University of Siena – Department of Medical Biotechnologies

Doctorate in Genetics, Oncology and Clinical Medicine (GenOMeC)

XXXIV cycle (2018-2021)

Coordinator: Prof. Francesca Ariani

Integrating Patient Reported Outcomes, clinical data and quality indicators to physician driven data in clinical management of chronic rheumatic diseases: the paradigm of Systemic Lupus Erythematosus (SLE)

Scientific disciplinary sector: MED/16 – Rheumatology

Tutor

Prof. Marta Mosca

PhD Candidate

Elena Elefante

Academic Year 2020/2021

INDEX

1. SYSTEMIC LUPUS ERYTHEMATOSUS AND QUALITY OF LIFE

1.1 Quality of Life in Medicine

Since the 1980s, the traditional assessment of the health status of a population, based exclusively on objective measurements of mortality and morbidity, has become progressively inadequate for a medicine that was going through a phase of epidemiological transition in which infectious diseases were increasingly being replaced by chronic and degenerative diseases. It has gradually moved, therefore, from the concept of "saving life" to the concept of "improving life".

In this context, to obtain a comprehensive assessment of the health status, it became necessary to measure the Quality of Life (QOL), as the goal of the care process. It appeared essential to include the direct perspective of the patient in the evaluation of health status, since he or she, and not the physician, is the only one capable of effectively judging his or her own QOL [1].

Quality of life is defined by the WHO as the *"individual perceptions of their position in life, in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns"*. This definition reflects the view that quality of life refers to a subjective evaluation that is embedded in a cultural, social and environmental context. It is a multidimensional concept, and the individual dimensions that comprise it and their relative weight may be significantly different from one individual to another and may vary over time for the same individual [2].

In order to define such a broad notion, it was considered more useful to create models in which the object of observation was limited only to dimensions strictly related to health, introducing the idea of health-related quality of life (HRQOL). The HRQOL is the set of qualitative aspects of an individual's life correlated to the domains of disease and health and, therefore, modifiable by medicine [3]. Specifically, the concept of HRQOL refers to the impact that a disease and its treatment have on an individual's functionality and perception of physical, mental, and social well-being (Figure 1) [4].

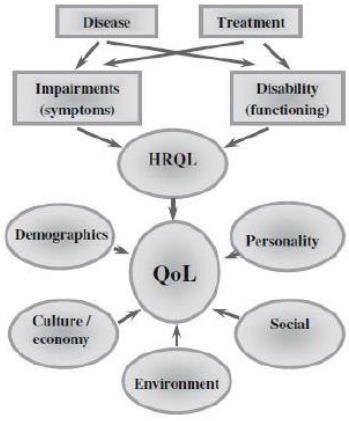

Figure 1. Factors influencing QoL

(Panopalis P, Clin Dev Immunol 2006)

The first quality of life measures to be used in health care were functional ones, i.e. those referring to the ability to carry out activities of daily living, simple or complex, generic or specific, in terms of frequency of certain behaviors or ability, autonomy or speed in performing tasks. These are the least subjective aspects of QOL, with the most immediate social, work and economic implications, as well as the most easily observed and described from the outside. Often, these instruments were designed to be completed by the health care personnel and not directly by the patients themselves [5].

In Medicine, the first article to mention quality of life in the title was an editorial in the Annals of Internal Medicine in 1966 [6].

Later on, thanks to the contribution of psychometry and statistics and the application of the rigorous criteria of Evidence Based Medicine, the dimension of quality of life, for a long time neglected in favor of other more measurable outcomes of treatment, acquired scientific validity [7].

1.2 Patient Reported Outcomes: generic and specific questionnaires used in Systemic Lupus Erythematosus

Patient Reported Outcomes (PROs) are health status evaluations directly reported by the patient without interpretation by a physician or anyone else; they are important instruments and provide SLE patients with an opportunity to participate in their treatment [8]. Physician-assessed health outcomes and patient-reported outcomes capture unique and complementary information.

In clinical practice, PROs can facilitate doctor-patient communication and seem likely to improve satisfaction with the care received [9]. They can also be used to simplify and standardize clinical information collection procedures, eliminating bias and variability in the wording of questions and recording of responses as well as helping the patient remember relevant information. In addition, PROs are tools to be used in clinical trials to measure response to a treatment from the patient's perspective.

The collection of PROs is mainly performed through questionnaires that represent a tool to quantify qualitative information. In the guidelines drawn up by the FDA in 2009 on the characteristics of PROs used in clinical trials, the main aspects characterizing these instruments are listed: clinical use, concepts measured, number of items, reference medical condition, reference population, method of data collection, method of administration, response options, recall period and frequency of administration, assessment modality, the weight of items or domains, modality of presentation, burdensomeness for the patient, availability of translated and culturally adapted versions [10].

PROs for measuring HRQOL are traditionally divided into two categories: generic questionnaires and questionnaires specific for disease, symptom, or condition.

Generic questionnaires allow for comparison with other groups and other conditions and allow measurement of dysfunction for individuals experiencing more than one condition [8]. Anyway, they may lack domains that are particularly relevant to a population with SLE, such as fatigue or sleep, body image or family planning, and they may not be sensitive enough to capture the frequent fluctuations in health status that is seen with SLE [8].

Among generic questionnaires, SF-36 (Medical Outcomes Study Short Form 36) has found wide use in rheumatology clinical trials and in observational studies. It addresses 8 domains; domain scores can be summarized into two global scores: the physical component summary (PCS) and the mental component summary (MCS). Each score ranges from 0 to 100, with higher values representing better self-perceived HRQoL.

Conflicting evidences are present in the literature regarding the sensitivity of this questionnaire in capturing the variations of QoL in SLE patients. If on one side, this generic questionnaire seems to be a potentially sensitive outcome measure in early disease [11], on the contrary, it didn't prove to be sensitive to change, over a period of 8 years, in a group of patients with late stage disease in the study by Kuriya et al. [12].

The FACIT-F represents an example of a symptom-specific questionnaire; it was developed to measure fatigue in oncology and later extended to numerous chronic conditions, including SLE. It assesses fatigue perceived in the physical, emotional, functional domains, its impact on daily activities and its social consequences, in a "recall period" of 7 days. It consists of 13 items; the score ranges from 0 to 52 with higher scores indicating a lower symptom incidence. It was validated for SLE in 2011 [13]. It demonstrates a strong correlation with the SF-36 vitality domain; it is considered one of the instruments with the best psychometric properties among those used in SLE for acceptability, conceptual coverage, ability to distinguish between groups, and sensitivity to change [14].

Disease-specific questionnaires incorporate elements specific to SLE and for this reason they are believed to be more responsive than generic instruments.

In 2013, Castelino et al. reviewed the literature to evaluate the development and psychometric properties of HRQoL measures used in adults with SLE. Direct comparison of the psychometric properties was difficult because of the different methodologies employed in the development and evaluation of the different HRQoL measures. Overall, multidimensional disease-specific measures, compared to generic ones, appear to have the strongest evidence for use in studies of adult patients with SLE, especially in terms of reliability and validity. Further studies are required to evaluate these instruments for responsiveness [15].

The first questionnaires specifically designed as PRO measures to assess quality of life in SLE patients and with published validation testing are: Lupus Quality of Life (LupusQoL), SLE-specific Quality of Life questionnaire (SLEQoL) and SLE Quality of Life Questionnaire (L-QoL).

Among these available measures, the one that has undergone the most validation process is the LupusQoL questionnaire. The original development and validation study of LupusQoL was performed in the United Kingdom and published by McElhone et al. in 2007 [16]. The questionnaire includes 34 items total covering eight domains (physical health, emotional health, body image, pain, planning, fatigue, intimate relationships, and burden to others). The items and response scale have been generated by the patients as the primary source. Score ranges from 0 (worst HRQoL) to 100 (best HRQoL). It takes little time to be completed (<10 minutes). This questionnaire has been validated for U.S., Spanish and Italian populations. Moreover, translations are available in numerous languages, although psychometric evaluations of these translations have not yet been published. Currently, this measure seems to be most appropriate for cross-sectional evaluations of HRQoL in SLE.

The English language version of the SLEQoL was developed and validated in the study performed in Singapore by Leong et al. in 2005 [17]. The questionnaire includes 40 items covering six domains (physical functioning, activities, symptoms, treatment, mood and self-image). Its items were derived from health professionals and were subsequently verified by patients. Scores range from 40–280, with higher values corresponding to worse quality-of-life. Time to respond the questionnaire is less than 5 minutes. Concurrent validity with the SF-36 is relatively poor, suggesting that this instrument should be used primarily in conjunction with other validated measures of HRQoL. But the SLEQoL has an important strength, that is that information is available on its responsiveness and the minimally important clinically difference. The concept of unpredictability of the disease course and the outcome of treatment is well represented in SLEQOL. On the contrary, it contains no items related to body image.

L-QoL was developed by Doward et al. in 2008 [18]. The questionnaire is based on the needs-based QoL model, which presumes that life gains its quality from the ability and capacity of individuals to satisfy their needs. The questionnaire includes 25 items (assessing self-care, fatigue and emotional reactions) that were derived from qualitative interviews of 50 SLE patients. The instrument has not yet been used in published clinical or observational studies of SLE. Score range is 0–25, with higher scores indicating worse QoL. Time to complete < 5 minutes. The L-QoL provides a single unidimensional score that indicates the SLE impact. It was validated against the Nottingham Health Profile and patient-perceived disease severity. Validity against better known measures in SLE, such

as SF-36, and physician assessed disease activity measures are not available, and the psychometric properties of the questionnaire have to be investigated [19].

More recently, in 2012, Jolly et al. developed and validated a new tool, called LupusPRO. It was developed from feedback from US patients of an ethnically heterogeneous background and both genders. It has 44 items that cover both HRQoL and non-HRQoL and is presented in a gender-neutral language. LupusPRO is self-administered and completed in less than 10 minutes. LupusPRO has been validated against SF-36, EQ-5D, LupusQoL, generic body image tools, depression, and physician-assessed disease activity and damage measures. So, for US patients with SLE, LupusPRO could represent a valid disease-targeted health outcome tool, to use together with a generic PRO measure to provide complementary information. Further studies are needed to understand its responsiveness to change and to determine the minimal clinically important difference dimension [20].

In 2014, the same group derived a short form instrument from the LupusPRO, the Lupus Impact Tracker (LIT). The questionnaire includes 10 questions about cognition, lupus medications, physical health, pain/fatigue impact, emotional health, body image, and planning/desires/goals. It has been validated against the SF-36, LupusQoL, disease activity and damage measures. It appeared to be reliable, valid and responsive to changes in tests conducted in 2 different samples of patients. Differently from other HRQoL measures, the LIT provides one summary score that captures the overall impact of lupus on patients' health status [21]. Recently, the cross-cultural validity of LIT was also evaluated in five European countries (France, Germany, Italy, Spain and Sweden). Both patients and physicians participating in this study found that the LIT improved the communication between them, helping them to discuss the real impact of the disease. Moreover, the LIT appeared feasible in routine clinical practice thanks to its brevity. The main limitation of this LIT European study is that the study mainly included outpatients, who were recruited in centres specialized in lupus care management and presented generally a well-controlled disease [22].

1.3 Major determinants of Quality of Life in patients with Systemic Lupus Erythematosus

In the last decades, the prognosis of patients with Sistemic Lupus Erythematosus (SLE) has improved significantly, from a survival of less than 50% at 5 years reported in one study in 1955 to a survival of 85% at 10 years and 75% at 20 years in the early 2000s (Figure 2) [23].

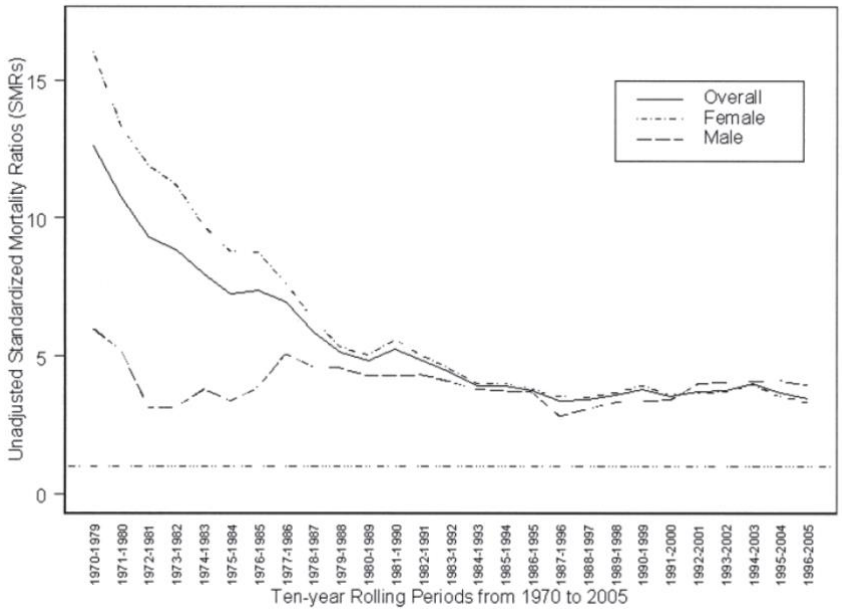

Figure 2. Unadjusted rolling 10-year standardized mortality ratios for the period 1970 to 2005

(Urowitz MB, J Rheumatol 2008)

However, this improvement in survival has not reflected a similar improvement in patients' QOL. SLE, with its wide range of manifestations and its unpredictable course, has a significant impact on patients' daily living.

In a recent survey performed among the Lupus UK members, almost three-quarters of individuals had problems limiting their ability to carry out their usual daily activities and only 15% of individuals worked full time. Moreover, many patients declared that they require day-to-day support, not only from health care professionals, but also from a partner, family member and friends. So, SLE determines significant limitations in daily living, work loss and a need for ongoing support from others [24].

Similarly, the considerable burden of SLE for patients and their carers has emerged from an online survey conducted in UK. SLE showed a considerable impact on patients' physical, social and financial status. In particular, most patients (89%) reported reduced ability to socialize; 76% of them had changed employment; of these, 52% stopped working completely. But SLE also showed a heavy impact on carers, as for their financial status and their social activities [25].

SLE can affect many aspects of patients' lives. Gallop et al. attempted to develop a conceptual model of HRQOL in SLE, starting with interviews with a small group of patients, and attempting to capture the presence of relationships between different areas of the patient's life that are affected by the disease in an interdependent manner (Figure 3) [26].

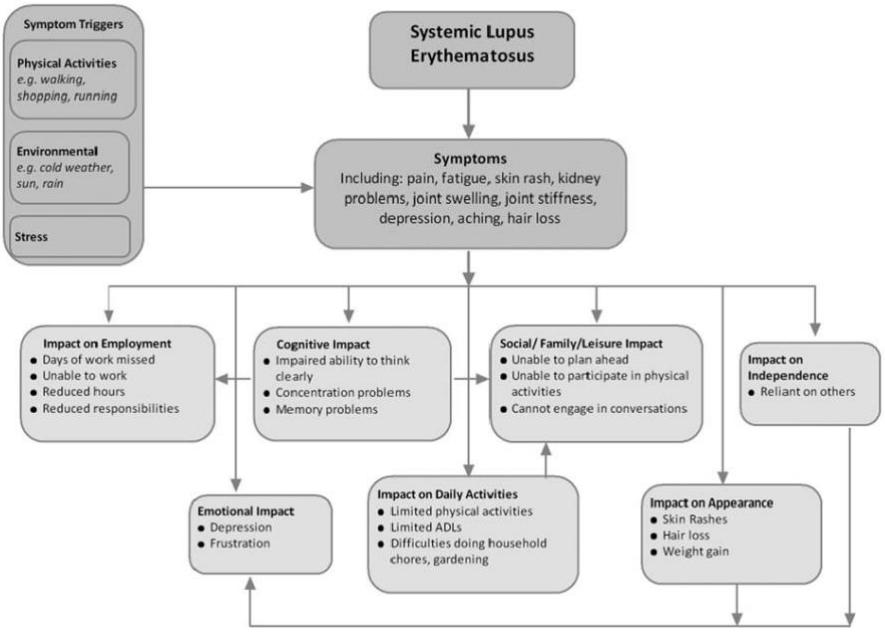

Figure 3. Conceptual model of the impact of SLE on HRQoL

(Gallop K, Lupus 2012)

HRQOL of SLE patients is consistently lower not only when compared with that of matched healthy subjects [27], but also when compared with patients with other chronic diseases. In 2005, Jolly et al. compared the Short Form 36 (SF-36) results of 90 patients with SLE with those of a comparison population of patients with other chronic diseases. The results of this work showed that patients with SLE, on average younger than the other subpopulations, had scores indicative of worse QOL in all domains of the SF-36 than patients with hypertension, diabetes mellitus, or myocardial infarction; patients with heart failure did not have worse QOL in the domains of physical function, role related to physical health and emotional state, and vitality, whereas they had significantly better QOL in the domains of physical pain, mental health, social role, and general health [28]. Moreover, SLE is also known to have a different impact on health status than other chronic rheumatic diseases [29,30]. For example, in a recent study by Chaigne and coworkers, HRQOL in patients with SLE and Rheumatoid Arthritis (RA), matched by age, sex and disease duration, was evaluated by the SF-36. Patients with SLE had lower Mental Component Summary (MCS) scores, whereas patients with RA had lower Physical Component Summary (PCS) scores and these differences remained even after adjustment for patient characteristics, treatment and activity of the disease, and even over 1 year of follow-up [29]. Literature data on the correlation between disease activity/severity and patients' HRQOL are a bit conflicting.

