstrated reliability and validity in assessing HRQoL in SLE

patients, with common domains in each of these questionnaires strongly correlated [99]. Both SF-36 and EQ-5D yield health utility measures [102], useful for economic evaluation, particularly as they can be compared to healthy and other chronic disease populations [81, 82].

The Patient-Reported Outcomes Measurement Information System (PROMIS) is a more recent initiative by the National Institutes of Health to develop self-reported measures of adult and pediatric health status across a wide variety of chronic diseases [40]. As a generic questionnaire, PROMIS is not disease specific, but rather, domain specific—allowing comparisons between different health conditions. However, it was not developed with patient input, but by selecting preferred items from multiple PRO questionnaires. The use of PROMIS is still in its early stages, as it is in SLE—where patient input is necessary in determining which item banks are most relevant/important to their disease experience. While a study in multiethnic Asian individuals has shown that PROMIS domains align closely with priority areas reported by SLE patients, identified content gaps indicate need for further attention and development—including dependence, burden on others, and SLE-specific symptoms [103]. Using item response theory (IRT) to develop PROMIS' item bank [40] allows researchers to administer PROMIS using computerized adaptive testing (CAT)—selecting the most informative questions from the item bank, based on patients' previous responses, to permit use of fewer questions per domain with more precision [104]. The efficiency and precision of PROMIS CATs has been demonstrated in a cohort of Dutch RA patients, as well as in US patients with RA and osteoarthritis [105, 106], although studies of PROMIS CAT in SLE are still in early stages—a recent study by Kasturi et al. demonstrated its validity and reliability in SLE patients [104].

While generic questionnaires allow comparison of HRQoL between patients with SLE and patients with other diseases as well as the general population, they are limited when it comes to assessing more SLE-specific outcomes, such as body image, appearance, self-confidence, and social supports—domains reported as important to SLE patients [107]. As a result, researchers have developed a number of disease-specific questionnaires that more adequately address these SLE-specific domains, including LupusQoL [47], LupusPRO [48], SLE-specific Quality of Life Questionnaire (SLEQOL) [21], and the SLE Quality of Life Questionnaire (L-QoL) [98]. LupusQoL assesses eight HRQoL domains, which include physical health, emotional health, body image, pain, planning, fatigue, intimate relationship, and burden to others. Originally developed in the UK [47], it has since been validated in Canada [5], the USA, [108] and other countries—demonstrating favorable psychometric measures in a number of different language cohorts [109–111]. LupusQoL has been used in a number of LOS [78, 112], and two recent RCTs [113].

Another SLE-specific questionnaire, LupusPRO, separates outcome measures into eight HRQoL domains and three non-HRQoL domains. The HRQoL domains include lupus symptoms, physical health (physical function, role physical), pain-vitality, emotional health (emotional function and role emotional), body image, cognition, procreation, and lupus medications. The non-HRQoL domains include available social support and coping, desires-goals, and satisfaction with medical care. LupusPRO was developed in a US SLE cohort and has shown strong correlations with SF-36, although correlations with disease damage were moderate in this validation study [48]. LupusPRO

has been validated in a clinical research study of SLE patients [114] and undergone translation and cultural adaptation into different languages [115, 116]; it has also been used to develop the Lupus Impact Tracker (LIT) for use in clinical practice [117].

Challenges and future directions of pros

Although PROs provide much promise in aiding HCPs and patients in the management of SLE, their widespread implementation in RCTs, LOS, and clinical practice still faces a number of significant challenges. In this review, we have highlighted a number of relevant PRO instruments that are currently utilized to assess a variety of domains pertinent to SLE patients. Further, a number of domains listed in Table 1 have not been described here in full, including those related to sleep function, and social relationships. Pain, physical function, fatigue, limited work/participation, and effects of skin and other internal organ system manifestations included in our review are among the most frequent health issues reported by patients [41]. There remains the need for further research to more fully investigate the impact of SLE on these domains, as well as the selection of appropriate PRO instruments for their assessment in RCTs, LOS, and clinical practice. Further efforts are needed to promote routine measurement of key impacts of disease currently not commonly assessed in SLE—including the impact of skin manifestations on self-image, adherence to medications, the impact of flares on humanistic burden, and treatment satisfaction [52]. As important PRO domains continue to be identified in SLE, new instruments will need to be developed to address these areas of unmet need. As for existing PRO questionnaires, further research may be required to validate and assess their psychometric properties in SLE patient cohorts.

Valid and reliable PROs targeting HRQoL in SLE clinical practice, LOS, and RCTs—including SF-36, EQ-5D, LupusQOL, and LupusPRO—have advanced the field due to their multinational and multiethnic versions to address issues of limited English literacy in patients. Other dedicated PROs focusing on less routinely assessed domains, such as self-reported cognitive impairment, anxiety, depression, and participation in social roles will also require a similar focus on cross-cultural adaptation. Since PRO instruments have been predominantly developed in Western societies, it will be important to consult patients of different socio-cultural backgrounds in the adaptation of these measures to prevent selection bias associated with studies that may not have included non-English-speaking patients in important clinical trials [118]. Furthermore, these cross-cultural and translated questionnaires will have to undergo further psychometric validation before their widespread use in clinical and research settings.

The use of PRO instruments in rheumatology has helped shift care from a physician- and symptom-driven outlook to one that incorporates the patient's voice and engages stakeholders, helping them monitor their own treatment progress. It will be important, going forward, to continue involving patients from a variety of cultural and socioeconomic backgrounds in the validation, as well as development, of novel PRO instruments to assess those domains most important to them. The future of PRO use in SLE is promising and continues to improve based on technologies that facilitate the format by which these

questionnaires are delivered—from paper questionnaires to electronic applications and adoption of IRT/CAT. In SLE, PROMIS CAT is still in its nascent stages with only one study demonstrating its validity [104]. Further studies will be needed to guide when changes in PRO measures should affect treatment decisions. However, regardless of what new instruments are developed, it is clear the future for PROs in SLE assessment and management is bright and that their use will become increasingly important.

Compliance with Ethical Standards

Conflict of Interest

Dr. Strand reports consulting fees from Abbvie, Amgen, Anthera, AstraZeneca, BMS, Boehringer Ingelheim, Celltrion, EMD Serono, Genentech/Roche, GSK, Janssen, Lilly, Novartis, Pfizer, Regeneron, Sanofi, and UCB outside the submitted work.

Andrew Kwan declare that they have no conflict of interest. Dr. Touma reports consulting fees from GlaxoSmithKline, AstraZeneca, Merck Serono and Janssen Pharmaceuticals .outside the submitted work.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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