SLE patients often present many disease manifestations that, even if not organ- or life-threatening, may equally have a significant impact on their QOL. In fact, among the disease manifestations that

most seem to influence the HRQOL of patients with SLE are undoubtedly the musculoskeletal ones [31]. In a recent cross-sectional study of patients included in the Swiss SLE Cohort Study between April 2007 and June 2014, it was demonstrated that an increase in SELENA-SLEDAI or in Physician Global Assessment was negatively correlated with PCS and/or MCS scores of the SF-36. In particular, the authors found that active lupus nephritis and musculoskeletal involvement were associated with physical limitations and emotional problems, increased bodily pain and poor social functioning, while the serological activity (low complement and/or presence of anti-dsDNA antibodies) was associated with increased fatigue and reduced mental health [32].

Appenzeller et al. reported worse QOL, as assessed by the SF-36, in patients with SLE and active kidney disease, compared with patients without renal involvement. However, the authors failed to demonstrate a correlation between changes in renal disease activity and changes in patient self-assessment of QOL [33].

More recently, Jolly et al. demonstrated that patients with active lupus nephritis have worse health-related and non health-related QOL assessed by the LupusPRO questionnaire. The use of this SLE-specific instrument allowed the assessment of domains relevant to patients with SLE, emphasizing that it is mainly aspects related to therapies and procreation that are affected in this subgroup of patients [34].

The SF-36 has also been used to assess QOL in patients with neuropsychiatric involvement. Specifically, in recent work on neuropsychiatric SLE, it was found that QOL assessed by the SF-36 is impaired in all patients with SLE and neurological events. However, over time, the SF-36 mental health score improves significantly, and consensually with clinical improvement, in patients who had an inflammatory-based event; in contrast, in patients who had ischemic-based events or non-SLE-related neurological events, no such improvement is observed [35].

As one might imagine, damage accrual also worsens the QOL of patients with SLE. Mok et al., in a case-control prospective cohort study, showed that there was a positive relationship between the development of new organ damage and the deterioration in HRQOL (evaluated by SF-36), over a period of 2 years [36].

It is interesting to note an aspect of the existing relationship between damage and HRQOL: as underlined in a work by Legge et al., damage accrual seems to determine in the immediate term a decline in the SF-36 scores while, in a second time, the HRQOL of these patients changes in a similar way compared to that of patients without damage progression and, substantially, in relation to age. A possible explanation for this phenomenon is to be found in the greater ability of the patient to adapt to past damage compared to more recent damage that, in the short term, causes a worsening of

HRQOL. In this study, in fact, the General Health domain of the SF-36 underwent a partial recovery after the initial decline shown following the development of a new injury [37].

Despite this evidence, the relationship between activity, organ damage, and HRQOL remains complex and controversial, and the value of activity and damage indices as predictors of patient quality of life remains debated. HRQOL, therefore, appears as an independent domain and needs to be assessed distinctly with appropriate tools to measure it, to capture its different aspects [38].

In fact, many other studies in the literature seem to contradict what has been said so far, failing to demonstrate a direct correlation between the physician's assessment of the disease and HRQOL. Jolly et al., for example, in 2004, did not find a correlation between SLEDAI and SLICC and HRQOL assessed by the SF-36 [39]. Similarly, Doria et al. also did not find a correlation between the SF-36 and ECLAM in a cohort of 126 outpatients with SLE [31]. Subsequently, McElhone et al. failed to find statistically significant correlations between activity and disease damage and QOL as measured by the LupusQoL, a disease-specific questionnaire [40].

In a recent German longitudinal study on 169 SLE patients, a higher PCS over time resulted significantly associated with concurrent parameters, such as intake of antimalarial drugs, no glucocorticoid use, less fatigue, lower disease activity as well as to the baseline parameters of younger age and higher PCS. Whereas a higher MCS was associated with concurrent use of glucocorticoids and a higher baseline MCS. Interestingly, the authors estimated that 60% of the physical component of the SF-36 is explained by clinical and laboratory findings in SLE and may therefore follow clinical remission, compared with only 25% of the mental component [41].

Similarly, a recent meta-analysis explored the relationship between disease activity, organ damage and HRQOL, assessed by both generic and disease-specific scales, in SLE. In all eight domains of SF-36, disease activity showed modest correlation with HRQOL, with bodily pain ($r = -0.13$; $p = 0.001$) being highest and physical functioning ($r = -0.07$; $p = 0.013$) being the lowest. Lupus-specific QOL measurements, like LupusPRO, were relatively sensitive to the changes of disease activity and organ damage compared with generic SF-36 scale. Importantly, according to this work, mental health-related domains showed less relationship with clinical outcomes, such as organ damage and remission status, when compared to SF-36 domains related to physical well-being [42].

It is therefore evident that there are many factors that determine the patient's perception of his or her own health status, not only symptoms strictly related to disease activity and damage. The unpredictable course of the disease itself, comorbidities, therapies and their side effects, for example, must also be considered; a lower level of education, lower socioeconomic status, and depression have also been associated with worse QOL in SLE [43].

The impact of treatment on patients' HRQOL has to be considered, also in order to share therapeutic strategies with the patient and improving adherence to treatment.

For example, a study compared the QOL of patients with active lupus nephritis treated with Mycophenolate Mofetil (MMF) and Cyclophosphamide (CFX) as induction therapy. With the same rate of remission achieved (83.3% in both groups), MMF-treated patients reported higher scores in all domains of the SF-36, with a statistically significant difference especially for less fatigue, less limitation of physical and social functioning, and better psychological status. The difference in patients' perceived health status in this study appears to be primarily related to increased concern about side effects due to CFX therapy. Specifically, patients reported being concerned about alopecia, menstrual cycle alterations, risk of infection, and the development of a Cushingoid appearance [44].

A probably even greater impact on HRQOL is determined by chronic steroid therapy. Indeed, some work in the literature seem to demonstrate that the daily dose of steroids is negatively correlated to the quality of life of patients with SLE, regardless of disease activity and damage [45–47].

This growing interest in capturing the impact that therapies have on the health status of patients with SLE has recently led to the development of a specific questionnaire, the Lupus Satisfaction Questionnaire (LSQ), which aims to assess patient satisfaction with the treatment and medical care received. In the questionnaire validation study, 58% of the cohort of SLE patients reported being "somewhat satisfied" with the treatment they received for SLE [48]. The same authors also developed a questionnaire aimed at capturing the benefits, side effects, and overall impact of steroid therapy on the patient: the Systemic Lupus Erythematosus Steroid Questionnaire (SSQ) [49].

Psychological factors, particularly anxiety and depression, also play a very important role in determining worse HRQOL in patients with SLE [31,50,51]. Mood disorders can alter the patients' perception of the disease, reducing their ability to manage it [52]. Among comorbidities, fibromyalgia that has a prevalence of almost 22% among SLE patients [53], must be considered. Fibromyalgia (FM) does not correlate with disease activity, but its clinical features may lead to misinterpretation of SLE manifestations [54]. Fibromyalgia also appears to be associated with impaired patient coping capacity with systemic autoimmune disease [55]. Data from the literature agree in showing that FM is associated with worse quality of life in patients with SLE, as for example emerges from the study by Gladman et al. who showed that patients with SLE and FM, even without disease activity or damage, have worse QOL in all domains of the SF-36, compared with patients with SLE but without FM [53].

In this context, meaningful effects on QOL are seen by physical training, which significantly improves vitality and the physical domains of SF-36 [56], and by psychotherapy and cognitive behavioral therapy that may improve the mental component score of the SF-36 [57]. In a German cohort of SLE patients suffering from disease burden, psychoeducation led to significant and prolonged

response in all SF-36 domains but physical function. The sessions focused on information about the disease and specific problems of SLE patients, combining psychoeducative and psychotherapeutic elements. Patients enrolled improved significantly over a six-month period on most of the psychological measuring instruments applied, such as depression, anxiety, and overall mental burden [58].

Social relationships also have a great influence on patients' QOL. A recent longitudinal study has shown that a denying or uninformed support from parents and friends produced a negative impact, indicating that HRQOL is compromised when patients feel that their emotional needs are unrecognized. On the contrary, the study highlighted that HRQOL was positively influenced by the patients' perception of a greater "self-efficacy" in the management of their disease [59].

1.4 Quality of Life as treatment target in Systemic Lupus Erythematosus: myth or reality?

SLE is not a single-target disease due to its complexity and heterogeneity. Many aspects have to be taken into consideration in the management of the disease: controlling disease activity, preventing damage accrual, minimizing treatment-related toxicities or improving the quality of life of the patients. When defining a treatment target, the ultimate goal should be to change the natural course of the disease.

Since when the principle of "treat to target" (T2T) has been applied in SLE and the recommendations of an international and multidisciplinary task force have been published [60], the real challenge has been the definition of the most meaningful treatment targets.

The DORIS definition of remission [61] and the LLDAS definition of Lupus Low Disease Activity [62] have been the subjects of multiple validation studies and encouraging data are emerging from large independent cohorts. Indeed, remission and a low disease activity state (LLDAS) are linked to better outcomes in terms of organ damage preservation [63], fewer incidences of hospitalization and improved mortality [64].

No study has performed a direct comparison between both of these states, but there is indirect information regarding that probably remission would lead to lower damage accrual and higher glucocorticoid reduction compared to LLDAS [65]. Several studies published in the last years have focused on the importance not only of achieving remission/LLDAS but also of maintaining it over time [66,67]. Importantly, HRQOL improvement in SLE patients is defined as one of the treatment goals in the 2019 EULAR recommendations for the management of SLE [68]. However, the definitions of remission and LLDAS do not address the health-related quality of life or disease burden.

The physicians' view on lupus dominated the development of remission criteria and it was postulated that a control of disease activity would improve the QOL in SLE.

Available studies about the relationship between disease targets and HRQOL are often difficult to compare due to the heterogeneity of the cohorts, the different definitions of remission/low disease activity used, and the different Patient Reported Outcomes (PROs) adopted to assess HRQOL.

However, some recent studies have demonstrated an association between remission or LLDAS achievement and better HRQOL in SLE patients, although this may sometimes prove to be a weak association. In particular, a stable condition of remission seems to be associated with an improvement of the physical component of HRQOL [69,70].

Mok et al., on a large cohort of SLE Chinese patients, demonstrated that a durable remission could be achieved in almost a quarter of patients; however, only patients with remission of ≥5 years presented a significantly better QOL assessed using both SF-36 and Lupus-PRO [71]. In two Italian cohorts including 136 female SLE patients, Margiotta et al. have recently demonstrated that prolonged remission alone is important but not sufficient: to optimize patient HRQOL, it is also crucial to evaluate and manage other symptoms, like depression and fatigue [72].

Looking at the evidence of PROs as treatment targets for SLE, it is important to consider that, in clinical trials, the target response is mostly defined by changes in disease activity instruments and physician global assessments, while PROs were never used as the primary end point. However, PROs were often collected and analysed, showing that QOL and fatigue may respond to therapy [73]. This has been the case, for example, for belimumab, an anti-Blyss monoclonal antibody, which has demonstrated in registration trials to be able to significantly improve, compared with the control group, the SF-36, including the mental domains, and FACIT scores at week 52 of treatment [74]. Six-year follow-up data for belimumab also confirmed the positive effect on QOL and fatigue, but exhibited clearly the significant effect on the physical component of SF-36 [75]. A similar improvement of fatigue was reported by data analysing the effect of subcutaneous blisibimod and sifalimumab [76,77].

So, at the moment, the attainment of remission in SLE represents the main treatment target, but QOL and fatigue are still insufficiently controlled in the state of remission and, despite improvement of disease activity, QOL can remain unchanged over several years [78].

A patient's perspective is still not accepted as equivalent to the physician's perspective in treatment decisions. HRQOL is neither directly nor indirectly captured by disease activity instruments [79]. Some physicians fear looking at the patient's perspective, because of uncertainties of how to face and treat it [73] .

Our actual recommendations do not only call for T2T; shared decision-making is also endorsed in the overarching principals [68].

Therefore, a better understanding of the patients' experiences with the disease is crucial. HRQOL has to be considered an independent outcome measure and, as such, has to be routinely evaluated in SLE

patients. A positive patient-physician communication and a growing engagement of patients in the management of their disease are increasingly recognized as important instruments to improve patients' perception of health status.

2. PATIENT-PHYSICIAN DISCORDANCE: DATA FROM THE LITERATURE AND EXPERIENCE FROM THE LUPUS PISA COHORT

2.1 Patient-physician discordance in Systemic Lupus Erythematosus

SLE imposes a great burden on patient life and patients have to cope with a number of symptoms and limitations in daily life activities.

Some patients report that they find difficult to cope with their disease and 35-50% of patients perceive their health as 'far/not so good' or 'poor'. Living with SLE is therefore difficult, as patients will have to face phases of activity of the disease, accept long term therapies and make compromises with side effects, accept the risk of potential risks related with therapies, in the longstanding disease will have to cope with fatigue, pain, limitation of daily life activities at work as well as in the family [78,80–82].

In a recent European patient survey conducted among 4375 SLE respondents with the aim of investigating the 2020 burden of the disease from the patient's perspective, fatigue was reported as the most frequent (85.3%) and bothersome symptom. Respondents reported significant impact over their studies, career and emotional/sexual life in 50.7%, 57.9% and 38.2%, respectively [83].

In this context, physicians may not be fully able to evaluate the effect of SLE on their patient's quality of life; on the other side, patients may not be aware of clinically important signs of disease activity in such a complex and systemic condition.

There is a need to have a holistic view of the patient with SLE [26] and, to this purpose, HRQOL remains one of the most difficult aspects for the doctor to explore, because it is influenced by several factors and because there are still no assessment tools able to really grasp the weight that the disease determines on the patient's life.

In order to obtain a complete assessment of patients with SLE, it appears necessary to overcome the communication gap between doctors and patients. In the literature, this is referred to as "discordance", a term that implies that doctor and patient evaluate the disease differently but that there is no a right and a wrong view. In chronic diseases, such as SLE, it is important that the physician and the patient share which are the problems to face, which are the treatment goals and which are expected risks and benefits, in order to improve the management of the disease itself [84]. Furthermore, a better doctor-patient interaction and a greater participation of the latter in the management of his own disease certainly positively influence patient's adherence to treatment [85].

It is evident from the literature that the disease outcomes important to the physician do not correspond to those that are important to the patient. The doctor is mainly focused on preventing organ damage, while the patient gives more importance to symptoms that have a greater impact on daily life [86].

In the study by Alarcòn et al. in 2002, the evaluation of disease activity between doctors and patients was compared in a multi-ethnic cohort of 300 subjects with SLE. A discrepancy was found in 58%

of patients and in most of these cases disease activity assessed by the patient was greater than that assessed by the doctor. In particular, it emerged that clinicians give more importance to alterations in laboratory tests (that patients are not able to interpret correctly), while patients evaluate the activity of their disease mainly in relation to joint pain and perception of their degree of functioning, an aspect that is difficult for the doctor to appreciate [86]. In a cohort of Asian patients, Leong et al. found that patients tend to judge their disease more active than doctors when they have: a poorer overall health status (self-assessed by SF-36), thrombocytopenia, high blood pressure, urinary sediment changes, and some functional limitations in daily activities. Doctors, on the other hand, judge the disease to be more active than patients in the presence of: proteinuria, haemolysis, cylindruria, use of immunosuppressants such as azathioprine and cyclophosphamide, higher SLAM scores, patient-reported fatigue, photosensitivity and the patient's perception of getting sick more easily compared to other people. These data highlight, on the one hand, the patients' lack of understanding of the real meaning of some laboratory alterations, which should be better explained; on the other hand, physicians' limited ability to grasp the aspects of HRQOL that are most significant for the patient, although they try to include patient-reported symptoms in their assessment [87]. Similarly, Yen et al. tried to identify determinants of patient-physician discrepancy in SLE. In their study, conducted in a group of 208 women with SLE, the discordance was measured as the difference between the doctor's and the patient's VAS for the evaluation of the overall disease activity. It emerged that the most strongly predictor of discordance was physical pain, followed by components related to skin and kidney manifestations of SLAM [88]. It is clear from what emerged from these works that SLE is a complex disease and therefore difficult to understand by patients. According to Neville et al., patients rate their disease primarily on the basis of their psychological state, while physicians rely primarily on the physical effects of the disease [89].

In other “less complex” rheumatic diseases, the problem of discordance appears to be less evident. For example, in RA there seems to be a quite good correlation between the patient and the physician's assessment of disease activity (measured by DAS28, CDAI, SDAI) [90,91].

Recently, Golder et al. performed a very interesting study in a third level center for the treatment of SLE patients in Australia. Doctors and patients were asked to complete a questionnaire that included questions relating to QOL (derived from the LIT) and questions relating to disease activity and damage (derived from SLEDAI-2K and SLICC-DI respectively). In response to each question, doctors and patients had to declare their degree of concern about that item, on a 5-point Likert scale. In addition, doctors were asked if any particular aspects of the disease were routinely evaluated during a visit, and patients were asked if they had ever experienced the individual manifestations of SLE in the course of their disease. The results of the survey revealed an important discrepancy between

doctors and patients. In particular, patients' main concerns were found to be related to aspects of HRQOL, such as fatigue and degree of functioning. Conversely, doctors said they were more concerned about the manifestations related to organ damage. Furthermore, the three main concerns reported by patients (all related to functioning) were not routinely assessed by most physicians in clinical practice (Figure 4 and 5) [92].

	Concern ranking Patients (N = 84)	*Patients who rated '5'* n (%)	*Patient concern rating Median (IQR)*	*Physician concern rating Median (IQR)*	p-value
1	Reduced ability to perform usual activities of daily living due to pain or fatigue	44 (62.9)	5 (4–5)	4 (4–4.25)	**0.02**
2	Reduced ability to perform physical activities due to pain or fatigue	43 (60.6)	5 (4–5)	4 (4–4.25)	**0.04**
3	Waking up feeling worn out	44 (60.3)	5 (4–5)	3 (3–4)	**<0.001**
4	Fatigue	45 (58.4)	5 (4–5)	4 (3–4)	**<0.001**
5	Lupus-related skin rash	38 (52.1)	5 (4–5)	4 (4–5)	0.28
6	Kidney disease	29 (51.8)	5 (3–5)	5 (5–5)	**0.02**
7	Reduced ability to maintain an adequate level of performance at work (education, employment, home duties)	34 (50.0)	4 (3.5–5)	4 (4–5)	0.64
8	Joint pain	35 (49.3)	4.5 (4–5)	4 (4–5)	0.75
9	Heart disease	25 (48.1)	4.5 (3–5)	5 (4–5)	**0.05**
10	Sensitivity to the sun	37 (48.1)	4 (4–5)	4 (3–4)	**0.03**
	Concern ranking Physicians (N = 21)	*Physicians who rated '5'* n (%)	*Patient concern Median (IQR)*	*Physician concern Median (IQR)*	p-value
1	Seizures	18 (85.7)	4 (2–5)	5 (5–5)	**0.003**
2	Strokes	18 (85.7)	3.5 (2–5)	5 (5–5)	**0.002**
3	Kidney failure	18 (85.7)	4 (3–5)	5 (5–5)	**0.003**
4	Kidney disease	17 (81.0)	5 (3–5)	5 (5–5)	**0.02**
5	Blood clots	16 (80.0)	4 (3–5)	5 (5–5)	**0.001**
6	Osteoporosis caused by lupus medication	16 (76.2)	4 (3–5)	5 (5–5)	**0.01**
7	Shortness of breath	14 (66.7)	4 (4–5)	5 (4–5)	**0.05**
8	Vision changes	14 (66.7)	4 (3–5)	5 (4–5)	**0.03**
9	Heart disease	13 (61.9)	4.5 (3–5)	5 (4–5)	**0.05**
10	Lung disease	13 (61.9)	4 (2.5–5)	5 (4–5)	**0.01**

Figure 4 The highest ranked concerns by patients and physicians

(Golder V, Lupus 2018)

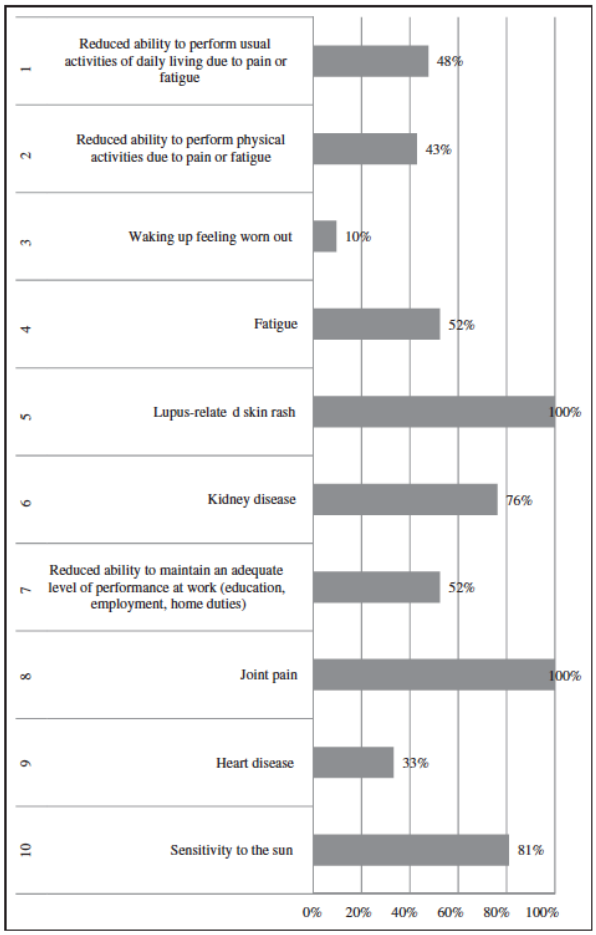

Figure 5 Proportions of physicians who routinely assessed 10 highest ranked patient concerns

(Golder V, Lupus 2018)

Fatigue and chronic pain represent two of the most pervasive and debilitating symptoms for patients with SLE. They are often "invisible" symptoms, difficult to explain to others, including some physicians, that may underestimate the severity of these manifestations.

LUPUS UK, a national UK-registered charity supporting people with systemic and discoid lupus, has recently conducted a UK-wide survey of individuals living with lupus in order to provide information to identify gaps needing further research to improve patients' well-being.

Fatigue/weakness (91%, n= 2299) and joint pain/swelling (77.4%, n= 1957) were the most common symptoms that interfere with daily activities. When asked to rank the top three symptoms most difficult to live with, these first two symptoms were also ranked in their 'top three' by 80.9% (n= 2044) and 60.4% (n= 1527) of individuals, respectively (Figure 6) [24].

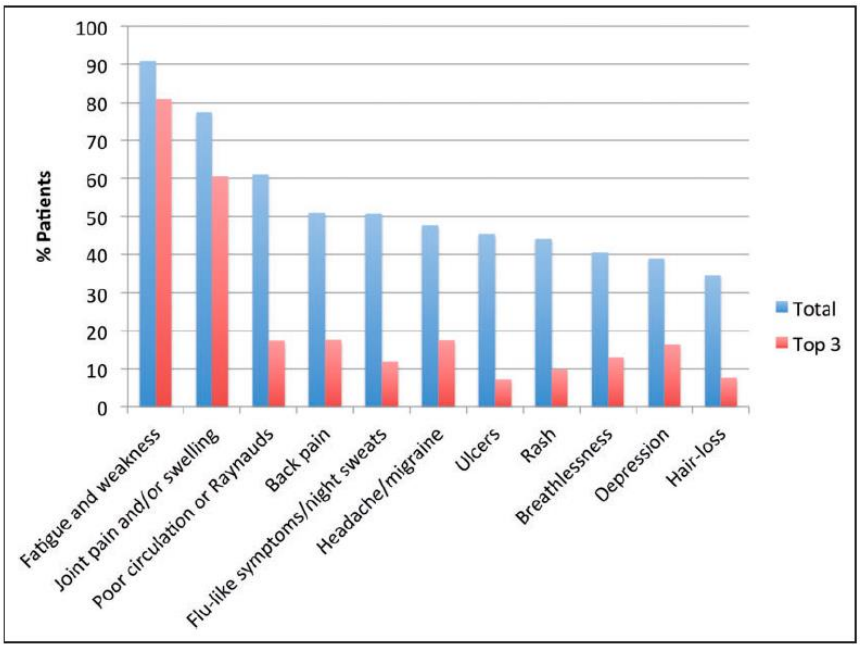

Figure 6 Most frequently reported symptoms to suffer from stratified by total number of participants experiencing a symptom and number of participants ranking symptoms in the top three of most difficult symptoms to live with

(Morgan C, Lupus 2018)

Interestingly, Piga et al. have demonstrated that musculoskeletal manifestations, including active arthritis as well as Jaccoud's deformities and fibromyalgia, are associated with a poorer HRQOL (as measured by SF-36) and a negative disability perception (evaluated by the HAQ) in SLE patients [93]. Similar results were obtained from another Italian work on 50 consecutive patients with SLE in which the presence of arthritis, clinically and ultrasonographically assessed, was correlated with VAS score for pain and a worse perception of global health and disease activity [94]. Zhu et al., in a retrospective study, demonstrated the correlation between disease flares characterized by musculoskeletal manifestations and lower HRQOL levels, in a large cohort of Chinese patients with SLE [95].

In a recent online survey of US adult patients with SLE, despite substantially high rates of satisfaction with current treatments, patients identified residual pain and fatigue as the main unmet needs and declared that reduced fatigue, pain, and flares were the most important treatment goals from their point of view [96].

These data has been confirmed in a recent work done in the framework of the ERN ReCONNET in which existing clinical practice guidelines on SLE have been reviewed with the aim of outline the state of the art and identify current unmet needs: the persistence of symptoms like pain and fatigue, even when remission of SLE disease activity has been achieved, has emerged as an unmet need from patients' perspective [97].

Recent findings from a population-based registry of 766 people with SLE suggest that multilevel interventions may be needed to tackle the negative impact of pain in SLE. In this cross-sectional

analysis of patient-reported data, predictors of pain intensity and interference (defined as pain that hinders major life activities) were examined. It emerged that disease activity and organ damage explained only 32-33% of the variance in pain intensity and interference. Sociodemographic factors accounted for an additional 4-9% of variance in pain outcomes, with older age and black race being associated with increased pain intensity and higher socioeconomic status being protective for pain outcomes. Finally, psychosocial/behavioural factors accounted for the final 4% of variance [98].

Among subjective factors influencing patient perception of disease status, fatigue represents one of the most prominent symptoms of SLE and a major contributor to QOL, although it is only addressed in a few instruments used in clinical practice to monitor the disease.

Fatigue is reported by approximately 50% of patients at least once in their disease history. Patients report that there is a significant difference between “SLE-related fatigue” and "normal fatigue", although they are often unable to adequately explain this difference. Pettersson et al. attempted to describe the various aspects of the concept of fatigue through the experience of 33 women with SLE interviewed in focus groups. Four main themes emerged: the "nature" of the symptom, which in turn includes 3 categories (the type of sensation, the way it presents itself and its characteristics); the aspects of life affected by fatigue, which mainly include the effects of the symptom on emotions and social relationships; the strategies used to manage the symptom on a daily basis and the factors that influence the perception of fatigue, mainly pain and lack of understanding from others. Figure 7 shows the results of the analysis of what emerged from the work in the focus groups [99].

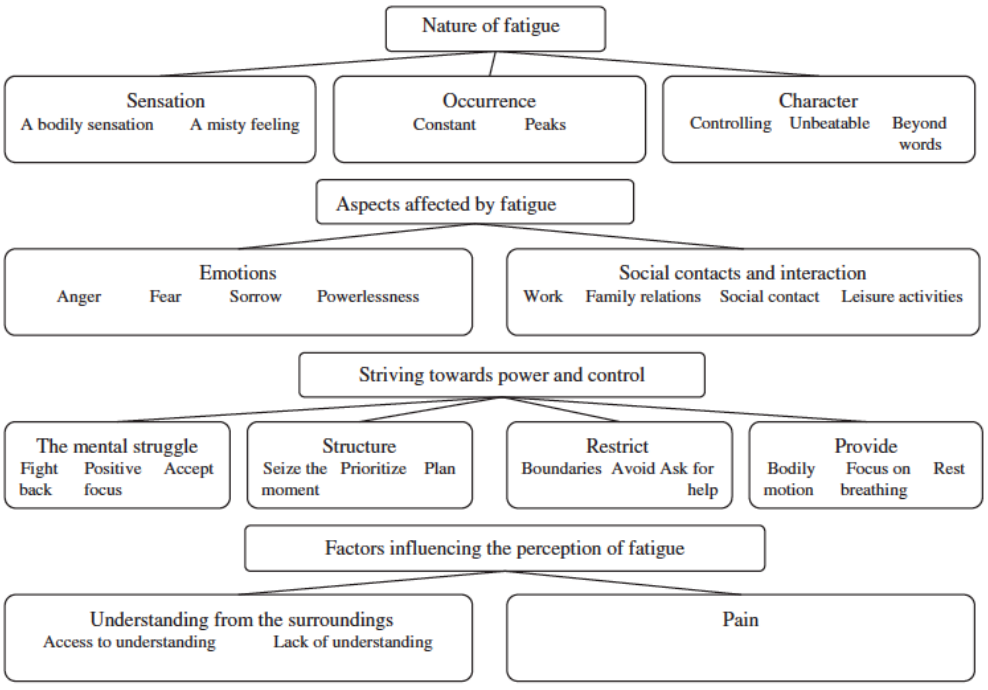

Figure 7 The concept of "SLE-related fatigue"

(Pettersson S, Rheumatol Oxf Engl 2010)

From literature data, it appears that patients with SLE report greater fatigue not only compared with the general population, but also compared with patients with other diseases, for example, when compared with cancer patients with anemia and also compared with patients with rheumatoid arthritis [13,100]. The pathophysiological mechanism of fatigue in SLE is unclear, but its cause is probably mutlifactorial and it seems that disease activity per se contributes only minimally to the genesis of fatigue. In fact, many studies in the literature have not demonstrated an association between fatigue and indices of SLE activity and damage, but on the contrary have found a strong association with other conditions often present in SLE patients, such as fibromyalgia and depression, which may reflect a reduced ability of the patient to live with and adapt to their disease [101]. Moazzami et al. recently analyzed data from an inception cohort of adult patients from the Toronto Lupus Clinic over 10 years (from 1997 to 2018), determining if different trajectories of fatigue associate with specific latent classes of disease activity. They found that fatigue and disease activity follow distinct trajectories and disease activity alone cannot fully explain fatigue trajectories. Trajectories with higher fatigue were associated with more fibromyalgia and trajectories with higher disease activity were associated with higher cumulative glucocorticoid use. Moreover, higher baseline glucocorticoid use was more likely associated with more fatigue [102].

An interesting study have recently analyzed potential risk factors for fatigue in the peculiar subgroup of SLE patients with neuropsychiatric symptoms (NP). SLE patients were classified as having neuropsychiatric symptoms of inflammatory origin (inflammatory phenotype) or other origin (non-inflammatory phenotype) and importantly it emerged that fatigue was similar in patients with an inflammatory phenotype compared to patients with a non-inflammatory phenotype. Moreover, there was no association between disease activity and fatigue, but symptoms of anxiety and depression (evaluated by the HADS) were strongly associated with all fatigue measurements, suggesting that intervention strategies to target fatigue in (NP)SLE patients may need to focus on symptoms of anxiety and depression rather than immunosuppressive treatment [103].

In the LuLa cohort, fatigue was assessed in 2011; 40% of patients reported a severe fatigue. A higher level of fatigue resulted associated with a higher level of patient-reported disease activity (SLAQ) and accrued damage (BILD), a higher number of comorbidities and SLE medications and a worse physical and mental HRQOL (PCS and MCS SF-12) [104]. Data from the literature, in fact, demonstrate that patient self-rated fatigue severity has a strong negative correlation with all domains of the SF-36 [105–107]. The figure below (Figure 8), derived from a paper by Kiani et al. [43], summarizes some of the

studies related to fatigue in SLE that all agree in demonstrating a negative impact of fatigue on QOL, regardless of the instrument used to measure it.

Study (year)	SLE patients, *n*	Controls		Measures of disease activity	Measure of damage	Measures of QoL	Result
		Disease, *n*	Healthy, *n*				
Bruce et al. [5] (1999)	81	0	0	SLEDAI; SLAM-R	SLICC/ACR SDI	FSS; SF-36	Negative correlation with disease activity and QoL
Tench et al. [6] (2000)	120	0	0	SLAM; ECLAM	SLICC/ACR SDI	FSS; CFS; VAS; PSQI; SF-36; HAD	Negative correlation with SF-36
Godaert et al. [4] (2002)	20	28 (primarily Sjögren's syndrome)	30	–	–	MFI; Zung Self-Rating Depression Scale	Worse fatigue and depression in SLE
McKinley et al. [8] (1995)	48	0	27	SLAM	–	PFS; SSQ; CES-D	Worse fatigue in SLE

CES-D Center for Epidemiologic Studies Depression; *CFS* Chalder Fatigue Scale; *ECLAM* European Consensus Lupus Activity Measurement Index; *FSS* Fatigue Severity Scale; *HAD* Hospital Anxiety and Depression Scale; *MFI* Mean Fluorescence Index; *PFS* Piper Fatigue Scale; *PSQI* Pittsburgh Sleep Quality Index; *QoL* quality of life; *SF-36* Medical Outcomes Survey Short Form 36; *SLAM* Systemic Lupus Activity Measure; *SLAM-R* Systemic Lupus Activity Measure-Revised; *SLE* systemic lupus erythematosus; *SLEDAI* Systemic Lupus Erythematosus Disease Activity Index; *SLICC/ACR SDI* Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; *SSQ* Social Support Questionnaire; *VAS* Visual Analogue Scale

Figure 8 Fatigue and quality of life in SLE

(Kiani AN, Curr Rheumatol Rep 2010)

All this considered, the rational assessment and treatment of fatigue remains a major challenge in SLE.

Obviously, it is important to distinguish between fatigue in patients with high disease activity, in whom remission or at least low disease activity should be targeted, and fatigue in mostly inactive patients, with a very high load of anxiety and depression, for whom psychological and behavioural assessment represents a key step [108].

Jump et al. described how a positive effect on fatigue is exerted by the social support the patient perceives to receive, thus underlining how probably psychosocial interventions, different from the traditional therapeutic approach, could improve the outcomes and the quality of life of patients with SLE [109]. Moreover, the role of physical exercise in improving fatigue is debated [106]. Mertz P. et al. suggested a practical step-by-step algorithm for the general assessment and management of fatigue in SLE. Importantly, the authors underlined that because fatigue is a highly subjective symptom, the standardized assessment of fatigue using validated PROs represents an important step. The use of validated PROs also allows for an individual follow-up of fatigue intensity and symptoms over time and may help in underlining the benefit of a therapeutic intervention at the patient level. Moreover, this approach may help to establish a trusting physician–patient relationship [110].

2.2 Experience from the Lupus Pisa cohort

On the basis of these evidence, we have investigated the main determinants of patients' HRQOL and the relationship between patients' and clinician's evaluation of health status in our cohort of adult patients with SLE, regularly followed at the Lupus clinic of the Rheumatology Unit of Pisa.

First of all, we investigated fatigue determinants and its impact on illness perception. In our study cohort, principally of outpatients with mild-moderate disease activity, we found a median FACIT-Fatigue score of 40 (IQR 32-46, minimum 7- maximum 52). This appeared to be better compared to that of other SLE cohorts (for example the cohort of the EXPLORER trial) [13], however patient FACIT-F scores were significantly lower (more severe fatigue) compared to those of a group of matched healthy controls (47 *vs* 40; $p < 0.001$).

In our study cohort, 78.5% of patients were at least in LLDAS. This underlines that, even in a group of SLE outpatients who are predominantly in remission or in LLDAS, fatigue continues to be an important symptom characterizing this condition. In our study, no correlation emerged between the level of fatigue and age, disease duration, disease activity and organ damage evaluated by the physician. Fibromyalgia demonstrated to have a strong negative impact on fatigue irrespective of other factors. Importantly, in our cohort FACIT-F scores were significantly associated with the results of the other PROs used. In particular, FACIT-F scores showed a significant positive correlation with all the domains of SF-36 ($p < 0.001$; r between 0.53 and 0.77), suggesting that a lower level of fatigue was associated with a better HRQOL; a strong negative correlation was apparent between FACIT-F and LIT scores (r = -0.78; p <0.001) suggesting that fatigue is an important determinant of SLE burden on patients' life. As a final point, we found that higher levels of fatigue in our patients significantly correlated with higher SLAQ scores (r = - 0.72; $p < 0.001$), irrespective of fibromyalgia and disease activity or damage. This suggests that fatigue represents a puzzling factor in the complex clinical picture of SLE patients, which leads them to overestimate SLE activity and severity and therefore become dissatisfied with the care process and health status [111]. As already known in the literature, many factors can influence HRQOL in SLE patients, including mood disorders [43].

In a recent study by Cui C et al., the authors found a very high prevalence of depression and anxiety symptoms (79.5% and 86.8%, respectively). Interestingly, they found that illness uncertainty was positively associated with psychological distress and may contribute to the development of depression and anxiety in women with SLE [112].

In our outpatient SLE cohort, 37.4% of patients presented symptoms of anxiety and 25% of depression, according to the *Hospital Anxiety and Depression Scale* (HADS) questionnaire.

In the multivariate analysis, patients with active disease were more anxious and depressed (p <0.01) than patients in LLDAS. Active skin involvement was associated with depression (p <0.05). Fibromyalgia and higher age were independently associated with anxiety and depression, respectively (p <0.05). Higher scores on the HADS were significantly associated with a subjective perception of higher disease activity (SLAQ, p <0.001) and a worse HRQOL (PCS - p <0.05; MCS, FACIT, LIT -

p <0.001), irrespective of other factors (data not published, abstract accepted for Poster presentation at the Lupus Cora congress 2021).

Considering the multidimensional impact of the disease burden on patients' life, we also wanted to evaluate, in our SLE cohort, which aspects are more difficult to identify for the clinician, using traditional clinical evaluation and disease activity measures.

For this purpose, we used a disease-specific instrument, the Lupus Impact Tracker (LIT), able to identify the impact of specific disease manifestations and treatments with greater precision on those aspects that matter the most for SLE patients.

In our cohort, the LIT items that received the highest score, suggestive of a severe disease impact, were: anxiety, fatigue, difficulty concentrating and pain.

The results of the LIT questionnaire showed a median score of 22.5 (IQR 7.5–40), suggesting a mild-moderate impact of SLE on patients' life. These results seem to indicate a lower disease impact in our cohort compared to other studies. Specifically, the median LIT score was 32.5 in the multicenter European validation study, despite similar clinical characteristics (such as median age, disease duration, global disease activity, organ damage) compared to our cohort [22]. However, different kinds of active disease manifestations are not detailed in the European validation study therefore differences in the prevalence of certain instances of organ involvement may explain the lower LIT score in our population.

Importantly, we found no correlation between the SELENA-SLEDAI score and the LIT score, suggesting that global disease activity indices may not be sufficient to reflect the real burden of the disease on patient life. In the multicenter European validation study, LIT scores increased proportionately with the level of Physician Global Assessment (PGA) and SLEDAI; LIT scores were also higher in patients presenting a flare at enrollment [22]. However, in the prospective validation of the LIT in 20 North American sites, the score was not indicative of a correlation with the SELENA-SLEDAI score [113]. Similarly, in the LIT validation study in an Australian cohort, the LIT score did not demonstrate a significant correlation with PGA and SLEDAI-2k [114].

Therefore, to better explore the relationship between disease activity and SLE impact on patient life, we aimed at identifying which type of disease activity was the most reliable indicator of the majority of patients' perception of SLE burden.

In the multiple linear regression analysis, active arthritis ($p<0.01$) and ongoing glucocorticoid (GC) treatment ($p<0.001$) proved to be independent factors significantly linked to more severe disease burden, expressed by higher LIT scores, irrespective of age at enrollment and fibromyalgia.

In particular, we found that active arthritis has a negative impact on several aspects of patients' daily living including not only pain but also patients' ability to perform daily activities, fulfil family

responsibilities and plan activities and future events. This confirms literature data showing that musculoskeletal involvement is arguably one of the most important determinants of quality of life and one of the unmet needs in SLE patient management. Another disease manifestation that emerged as a determinant of disease burden is skin involvement. Patients with active cutaneous manifestations produced a significantly higher score of the LIT item relative to discomfort due to physical appearance (Figure 9).

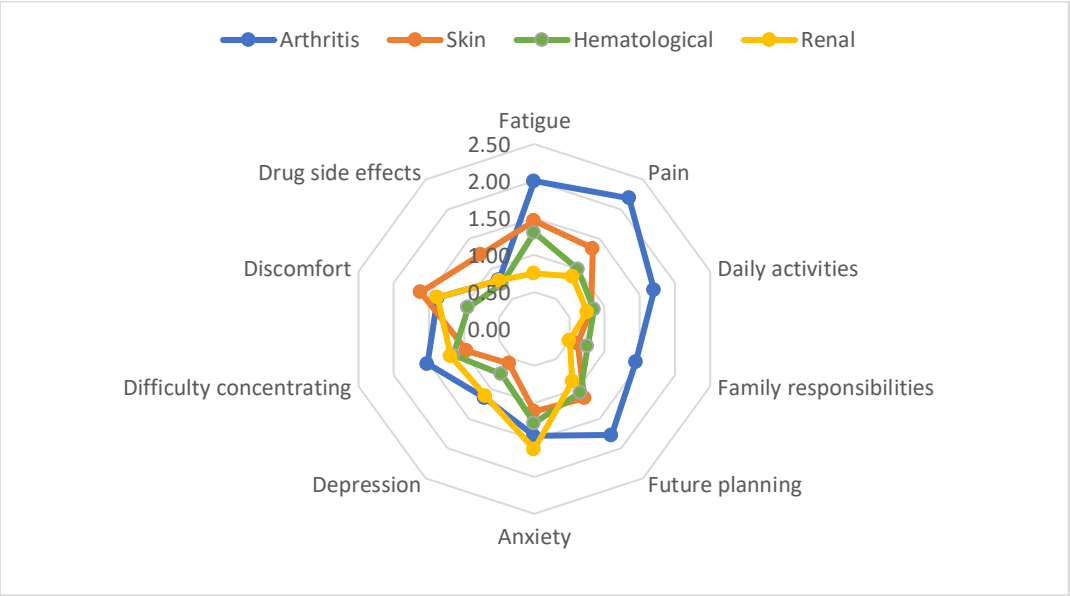

Figure 9 The impact of active disease manifestations on LIT items in Pisa SLE cohort

Data from the literature suggest that patients with Cutaneous Lupus Erythematosus (CLE) have poorer HRQOL compared to the general population and to patients with other dermatological and medical conditions. According to a recent review, disease activity, pain, photosensitivity, female gender, low income and African American ethnicity are predictive factors of poor HRQOL in CLE patients. Specifically, emotions, daily functioning, general and mental health are domains significantly affected in CLE patients [115].

Overall, our data confirm that clinical manifestations, such as arthritis and skin involvement, which are usually considered “mild” and for this reason sometimes overlooked by physicians, actually represent an unmet need in the management and treatment of SLE patients, because they play a major role in determining the disease burden and negatively affect patients’ daily functioning.

The most original data arising from our cohort is the role of ongoing treatment in determining SLE burden. Indeed, ongoing glucocorticoid therapy, even at low doses (median daily dose of our patients was 5 mg of prednisone equivalent) and after adjusting for potential confounders, proved to be an independent factor with a negative impact on several aspects of patient life. Previous studies have

analysed the influence of GC therapy on HRQOL in SLE. Choi et al., in a cohort of 108 SLE patients, found that QOL was negatively affected by glucocorticoid dose, rather than by disease activity and damage and in particular, GC treatment had greater effects on physical QOL [45]. Moreover, a Swedish nationwide study based on patient reports demonstrated that patients on GC had a statistically significantly lower HRQOL (evaluated with the EQ-5D) than GC-free patients [116]. Our study's analysis of the correlation between GC treatment and each item of the LIT enabled us to highlight how glucocorticoids represent one of the most important factors that contribute to determining SLE burden with a negative impact on several domains, including daily activities, family responsibilities, future planning, discomfort due to physical appearance and drug side effects (data not published, abstract accepted for oral presentation at the 13th International Congress on Systemic Lupus Erythematosus, San Francisco 2019, article under revision).

As already said, despite HRQOL improvement is considered to be a major outcome of the SLE management, literature data show that traditional clinical indicators for disease activity and/or organ damage possess only a weak correlation to quality of life measures, suggesting that such measures assess different aspects of patient status and that a discrepancy exists between patient assessment and the physician-driven definitions of SLE status [69,70]. Therefore, we wanted to further explore which were the main determinants of patient-physician discordance in our cohort of Lupus patients. Applying the *Lupus Low Disease Activity State* (LLDAS) definition [62] and the SELENA-SLEDAI score to define disease activity from the clinician point of view and using the SLAQ questionnaire for the patients' self-evaluation of disease activity, we found that 72.6% of patients in LLDAS actually considered their disease as active, as expressed by the SLAQ score, in disagreement with the treating physician. In line with literature data, we found that musculoskeletal symptoms are among the most important reasons of patients' dissatisfaction in SLE management. In fact, we found that past and ongoing joint involvement, a concomitant diagnosis of fibromyalgia and ongoing GC treatment (even at a low dosage) were the main determinants of this patient-physician discordance in our cohort. Moreover, we observed that "discordant" patients reported a poorer HRQOL, as measured by all the PROs used, compared to patients who were "concordant" with the clinician's evaluation. This underlines that patient-physician discordance is strongly linked to a patient's negative perception of their health status [117].

Discordance between patients and physicians carries clinical significance: it can negatively affect patient care, adherence to treatment, and outcomes of disease [118]. For example, the patient who assesses his/her disease as inactive when the physician regards it as active, may see no reason to adhere to treatment. On the other hand, doctors may not be able to understand what patients expect

from treatment that is, first of all, an improvement in the limitation in carrying out daily activities and their HRQOL [119].

Patients themselves and physicians lost much information about the disease and its impact. It is increasingly evident that the ways to improve outcomes in SLE patients could benefit from patient-oriented research focusing on the multifaceted dimensions of the disease burden. To bridge the communication gap between patients and physicians appears crucial in this context.

3. INTEGRATING PATIENTS REPORTED OUTCOMES, CLINICAL DATA AND QUALITY INDICATORS TO PHYSICIAN DRIVEN DATA IN CLINICAL MANAGEMENT OF CHRONIC RHEUMATIC DISEASES: THE PARADIGM OF SYSTEMIC LUPUS ERYTHEMATOSUS

3.1 Background

The discordance between patients and physicians in the assessment of SLE is reflected in the high prevalence of unmet needs, relating primarily to physical, daily living and psychological concerns, reported by patients with SLE. This suggests the needs to emphasize more patients' psychological and physical well-being and less clinical and laboratory measures [79]. A more patient-oriented research to address the multifaceted dimensions of the disease burden is warranted.

Therefore, the aim of this study was to investigate patients' needs and expectations about their medical care, with the objective of integrating patient-reported data to the traditional physician evaluation towards a new shared strategy for disease management, starting from the paradigm of SLE, which may serve as a prototype for other chronic diseases.

The project was funded by European Commission, 3rd Health Program, Proposal ID 769736 and from the University of Pisa (BIHO) and have been developed by the Rheumatology Units of Pisa (Italy) and Dusseldorf (Germany) and by the economists from the Institute of Management of the Scuola Superiore Sant'Anna of Pisa (Italy).

3.2 Objectives of the study

The **general objective** of the study is to develop a strategy for the monitoring of SLE relying on the integration of QOL data, Patient Reported Outocomes (PROs) and other patient-driven data to the traditional physician's evaluation.

The **specific objectives** of the study are:

- mapping current evidence on indicators (including "patient-driven" data and "physician-driven" data) for the management of SLE
- mapping existing IT systems useful for the management of SLE
- assessment of physicians' current practice in the management of patients with SLE
- assessment of patients' knowledge, needs and expectations to identify the patients' ideal context
- assessment of physicians' needs and expectations to identify the physicians' ideal context
- merging all the different perspectives and highlight the main points for the development of a new ideal strategy for the management of SLE

3.3 Methods

The study work has been divided into three main steps (Fig. 10):

1. systematic literature review of existing clinical and non-clinical indicators for the management of SLE and of currently available SLE-dedicated IT tools (Apps) designed to involve the patient in the gathering of clinical and quality of life data about their health;
2. based on the results obtained from the literature review, ad hoc on-line surveys have been designed targeting European experts in the field and SLE patients. The aim was to investigate both the real use of such tools and indicators in clinical practice and to identify critical issues, needs and expectations experienced by doctors and patients in management of the disease;
3. the survey results have been discussed in dedicated focus groups of patients and clinicians. The final step of the process was a mixed focus group, designed to bring together not only patients and clinicians but also general practitioners, nurses and one caregiver. Based on the earlier focus groups, the main subjects were discussed with the aim to identify the key elements for the development of a new paradigm for SLE management.

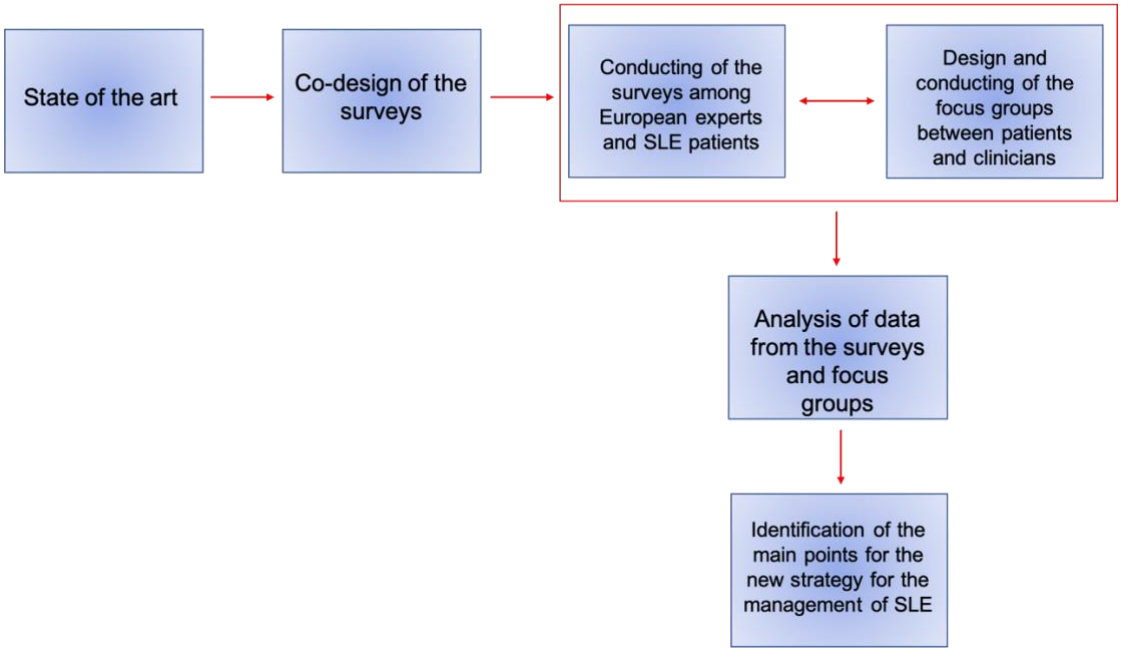

Figure 10 Steps of the project

3.3.1 Literature review of existing clinical and non-clinical indicators and SLE-dedicated IT tools

Mapping current evidence on clinical indicators used for the management of SLE

A review of the existing evidence about clinical indicators mostly used in clinical practice in the management of patients with SLE, from the clinical perspective, was performed.

The search was restricted to English language evidence-based recommendations, clinical practice guidelines, expert consensus, focusing on SLE adult patients and published between January 2007 and December 2018. PubMed database, EULAR web site and ACR web site have been analysed.

Papers included in the literature review have been detailed in tables of evidence in terms of:

- *Source*
- *Year*
- *Country/Countries*
- *Indicator(s) identified*
- *Clinical use/significance*
- *Grade of the evidence*
- *Strength of the recommendations*
- *Related literature references supporting the use of the indicators*

The original primary studies informing the evidence were retrieved and listed in the references list.

Clinical indicators identified have then been categorized according to the following main areas:

- indicators for disease activity, damage and treatment response
- indicators for comorbidities
- indicators for pregnancy
- quality indicators

For each of these areas, instruments/variables identified have been categorized as the following:

a) Disease-specific instruments (i.e. SLE-specific disease activity scores, damage scores, recommendations and quality indicators for SLE...)

b) Non disease-specific instruments (i.e. general instruments to assess fracture risk, bleeding risk, drug toxicity…).

Mapping current evidence on non-clinical indicators and PROMs relevant for SLE

To identify relevant non-clinical indicators, a systematic literature search was initially performed using the PubMed database. The search query aimed at identifying all clinical trials, validation studies, evaluation studies and meta-analysis in patients with SLE for the past thirty years. In addition, the full text of known guidelines, recommendations, consensus reports from international task forces on the management and monitoring of patients with SLE as well as selected review articles on quality of life, disease burden, and patient-reported outcomes were screened to identify additional

recommended non-clinical quality indicators and PROMs. The abstracts were manually evaluated for the use or demonstration of relevant non-clinical indicators.

In the second step, a literature search was conducted for each identified non-clinical indicator/PROM using various abbreviations and names. The search was again restricted to patients with SLE. The abstracts were first checked for relevance (i.e. type of study, patient population) and, if necessary, excluded from further evaluations and statistics. When identifying a patient-reported questionnaire for the non-clinical indicator, it was added to the queue for this second investigation step.

For each identified PROM the following information have been detailed:

- *Name*
- *Abbreviation*
- *Domains investigated*
- *Reference (Direct Object Identifier; DOI)*
- *Internet URL (if applicable)*
- *Number of relevant entries in publications*
- *Chart with entries per year*
- *Table with frequency of entries in named journals*

Mapping currently available SLE-dedicated IT tools (Apps)

The review of the existing evidence and Apps supporting the management and self-management of SLE has been performed. The analysis is based on the existing contributes in the literature and Apps up to February 2018.

Considering the nature of the review the following databases have been analysed:

- CORDIS and CHAFEA, that collect all the financed EU project/programs;
- JMIR archives, that collect papers on the constellation of the Journals on Medical Internet research and the application of Information and Communication Technology (ICT) to medicine;
- PubMed, a clinical database;
- Research devoted to the application of ICT on medicine not included in JMIR;
- Google play-Apps.
- Only SLE-specific IC technologies and Apps (or paper related to), focused on adults and with English interface were included.
- Characteristics of available IT systems and health Apps have been detailed in terms of:
- *App name and developers*
- *The main market target*

- *Price*
- *Patients' feeling with the App*
- *Diffusion of App*
- *Socio-economic and cultural dimensions (if available): like organizational, cultural, institutional, ethical and legal barriers*
- *Contents*

3.3.2 Design of ad hoc online surveys

Based on the results obtained from the literature review, ad hoc surveys have been designed for the assessment of the perspectives of both patients and clinicians.

The surveys for patients and clinicians have been administered on-line through a dedicated link. Participation to the survey was voluntary both for patients and clinicians and data were collected anonymously.

Survey for patients

The survey for patients was targeted to patients with SLE that were invited to answer both through LUPUS Europe (and related national patients' associations) and through personal invitations of clinicians, in order to collect information from both patients belonging to patients' associations from the different European countries and from those not involved in any patients' associations.

In detail, the patients' survey covered two main areas:

1. Knowledge, practice, needs and expectations related to the management of SLE
2. Knowledge, practice, needs and expectations related to ICT systems.

The survey was translated into three languages: Italian, English and German. Before being administered, the questionnaires were revised with a selected group of SLE patients to obtain a feedback about the clarity and completeness of contents.

Survey for clinicians

The survey for clinicians was targeted to physicians that are usually involved in the treatment and management of SLE patients. Physicians were invited to answer by the European Lupus Society (SLEuro).

In detail, the clinicians' survey covered two main aspects:

1. "Knowledge and practice": the habits and feelings of clinicians on existing recommendations for the monitoring of SLE, regarding clinical indicators, quality indicators, pregnancy recommendations and PROMs;

2. "Needs and expectations": variables and issues that are not usually included in the formal SLE assessment but that, from the clinician's perspective, would be useful to improve the knowledge and the management of the disease, the physician-patient relationship and, at the end, patients' outcomes.

3.3.3 Focus groups

Focus group is an instrument for qualitative research that is used in many fields of research and is commonly conceived as an interview involving a group of participants with the aim of performing an in-depth assessment of topics previously evaluated through a survey [120]. In the medical field, the technique is mainly used in the context of the evaluation of health outcomes, the definition of guidelines and in pharmaceutical marketing.

In the context of this project, focus groups were planned to deepen and widen results from the surveys about knowledge, needs and expectations related to the management of SLE from the patient's and clinician's point of view.

An English mother tongue moderator was involved to conduct focus groups.

The topics for the focus group discussion and a list of questions were developed and prioritized together with the moderator for the exploration of the topics of interest. The questions could be open-ended because the intent of the focus groups was to promote discussion. The moderator also defined groups' composition essentially on the basis of participants' country of origin to ensure having representativeness of the different European areas within each group.

Overall, 9 focus groups were performed: two-hours sessions focus groups were repeated involving two different groups of patients, other two-hours sessions focus groups were organized involving two different groups of clinicians and a final single-session focus group was performed with two different groups composed by clinicians, patients, caregiver and healthcare professionals.

Proceedings of the meeting were audio-recorded (according to consent agreed by participants) and that recording was the basis for the report developed by the moderator at the end of the focus groups.

Patients' focus groups

Patients were invited to participate through LUPUS EUROPE representatives.

Fifteen patients took part in the focus groups. They worked in two groups, each attending two two-hour sessions.

According to the preliminary overview of data emerged from the survey, patients' focus groups were aimed at further exploring two main areas:

- patients' knowledge of their treatment, their involvement in the treatment and how they lived their disease (session 1);

- the features and capabilities that a projected SLE-dedicated App should have, and how it would help patients and clinicians (session 2).

Physicians' focus groups

Participants for clinicians' focus groups were recruited among expert specialists for the treatment of SLE in Europe. Fifteen rheumatologists took part in the focus groups.

They worked in two groups, each attending two two-hour sessions.

The aim of the focus groups was to build on the patients' survey results and to deepen and widen the findings in two main areas:

- clinicians' use of PROMs, involvement of patients in their treatment, their awareness of patients' need for information and education, their needs and expectations as clinicians (session 1);
- the features and capabilities that a projected SLE-dedicated App should have, and how it would help patients and clinicians (session 2).

Mixed focus groups

The final single-session focus group involved clinicians, patients, caregiver and nurses.

The moderator defined groups' composition. Groups were created trying to involve representatives of the different figures in each group and trying to match as much as possible patients/caregivers with clinicians/health professionals according to their countries.

Seventeen participants from European countries took part in the focus groups.

With the exception of three patients, none of the participants had taken part in the earlier focus groups.

Participants were divided into two groups, each attending a two-hour session.

The aim of the focus group was to build on the patients' survey results and to deepen and widen the findings in five main areas:

- Patients' involvement
- Self-management
- Education
- Communication
- Use of PROMs

A plenary session was organized at the end to further discuss topics emerged during previous focus groups.

3.4 Results

3.4.1 Literature review of existing clinical and non-clinical indicators and SLE-dedicated IT tools

Review of clinical indicators relevant for SLE

Disease activity and damage in SLE can be evaluated globally or for each organ independently. No one indicator exists that alone can cover diagnosis or disease monitoring requirements.

Papers included and related literature references have been detailed in tables of evidence reported in **Appendix 1**.

From the analysis of recommendations, clinical practice guidelines and expert consensus included in the study, clinical meaningful and worldwide available indicators, categorized according to the main areas identified (disease activity and damage, comorbidities, pregnancy and quality indicators), have been retrieved and detailed in tables of evidence in terms of:

- clinical use/significance
- total number of related literature references supporting the use of the indicators
- level of the evidence (the percentage indicated in the tables below refers to the proportion of related references reporting the corresponding level of evidence)

Relevant indicators found for each organ involvement and for global assessment of disease activity and damage are listed below.

Table 1. Clinical indicators for renal involvement.

Indicator	Clinical use	Tot number of related references	Level of the evidence
Kidney biopsy	Diagnostic and prognostic value, treatment decision. ISN/RPS classification.	35	2: 17% 4: 17% NA:66%
Renal function (serum creatinine or estimated Glomerular Filtration Rate -eGFR-)	Disease activity and damage evaluation Prognostic value	29	1: 21% 3: 7% 4: 29% 5: 7% NA:36%
Proteinuria/24h (or urine Protein/Creatinine ratiou -uPCr-)	Disease activity monitoring, Prognostic value	22	1: 15% 3: 8% 4: 30% 5: 8% NA: 39%
Urinary sediment	Disease activity monitoring	11	1: 25% 3: 12% 4: 12% 5: 12% NA:39%
C3/C4	Disease activity monitoring	8	1:16.5% 2:16.5% 4: 16.5% NA:50.5%

Anti-double stranded DNA (anti-dsDNA)	Disease activity monitoring	6	1: 16.5% 2:16.5% 4:16.5% NA: 50.5%
Blood pressure	Disease activity monitoring, prognostic value	5	1: 75% NA: 25%
Haemoglobin/Complete Blood Count (CBC)	Disease activity monitoring, prognostic value	2	2/3: 50% NA: 50%
Anti-phospholipid antibodies (aPL) positivity	Prognostic value	2	2: 50% N/A:50%
Dyslipidemia	Prognostic value	1	2:100%

Table 2. Clinical indicators for skin involvement.

Indicator	Clinical use	Tot number of related references	Level of the evidence
Skin biopsy	Diagnosis and differential diagnosis	1	5: 100%
CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index)	Disease activity and damage monitoring	3	5:100%
Rash	Disease activity monitoring,	1	5:100%

Table 3. Clinical indicators for Neuropsychiatric involvement.

Indicator	Clinical use	Tot number of related references	Level of the evidence
aPL	Diagnosis	5	2:100%
Magnetic Resonance Imaging (MRI)	Diagnosis and differential diagnosis	4	2:66.5% 3:33.5%
Neuropsychological assessment of cognitive function	Diagnosis and differential diagnosis	4	2:100%
Electroencephalogram (EEG)	Diagnosis and differential diagnosis	3	2:50% 3:50%
Global disease activity	Diagnosis and differential diagnosis	2	2:100%
Cerebrospinal Fluid (CSF) analysis	Differential diagnosis	1	3:100%
Electromyography and nerve conduction studies	Diagnosis and differential diagnosis	1	3:100%

Table 4. Clinical indicators for global assessment (activity and damage).

Indicator	Clinical use	Tot number of related references	Level of the evidence
Disease activity indices	Disease activity monitoring	**32**	
SLEDAI (SLE Disease Activity Index)		16	2:20% 3:20% 4: 60%

ECLAM (European Consensus Lupus Activity Measurements)		5	4:100%
BILAG (British Isles Lupus Assessment Group)		6	2:33.3% 3:33.3% 4:33.3%
SLAM (Systemic Lupus Activity Measure)		3	3:50% 4:50%
Any		2	5:50% NA:50%
Anti-dsDNA	Disease activity monitoring	20	2:40% 4: 60%
Disease damage indices (SLICC Damage Index)	Organ damage monitoring, Prognostic value	16	1: 50% 2:50%
C3/C4	Disease activity monitoring	14	2:40% 4: 60%
Haematologic manifestations		6	3:33.3% 4/5:33.3% 5:33.3%
Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)	Disease activity monitoring	5	2:50% 5:50%
Blood pressure	Prognostic value	4	1:100%
Anti-C1q	Disease activity monitoring	3	4:100%
Serum albumin		3	5:100%
Other auto-Ab		3	
Extractable Nuclear Antigen (ENA) (anti–Sjögren's-syndrome-related antigen A autoantibodies -Ro/SSA)	Diagnostic and prognostic value	1	2: 100%
aPL	Diagnostic and prognostic value	2	2:50% 4:50%

Relevant indicators for comorbidities have been categorized according to three main areas: cardiovascular risk, osteoporosis and infectious risk.

Table 5. Clinical indicators for cardiovascular risk/disease.

Indicator	Clinical use	Tot number of related references	Level of the evidence
Dyslipidemia	Risk estimation	17	1:14.5% 2: 14.5% N/A:71%
Glucose	Risk estimation	17	1:33.3% 2:33.3% N/A:33.3%
Blood pressure	Risk estimation	17	1:14.5% 2: 14.5% N/A:71%
Body Mass Index (BMI)	Risk estimation	17	1:33.3% 2:33.3%

			NA:33.3%
Lifestyle	Risk estimation	17	1:50% 2:50%

Table 6. Clinical indicators for osteoporosis.

Indicator	Clinical use	Tot number of related references	Level of the evidence
Bone Mineral Density (BMD)	Screening for OP and monitoring	9	1:12.5% 2: 12.5% NA: 75%
25(OH)-vitamine D	Screening for VitD deficiency	4	1:20% 2:20% NA: 40%
Fracture Risk Assessment Tool (FRAX) score	Risk estimation	4	NA:100%
Spine X-ray	Assessment of vertebral fractures	3	NA:100%
Procollagen Type 1 N-Terminal Propeptide (PINP)	Treatment monitoring	1	N/A:100%

Table 7. Clinical indicators for infectious risk.

Indicator	Clinical use	Tot number of related references	Level of the evidence
Neutropenia (<500 cells/mm3)	Risk estimation	1	N/A:100%
Lymphopenia (<500 cells/mm3)	Risk estimation	1	N/A:100%
Low IgG (<500 mg/dl)	Risk estimation	1	N/A:100%

Relevant indicators for the monitoring of SLE patients during pregnancy are listed below.

Table 8. Clinical indicators for pregnancy.

Clinical indicator	Clinical use	Total number of related References	Level of the evidence
Disease activity (validated disease activity indices or physician judgement)	Preconception counseling risk stratification pregnancy monitoring	10	1:100%
Serological activity (C3/C4, anti-dsDNA)	Preconception counseling risk stratification	8	1: 20% 2:80%

Supplementary fetal surveillance with Doppler ultrasonography and biometric parameters (placental insufficiency and small for gestational age fetuses)	Pregnancy monitoring Prognostic value	5	3:100%
Blood pressure	Prognostic value	4	2:100%
aPL	Preconception counseling risk stratification	3	1:100%
Renal function	Prognostic value Pregnancy monitoring	2	2:100%
Disease history (lupus nephritis, APS, previous adverse pregnancy complications)	Preconception counseling risk stratification	1	2:100%
Fetal echocardiography in patients with positive anti–Sjögren's-syndrome-related antigen A and/or B autoantibodies (anti-Ro/SSA and/or anti-La/SSB)	CHB diagnosis	2	2:100%
Anti-Ro/SSA, anti-La/SSB	Preconception counseling risk stratification	2	N/A:100%

The above-mentioned clinical indicators represent a list of clinical indicators to be used in the routine clinical practice in referral centres as well as in primary care; the list provides the necessary instruments to diagnose and to monitor disease activity and damage accrual over time, comorbidities assessment and prevention.

The second part of this analysis was focused on quality indicators, evidence-based processes of care designed to represent the current standard of care. The literature search was focused on papers relative to the development of quality indicators in rheumatology and for SLE in particular. The quality indicators listed below can represent a valid help in the rapid and efficient assessment of quality of care in SLE in routine clinical practice.

Table 9. Quality indicators.

Quality indicator	Clinical use/significance	Total number of related references
Antinuclear antibodies (ANA), CBC with differential, platelet count, serum creatinine, and urinalysis;	**Diagnosis:** initial work up	19

anti-dsDNA, complement levels, and anti-phospholipid antibodies, anti-Ro, anti-La, anti-RNP, anti-Sm	within 6 months of diagnosis	
Complete blood count, ESR, albumin, serum creatinine or e-GFR, urinalysis and protein/creatinine ratio (or 24h proteinuria), C3 and C4: at least every 6 months **Validated activity indices at each visit** **SLICC/ACR damage index annually** **Quality of life at each visit. visual analogue scale from 0 to 10 or validated index (SF-36, SLE-QoL)**	**General monitoring**	
Education about sun avoidance at least once in the medical record		
Vaccination history **Influenza vaccination (annually)** **pneumococcal vaccination**	**General Preventive Strategies**	
BMD testing and supplemental calcium and vitamin D		
anti-resorptive or anabolic agent	**Osteoporosis prevention and treatment**	
HCV, HBV, tuberculosis screening before high dose corticosteroids or immunosuppressive drugs **discussion with the patient about the risks versus benefits;** **baseline studies should be documented;** **monitoring for drug toxicity** **tapering of prednisone, steroid-sparing agent** **Ophthalmologic assessment in patients treated with HCQ** **Ophthalmologic assessment in patients treated with glucocorticoids**	**Drug monitoring**	
Comorbidities (a list of the more frequent comorbidities observed among SLE patients may help)		
CBC, serum creatinine, urinalysis with microscopic evaluation, and measurement of urine protein every 3 months;	**Comorbidities management**	
therapy with corticosteroids combined with another immunosuppressant agent within one month of this diagnosis; **pharmacologic therapy for hypertension** **ACE inhibitor or ARB**	**Renal disease diagnosis and monitoring**	
Risk factors for CV disease (smoking status, blood pressure, BMI, diabetes, and serum lipids) evaluated annually.		

anti-ssA, anti-ssB, and anti-phospholipid antibodies should be documented; **aspirin and heparin during subsequent pregnancies, If a patient has had pregnancy complications as a result of the anti-phospholipid antibody syndrome** **discussion with the patient about the potential teratogenic risks of therapy and about contraception**	**Cardiovascular disease prevention and management** **Pregnancy and reproductive Health management**	

Review of non-clinical indicators and PROMs relevant for SLE

From the analysis of guidelines, recommendations, and consensus reports from international task forces on the management and monitoring of patients with SLE, the following non-clinical indicators relevant for the management of SLE were extracted:

- Depression
- Education level
- Fatigue
- Fitness to work
- Health related quality of life
- Occupational problems
- Patient autonomy
- Quality of Life
- Shared decision making
- Social functioning
- Social participation
- Socio-economic factors

Additional non-clinical indicators were identified in the systematic literature search:

- Adherence
- Anxiety
- Body Image / Self Image
- Ethnicity
- Exercise
- Rural residence
- Sexual function
- Sleep disorders

- Smoking
- Social support (Family, spouse, friends)
- Uncertainty / Lupus education
- Work / Employment / Job loss
  - Absenteeism, disability, functioning, productivity

Indicators with overlapping domains have been grouped together (i.e. Work / Employment / Job loss / Occupational problems / Fitness to work).

Overall, 21 non-clinical indicators were identified, 7 of which did not have standardized questionnaires. For the remaining 14 relevant non-clinical indicators, a total of 50 different standardized PROMs, which have been used in SLE, were found (Table 10).

Table 10. Non-clinical indicators and PROMs relevant for the management of SLE.

Non-clinical indicator (Summarized when applicable)	PROMs
Adherence	Compliance Questionnaire for Rheumatology General Adherence Inventory Medication Adherence Self-report Inventory Morisky's Medication Adherence Questionnaire Self-efficacy for Appropriate Medication Use Scale
Anxiety	Beck Anxiety Inventory Generalized Anxiety Disorder Scale Hospital Anxiety and Depression Scale Self-rating Anxiety Scale The Screen for Child Anxiety Related Disorders The State-Trait Anxiety Inventory
Body Image / Self Image	Body Image in Lupus Scale Multidimensional Body Self-Relations Questionnaire-Appearance Scale
Depression	Beck Depression Inventory (-II) Center for Epidemiologic Studies Depression Scale Hospital Anxiety and Depression Scale Patient Health Questionnaire 9
Education level	
Ethnicity	
Exercise (Activity)	International Physical Activity Questionnaire Paffenbarger Physical Activity and Exercise Index
Fatigue	Fatigue severity scale Functional Assessment Chronic Illness Therapy - Fatigue Multidimensional Assessment of Fatigue Multidimensional Fatigue Inventory
Health related quality of life	European Quality of Life – 5D Health Assessment Questionnaire Lupus Impact Tracker Lupus Patient-Reported Outcome tool Lupus quality of life

	Medical Outcomes Study Short Form 12-Item Medical Outcomes Study Short Form 36-Item Modified Health Assessment Questionnaire Multidimensional Health Assesssment Questionnaire Patient Reported Outcomes Measurement Information System® Simple Measure of Impact of Illness in Youngsters SLE quality of life questionnaire Systemic Lupus Erythematosus Questionnaire on Family Role Functioning Systemic Lupus Erythematosus-Specific Quality of Life
Patient autonomy	
Quality of Life	Pediatric Quality of Life Inventory Simple Measure of Impact of Lupus Erythematosus in Youngsters
Rural residence	
Sexual function	Female Sexual Function Index
Shared decision making	
Sleep disorders	Insomnia Severity Index Pittsburgh Sleep Quality Index
Smoking	
Social functioning / participation	
Social support (family, spouse, friends)	Interpersonal Support Evaluation List Medical Outcomes Study (MOS) Social Support Survey Social Support Questionnaire-6 Social support rating scale
Socioeconomic factors	
Uncertainty / Lupus education / Needs	Rheumatology Attitude Index Systemic Lupus Erythematosus Needs Assessment Questionnaire
Work / Employment / Job loss / Occupational problems / Fitness to work (incl. absenteeism, disability, functioning, productivity)	Work productivity and activity impairment

Non-clinical indicators not represented by PROMs, as shown in the table, are not collected using dedicated instruments. However, they are extensively used in literature, not only as an investigated endpoint, but also to describe cohorts.

Review of current IT systems

SLE-specific Apps

Within Google-play, App subdirectory, 26 different apps were obtained; only 12 were Lupus-specific Apps. The first six dimensions of these Apps have been reported in the table below (Table 11): App name; Free to download: essentially if the app is free or it is required to pay a fee; Average score by users: the average score obtained by the application from users; Producer/Developer: Who has produced and/or developed the mobile application; Specific for Lupus: If the mobile application is

primarily designed for SLE or if it addresses a broader range of rheumatic diseases; Download range: it shows the range of downloads in which the Application fits.

Table 11. SLE-Specific Apps on Google-play.

	APP. NAME	FREE DOWNLOAD (YES/NO)	AVERAGE SCORE BY USERS*	PRODUCER /DEVELOPER	SPECIFIC FOR LUPUS (YES/NO)	DOWNLOAD RANGE
1	The Lupus App	Yes	4.1	ZK MediTechLabZ	yes	10.000 -50.000
2	Lupus Disease	Yes	1.5	SumedangSakti	yes	100 - 500
3	Lupus (SLE)	No	4.0	Personal Remedies LLC	yes	10 - 50
4	Lupus Support	Yes	4.3	MyHealthTeams	yes	10.000 - 50.000
5	Voyage Through Lupus	Yes	NA	Built by Doctors Europe Lda	yes	50 -100
6	Lupus Symptoms Treatment	Yes	3.8	Revolxa Inc	yes	1.000 - 5.000
7	We Can Beat Lupus	Yes	3.8	We Can Beat Lupus	yes	1.000 - 5.000
8	LupusMinder	Yes	3.1	Hospital for Special Surgery	yes	500 - 1.000
9	Lupus Diary	No	3.4	cellHigh LLC	yes	100 - 500
10	Lupus Rash Symptoms Treatments	yes	2.5	Revolxa Inc	yes	500 - 1.000
11	Treating and Curing Lupus	yes	NA	Keep Fit public health information and education	yes	1 - 5
12	Nutrition Lupus	yes	2.0	Built by Doctors World Ltd	yes	100-500

Contents of the SLE-specific Lupus Apps are specified below.

The Lupus APP

Developers of The Lupus APP declares it can:

- take charge of patients' Lupus
- help to know deep insights of patient's disease
- manage medications and appointments setting reminder(s)
- add ongoing symptoms
- add photos along with symptoms
- contact/email rheumatologists and specialists.

Lupus Disease

Lupus disease does not directly allow the management of SLE, but it gives information on the following dimensions:

- overview and facts

- symptoms and type
- diagnosis and test
- treatment and care
- living and managing.

Lupus (SLE)

It offers support for patients trying to answer to questions about suitability of various food items for personal situation, offering dietary guidance for Lupus. It is also integrated with information on the most likely health issues: excess weight, heart disease, high blood pressure, high cholesterol, osteoporosis and rheumatoid arthritis. Also included are anti-inflammation diet and considerations for those taking NSAID pain relievers.

It offers:

- recommendations on the best food choices within a food group, based on patients' personal profile: it says what is good, what is bad, and what is neutral for patients' condition(s);
- suggestions on appropriate life-style choices, alternative therapies, and natural remedies, when such options are promising and available.

Lupus Support

It is a specific social network that allows members to:

- keep up and follow members photos and updates
- post updates about the daily ups & downs
- get/give instant hugs, likes and comments of support
- search the section/ask and answer questions
- add others to the team
- find others near and like singular members
- add diagnosis and view others.

Voyage Through Lupus

It helps patients in the self-management of Lupus, using interactive tools. It gives information on Lupus and tests patients' knowledge through a brief quiz.

Lupus Symptoms Treatment

This app offers information on Lupus. The most important issues on the offered overview answer to these questions/themes:

- what is lupus?
- medical treatments for lupus
- who gets lupus?
- lupus symptom: butterfly rash
- living with lupus

We Can Beat Lupus

It offers information on Lupus, treatment, care, useful information on daily behaviours that avoid or increase the probability of flares.

Lupus Minder

Lupus Minder helps people to live with Lupus. It allows to:

- track and share symptoms
- record symptoms, add notes and photos and share them with doctor
- manage medications
- set reminders and record side effects
- get appointment reminders
- write down questions patients want to ask their doctor and note what doctor tells them
- be informed about lupus research, initiatives and support programs.

Lupus Diary

A specific consideration should be done on the app Lupus Diary. This app can allow patients to:

- enter, document, and track as much or as little information with a few screen taps;
- document and track symptoms and any warning signs;
- track riggers, food, stress, location, activity, weather patterns, and sleep pattern; which treatments really help and those that do not; details, including medications and side-effects; health records including hospital or doctor visits, surgeries and procedures, laboratory tests and results, procedures, vital statistics, and the mental and the experienced physical symptoms; appointments, doctor visits, test results, surgeries and procedures;
- record thoughts and notes;
- track multiple doctors and laboratories.

The App graphs patterns of experiences that can be send as attachments to doctors that can help the patient on the basis of the shared information.

Lupus Rash Symptoms Treatments

Lupus Rash Symptoms Treatment offers information about some dimensions related to SLE symptoms:

- Joint Pain
- Butterfly Rash
- Nail Changes
- Fever and Fatigue
- Light Sensitivity
- Hair Loss

Treating and Caring Lupus

It offers information on Lupus, treatment, care, useful information on daily behaviours that avoid or increase the probability of flares.

Although it is of enormous interest, with respect to health and socio-economic, as well as cultural dimensions related to technology in supporting the management and self-management of SLE patients, existing literature and the other sources of data offer no relevant information.

Nutrition Lupus

It informs Lupus patients on nutrition and:

- allows to know how many calories should be eaten;
- offers as functionality a food diary where the patient can record the food eaten and share this information with the doctor.

The user can test its knowledge on Lupus and nutrition through a dedicated quiz (the idea of a quiz to test patients' knowledge on Lupus is similar to that reported in the Voyage Through Lupus App, and it is because the two applications have the same developers).

Other ICT developed/applied for the management of Lupus

From the literature search, information on ICT developed or applied to the management of Lupus and its effect have also been collected. The adopted technology or technical solutions are usually not developed inside the healthcare sector, or they are not Lupus specific, but they have been applied for the management and self-management, and/or monitoring and/or for supporting patient-doctor interaction of this kind of patients.

The Lupus Interactive Navigator (LIN)

The Lupus Interactive Navigator has been developed by Neville et al. 2013; 2014; 2016.
It results as a technology developed starting from patient's needs. Medical researchers, writers, designers and programmers worked with clinical experts and patients to develop the LIN.
In details, Neville et al., 2013, aimed at identifying the needs of persons with SLE and healthcare providers through the realisation of 8 focus groups. The themes were: 1) information and resources needs, 2) barriers to engagement in healthcare, 3) facilitators for engagement in healthcare; 4) self-management tools. Four focus groups were carried out with patients (n=29), three with rheumatologists (n=20) and one with allied health professionals (n=8). According to clinicians, an informed patient usually adheres to treatments more than the uninformed one. Patients underline the need of information related to the disease in all its characteristics. All the participants affirmed that a tool for an easy management of clinical visits, medications and medical information is the most useful service an Interactive Navigator should deliver to patients. Finally, LIN was developed and tested for usability and acceptability (Neville et al., 2016). LIN was subdivided into six primary information topics: about lupus, symptom management and treatments, accessing healthcare, support service, family, friends and work, and living well with lupus. The LIN was enriched with interview videos featuring rheumatologists, allied health professionals, and patients with SLE.

Cellular text messaging remainders (CTMRs)

Ting et al., 2012 introduced cellular text messaging remainders (CTMRs). CTMRs were individualized for each patient by including the medication reminder and the schedule time of the upcoming clinical appointment. The cited authors suggested that cellular text messaging remainders could improve clinical visit attendance but appear not to have an influence on adherence to medication. The study has been conducted on 70 teenagers, mean age 18.4 years. Adherence to hydroxychloroquine (HCQ) of 41 patients was also compared: 19 patients received CTMR prior to each scheduled HCQ dose, 22 patients received standard of care education about HCQ.
At baseline, 32% of patients adhered to HCQ and 81% to clinic visits. Visit adherence improved significantly by > 80% among those who did not adhere to clinic visits at the baseline (p=0.01). CTMR did not influence adherence to drug over time.

Improving sleep quality in SLE patient through Actigraphy wristband

Balderas-Diaz et al. 2017 suggested a novel approach and a related technical system to assess (and so potentially to monitor) sleep quality in SLE patients combining traditional questionnaire evaluating sleep activity with an actigraphy (i.e., a modern technique that evaluates the quality of sleep by physical activity and patient movement, and a mobile system to collect more objective data and

information about the patient and their environment). This innovative system consists of a mobile device with built-in sensors providing input data and a set of services of the Environmental Monitoring System. Total patients enrolled amounted to 20 of which 9 in SLE group and 11 in healthy group. Patients were interviewed and filled a questionnaire. After the interviews, they received actigraphy wristband and mobile device. Actigraphy wristband was used for 7 days continuously and mobile device only the night. Patients group reported higher mean scores in the sleep scale, pain intensity, general fatigue and depression compared with healthy group. The study did not present difference in terms of actigraphy and variables related to environmental conditions. The authors affirmed that the use of actigraphy in combination with a new MHealth device permits a complete evaluation of patients.

3.4.2 Ad hoc online surveys for patients and clinicians

The complete English version of the surveys for patients and clinicians are reported in **Appendices 2.1, 2.2, 2.3**.

Results of patients' surveys

A total of 714 questionnaires were filled. After removing questionnaires partially completed because of user withdrawn and responders who declared to be diagnosed with disease other than SLE, a total of 608 questionnaires from SLE patients were collected. Main findings from the analysis of data related to European patients (n=554, 77.6%) are reported below.

Results of the survey on patients' knowledge, needs and expectations

Main characteristics of responders

Responders were mainly female (94.2%) and mean age was 44.3±13.1 years. >80% were at least "high school graduate" and more than half were employed. UK (n=171, 30.9%), Italy (n=159, 28.7%), Switzerland (n=52, 9.4%), Germany (n=36, 6.5%) were the countries most represented (also in reason of the available language at the lunch of the survey), while answers come from almost all European countries.

Details of the main socio-demographic characteristics of responders are shown in Table 12.

Table 12. Main socio-demographics characteristics of European SLE patients participating to the survey.

	Number of patients (%)
Gender	

Female	522 (94.2%)
Male	31 (5.6%)
Other	1 (0.2%)
Highest level of education	
Less than high school	63 (11.4%)
High school graduate	202 (36.5%)
Bachelors' degree	127 (22.9%)
Masters' degree	121 (21.8%)
Prefer not to answer	41 (7.4%)
Employment status	
Employed/self-employed	289 (52.2%)
Temporarily not employed (non medical reasons)	33 (6.0%)
Temporarily not employed due to SLE	27 (4.9%)
Temporarily not employed due to other medical reasons	8 (1.4%)
Unable to work because of SLE	86 (15.5%)
Unable to work because of other medical reasons	12 (2.2%)
Homemaker	34 (6.1%)
Retired	52 (9.4%)
Prefer not to answer	13 (2.4%)
Marital status	
Single	140 (25.3%)
Married or in a civil union	353 (63.7%)
Separated/Divorced	41 (7.4%)
Widowed	9 (1.6%)
Prefer not to answer	11 (2.0%)
Living with..	
Alone	84 (15.2%)
Family members	418 (75.5%)
With others	52 (9.4%)
Household income	
Very low	42 (7.6%)
Low	94 (17.0%)
Medium	319 (57.6%)
High	59 (10.7%)
Very high	5 (1.0%)
Prefer not to answer	35 (6.3%)

Knowledge of the disease and its management

In the survey, knowledge of facts related to SLE was mainly assessed by investigating patients' knowledge about treatment options, their effects, and disease management.

Although, for almost all aspects investigated responders declared good to very good knowledge in more than 50% of cases, it has to be noted that considerable percentage of patients answered to have fair to very poor knowledge of "available treatment", "side effects", "options for self-management",

"lifestyle habits" and "his/her healthcare pathway". Details of answers collected in this analysis are reported in Table 13.

Table 13. Knowledge of facts related to SLE and its management

	Number of patients (%)
What is your knowledge about available treatments for SLE?	
Very poor	16 (2.9%)
Poor	59 (10.7%)
Fair	160 (28.9%)
Good	205 (37.0%)
Very good	112 (20.2%)
I don't understand the question	2 (0.4%)
Do you understand why it is important for you to take prescribed medications?	
Very poor	3 (0.5%)
Poor	15 (2.7%)
Fair	55 (9.9%)
Good	158 (28.5%)
Very good	322 (58.1%)
I don't understand the question	1 (0.2%)
Do you know what each of your prescribed medications is used for?	
Very poor	5 (0.9%)
Poor	22 (4.0%)
Fair	97 (15.5%)
Good	186 (33.6%)
Very good	243 (43.9%)
I don't understand the question	1 (0.2%)
What is your knowledge about the side effects of treatments?	
Very poor	20 (3.6%)
Poor	50 (9.0%)
Fair	140 (25.3%)
Good	185 (33.4%)
Very good	158 (28.5%)
I don't understand the question	1 (0.2%)
Do you know how to manage your disease by yourself?	
Very poor	17 (3.1%)
Poor	35 (6.3%)
Fair	190 (34.3%)
Good	194 (35.0%)
Very good	114 (20.6%)
I don't understand the question	4 (0.7%)
Do you know practical lifestyle options to cope with SLE?	
Very poor	15 (2.7%)
Poor	63 (11.4%)
Fair	153 (27.6%)

Good	204 (36.8%)
Very good	118 (21.3%)
I don't understand the question	1 (0.2%)
Do you know your care pathway (treatment plan, periodic visist, etc.)?	
Very poor	23 (4.2%)
Poor	49 (8.8%)
Fair	115 (20.8%)
Good	195 (35.2%)
Very good	172 (31.1%)

Needs related to the disease and its management

As shown in Table 14, the assessment of needs related to SLE and its management underlined high level of needs related to the maintenance of social relationships and social life in general and involvement in decision about treatment and disease management. Whereas the need for sharing experience related to the disease or the demand for support with problems other than the emotional one is less perceived.

Specific questions related to women in childbearing age highlighted the need for more information about treatment during pregnancy.

Table 14. Needs related to SLE and its management.

	Number of patients (%)
Do you feel the need to talk with someone with similar experience?	
No need	42 (7.6%)
Low need	119 (21.5%)
Moderate need	221 (39.9%)
High need	126 (22.7%)
Extreme need	46 (8.3%)
Do you feel the need to maintain relationship with friends?	
No need	8 (1.4%)
Low need	39 (7.0%)
Moderate need	148 (26.7%)
High need	239 (43.1%)
Extreme need	120 (21.7%)
Do you feel the need to improve participation in social activities (i.e going out with friends, going to the cinema, etc.)?	
No need	34 (6.1%)
Low need	92 (16.6%)
Moderate need	211 (38.1%)
High need	139 (25.1%)
Extreme need	78 (14.1%)
Do you feel the need to have help with physical problems due to SLE?	
No need	84 (15.2%)

Low need	130 (23.5%)
Moderate need	167 (30.1%)
High need	116 (20.9%)
Extreme need	57 (10.3%)
Do you feel the need to have help with emotional problems due to SLE?	
No need	64 (11.6%)
Low need	136 (24.6%)
Moderate need	180 (32.5%)
High need	114 (20.6%)
Extreme need	60 (10.8%)
Do you feel the need to learn how to explain to people what it means to have SLE?	
No need	61 (11.0%)
Low need	88 (15.9%)
Moderate need	160 (28.9%)
High need	157 (28.3%)
Extreme need	88 (15.9%)
Do you feel the need to have assistance for activities of daily life?	
No need	164 (29.6%)
Low need	173 (31.2%)
Moderate need	138 (24.9%)
High need	53 (9.6%)
Extreme need	26 (4.7%)
Do you feel the need to be involved in decisions about your treatment?	
No need	12 (2.2%)
Low need	30 (5.4%)
Moderate need	101 (18.2%)
High need	227 (41.0%)
Extreme need	184 (33.2%)
Do you feel the need to have or increase coverage for payment of drugs/or examinations?	
No need	79 (14.3%)
Low need	85 (15.3%)
Moderate need	129 (23.3%)
High need	86 (15.5%)
Extreme need	97 (17.5%)
Not applicable	78 (14.1%)
Only for women in childbearing age (n=282, 50.9%)	
Do you feel the need to have information about treatment before pregnancy?	
No need	81 (28.7%)
Low need	27 (9.6%)
Moderate need	39 (13.8%)
High need	76 (27.0%)
Extreme need	59 (20.9%)
Do you feel/felt the need to find out how to get help with child care?	

No need	81 (28.7%)
Low need	27 (9.6%)
Moderate need	49 (17.4%)
High need	36 (12.8%)
Extreme need	22 (7.8%)
Not applicable	67 (23.8%)
Would you be interested to share with others how to involve partners in childcare?	
No need	114 (40.4%)
Low need	45 (16%)
Moderate need	76 (27.0%)
High need	35 (12.4%)
Extreme need	12 (4.3%)

Expectations (towards the rheumatologist/clinicians)

Expectations towards the treating clinicians were almost well satisfied according to responders. However, coherently to results from the survey about the assessment of knowledge, almost 40% of respondents declared that they were not completely satisfied with respect to the explanation of lifestyle options and way to manage the disease but also in relation to the description of side effects of treatments (Table 15).

Table 15. Expectations towards the treating clinician.

	Number of patients (%)
The rheumatologist/physician treats me with respect and dignity	
Strongly disagree	15 (2.7%)
Disagree	25 (4.5%)
Neither agree nor disagree	73 (13.2%)
Agree	167 (30.1%)
Strongly agree	274 (49.5%)
The rheumatologist/physician clearly explains to me my conditions	
Strongly disagree	22 (4.0%)
Disagree	61 (11.0%)
Neither agree nor disagree	83 (15.0%)
Agree	186 (33.6%)
Strongly agree	202 (36.5%)
The rheumatologist/physician clearly explains to me how to manage my disease	
Strongly disagree	28 (5.1%)
Disagree	75 (13.5%)
Neither agree nor disagree	117 (21.1%)
Agree	190 (34.3%)
Strongly agree	144 (26.0%)
The rheumatologist/physician clearly explains to me how to manage my pain	

Strongly disagree	40 (7.2%)
Disagree	94 (17.0%)
Neither agree nor disagree	144 (26.0%)
Agree	169 (30.5%)
Strongly agree	107 (19.3%)
The rheumatologist/physician clearly explains to me the side effects of my treatments	
Strongly disagree	36 (6.5%)
Disagree	120 (21.7%)
Neither agree nor disagree	150 (27.1%)
Agree	154 (27.8%)
Strongly agree	94 (17.0%)
The rheumatologist/physician clearly explains to me the consequences of not taking prescribed treatments or recommended lifestyle	
Strongly disagree	31 (5.6%)
Disagree	77 (13.9%)
Neither agree nor disagree	149 (26.9%)
Agree	176 (31.8%)
Strongly agree	121 (21.8%)
The rheumatologist/physician gives me the opportunity to discuss my doubts	
Strongly disagree	36 (6.5%)
Disagree	58 (10.5%)
Neither agree nor disagree	102 (18.4%)
Agree	193 (34.8%)
Strongly agree	165 (29.8%)
The rheumatologist/physician understands my health issues	
Strongly disagree	39 (7.0%)
Disagree	51 (9.2%)
Neither agree nor disagree	121 (21.8%)
Agree	199 (35.9%)
Strongly agree	144 (26.0%)

Results of the survey on patients' knowledge, needs and expectations related to ICT system

A total of 463 patients also completed the survey related to ICT system. Among these the majority (n=354, 76.5%) declared to use the web to find information about SLE, while just a small percentage of responders use mobile application for SLE (n=76, 16.4%).

Main reasons for not using the WEB to find information about SLE are "no need for information" (n=37, 8%), the belief the WEB does not provide reliable information (n=30, 6.5%) or other unspecified reasons (Figure 11). Similar reasons were also indicated in case of not using mobile application, but in this case the unavailability of specific App with the desired language was also reported as reason for not using them.

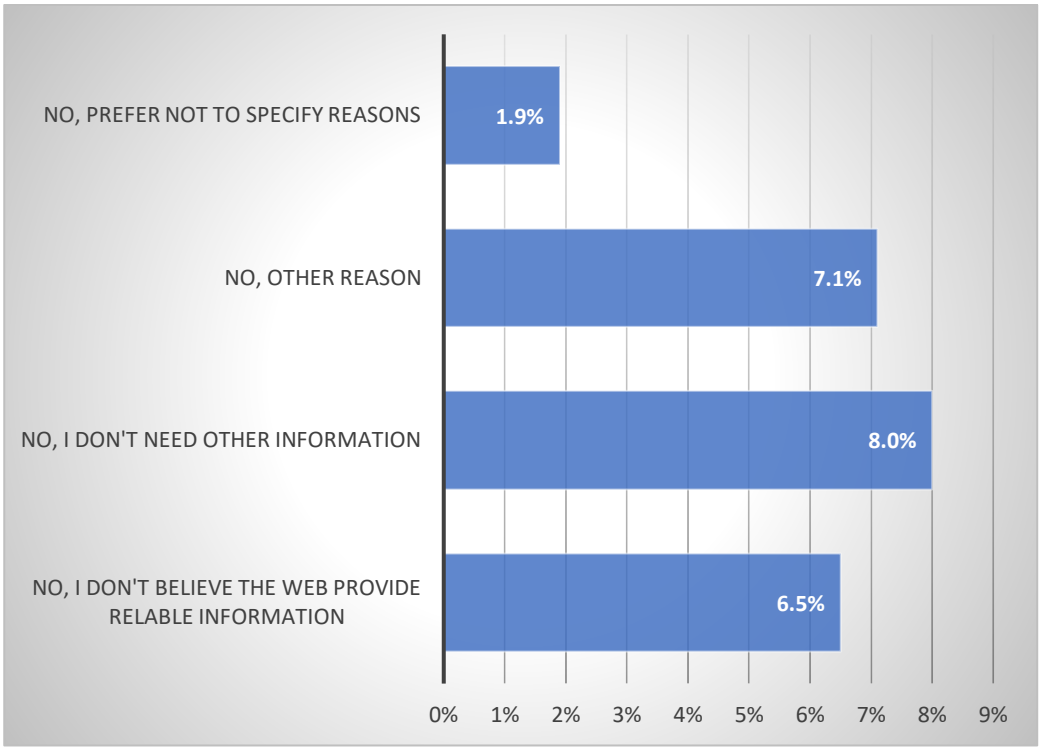

Figure 11 Main reasons for not using the WEB to find information about SLE

On the other hand, patients declared to use the web mainly to find general information about SLE (n=241, 68.1%), disease manifestations and possible complications (n=216, 61%), treatments and their effects (n=206, 58.2% and n=192, 54.2% respectively), the impact of lifestyle on the disease (n=176, 49.7%) but also to find available clinical studies and results of initiatives (n=131, 37%) and to “find patients like them” (n=170,48%) (Figure 12).

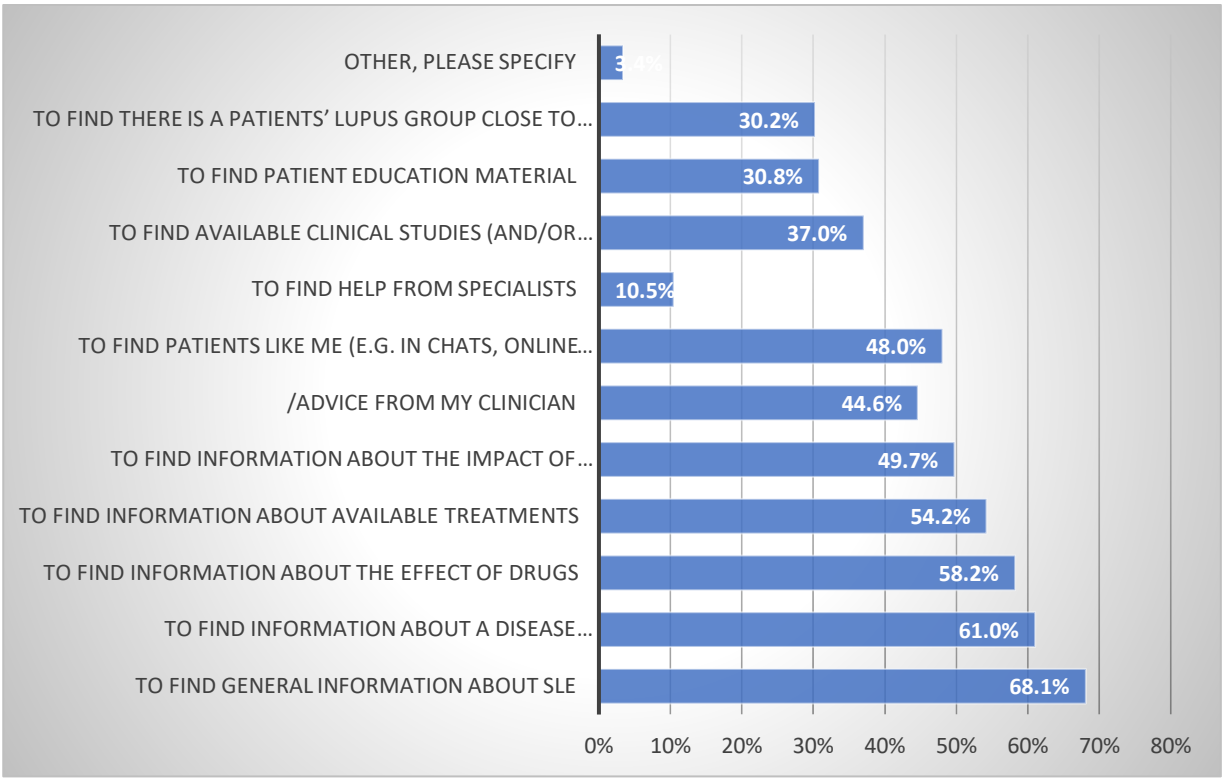

Figure 12 Main reasons for using the WEB to find information about SLE

Results of the survey for expert clinicians

A total of 167 clinicians completed the survey, 131 from European Countries (78.4%) and 36 from non-European Countries; 93 (55.7%) were female and more than half of responders (96, 57.5%), were representatives of a regional or national referral center for SLE; 52.7% declared to treat >60 SLE patients/year.

Main characteristics of the responders are summarized in Table 16.

Table 16. Main characteristics of clinicians answering the survey.

	Number of subjects (%)
Age	
<=30 yrs	11 (6.59)
31-40 yrs	67 (40.12)
41-50 yrs	46 (27.54)
51-60 yrs	31 (18.56)
61-70 yrs	12 (7.19)
Years of experience as physician	
0-5 yrs	15 (8.98)
6-10 yrs	34 (20.36)
11-15 yrs	44 (26.35)
16-25 yrs	38 (22.75)
>25 yrs	36 (21.56)
Years of experience as rheumatologist	

0-5 yrs	62 (37.13)
6-10 yrs	27 (16.17)
11-15 yrs	33 (19.76)
16-25 yrs	31 (18.56)
>25 yrs	14 (8.38)
Years of experience in the SLE patients care	
0-5 yrs	39 (23.35)
6-10 yrs	45 (26.95)
11-15 yrs	28 (16.77)
16-25 yrs	35 (20.96)
>25 yrs	20 (11.98)
Number of SLE patients in regular follow-up	
0-30	45 (26.95)
31-60	34 (20.36)
61-90	26 (15.57)
>90	62 (37.13)

The following thematic areas were explored in the survey:

- Use of clinical indicators in clinical practice
- Adherence to quality indicators
- Unmet needs and expectations
- Patients reported outcomes measures (PROMs)

Data related to the different areas collected through the survey are presented below.

Use of clinical indicators

Adherence to international recommendations on the management of SLE appeared suboptimal, especially for the use of composite clinical indicators (almost 40% of clinicians declared they don't regularly use them in routine clinical practice), while a very good adherence to the recommendations for renal involvement emerged. Overall, serological variables resulted as the most useful clinical indicators for global monitoring. In particular, more than 80% of clinicians declared that ESR/C reactive protein (CRP) and anti-dsDNA are useful or very useful in the monitoring of patients during follow-up and more than 90% of respondents stated that C3/C4 levels are useful or very useful for the monitoring of the disease.

Except for aPL testing and brain MRI, a big heterogeneity emerged for neuropsychiatric manifestations due to their protean clinical picture and the absence of a unique indicator.

Some discrepancies were also recorded in the assessment of skin involvement. Clinicians declared a good adherence to recommendations for the assessment of comorbidities (cardiovascular risk factors and osteoporosis), but only a moderate adherence to recommendations for infection preventive

measures: 72.5% of clinicians prescribe vaccinations to all immunosuppressed patients and 65.3% screen patients for viral hepatitis and latent tuberculosis before high doses of steroids and immunosuppressants. In Table 17, the most significant results about the use of clinical indicators have been reported.

Table 17. Use of clinical indicators

	Number of subjects answering "Yes" (%)
Disease activity and organ damage assessment and monitoring	
SLICC/DI (at least once a year)	104 (62.3)
Disease activity score (regularly)	102 (61)
Anti-dsDNA and Complement levels (regularly)	103 (61.7)
ESR and CRP (regularly)	132 (79)
Anti-C1q	8 (1.2)
Specific organ involvement assessment and monitoring	
Kidney	
Renal biopsy for suspected renal involvement (routinely)	126 (75.5)
Serum creatinine and/or eGFR (at each visit)	167 (100)
Proteinuria/24h or uPCr (at each visit)	154 (92.2)
Skin	
Skin biopsy (routinely)	31 (18.5)
CLASI (routinely)	10 (5.9)
NPSLE	
Cerebral MRI	100 (59.8)
aPL at the onset of NPSLE	154 (92.2)
EEG (routinely)	114 (68)
Neuropsychological tests (routinely)	21 (12.5)
CSF analysis (routinely)	74 (44.0)
EMG (routinely)	108 (64.6)
Comorbidities	
Vitamin D level	31 (18.5)
Bone mineral density	10 (5.9)
FRAX (fracture risk score)	100 (59.8)
Screening for chronic infections	109 (65.2)

Adherence to Quality Indicators

Regarding quality indicators, there is a general concordance on the measures of quality of care, with the exception of the treatment of the osteoporosis in patients taking glucocorticoids (GC) and on the

ophthalmologic screening for GC toxicity. Differences in local recommendations could be responsible for such heterogeneity.

Table 18. Adherence to quality of care indicators

Indicator	*Number of adherent subjects (%)*
Counselling on sun avoidance	164 (98.2)
Treatment for osteoporosis in patients on glucocorticoids	72 (43.0)
Regular ophthalmologic evaluation in patients on Hydroxychloroquine	125 (74.8)
Regular ophthalmologic evaluation in patients on GC	59 (35.3)
Pre-conception counselling	154 (92.2)
SSA testing before pregnancy	161 (96.4)
aPL testing before pregnancy	162 (97.1)
Collaboration with a gynaecologist during pregnancy	127 (76.5)

Unmet needs and expectations

Physicians were asked to rate the importance (on a scale from "very important" to "not at all important") of some aspects that are considered unmet needs on the management of SLE patients. Percentages of "important" and "very important" answers are reported in the Figure 13. It emerged that the most important unmet needs from the clinicians' point of view are about working together with other experts and being part of a network of specialists. Moreover, clinicians declared that they would need to have more individualized recommendations for the management of SLE.

On the contrary, it seems that clinicians do not feel the need to delegate some tasks to other figures involved in the management of SLE patients.

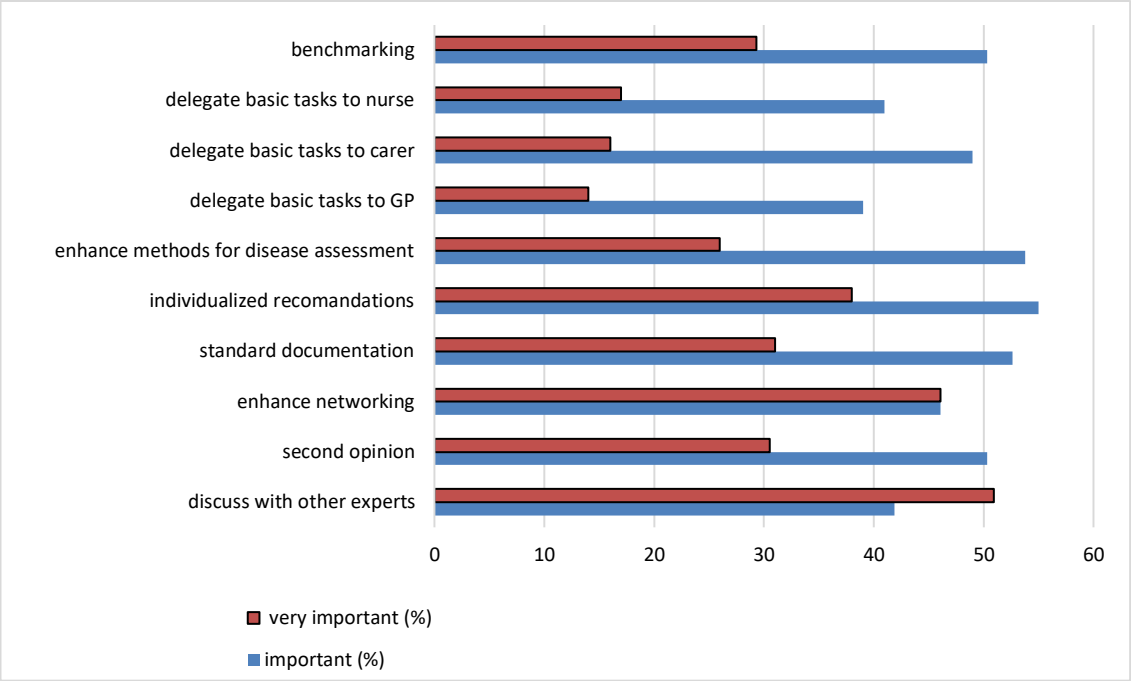

Figure 13 Aspects recognized as "important" and "very important" unmet needs

Physicians were also asked to rate the level of agreement about some potential expectations for the long-term care of SLE patients, as reported in Table 19. Overall, the highest level of agreement was reached for questions about the need for patients to comply with doctors' recommendations.

Table 19. Potential expectations for the long-term care of SLE patients.

Potential expectations	*Agree/completely agree, N (%)*
High level of shared decision making and self-determination by SLE patients	132 (79)
Patients' compliance with agreed treatment strategies	153 (91.6)
Patients' adherence to their medication	162 (97)
Patients' ability to recognise and communicate a flare on her/his own	124 (74.2)
Care in relation to problems not directly related to SLE (i.e. treatment of comorbidities, vaccinations) provided by the general practitioner	114 (68.3)

Patients Reported Outcomes Measures (PROMs)

As for PROMs use in clinical practice, only 31% of clinicians reported to use PROMs to monitor disease outcomes in their Lupus patients, i.e. for assessing (health-related) quality of life (22.9%) or fatigue (15.7%). The top 5 reasons for not using PROMs were: "Lack of time" (87%), "Lack of linguistically validated questionnaires" (32%), "Lack of validated questionnaires" (28%), "Discordance with my assessment/impression" (15%), and "Poor credibility of the results" (12%).

Physicians were also asked to rate the importance (on a scale from "very important" to "not at all important") of some patients reported outcomes domains. Percentages of "important" and "very important" answers are reported in the Figure 14.

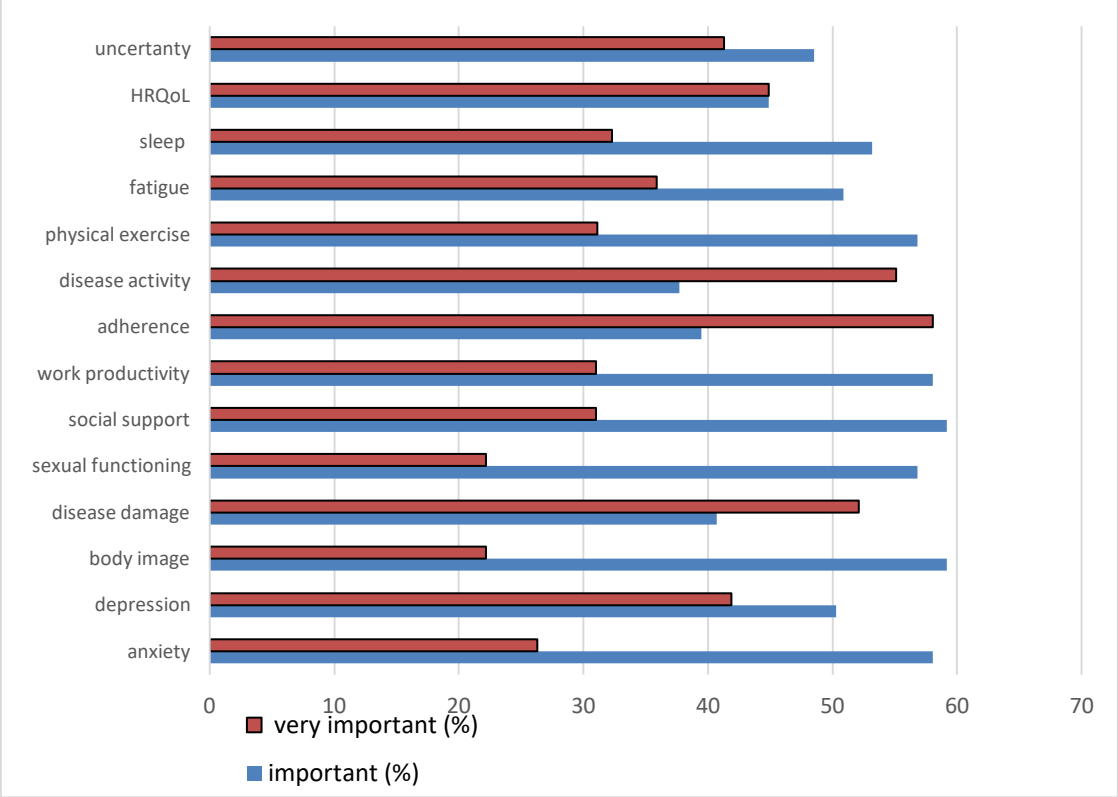

Figure 14 Domains related to PROMS rated as "important" and "very important" unmet needs

Adherence, disease activity and damage were considered the most important domains to be evaluated with PROMs.

3.4.3 Outputs from Focus Groups

Patients' focus groups

Fifteen patients took part in the focus groups. Participants were all female and were from twelve European countries: Denmark, Estonia, Finland, France, Ireland, Italy, Lithuania, Portugal, Spain, Sweden, The Netherland and UK. They were invited to participate through LUPUS EUROPE representatives, so they were mainly patients active involved in patients' association.

Results from the patients' focus groups are reported considering the results emerged from the two groups and distinguishing outputs from the two sessions foreseen in each focus group: a first session devoted to generally assess patients' knowledge, needs and expectations related to the management of the disease and a second session focused on ICT systems.

Patients' knowledge of their treatment, their involvement in their treatment and how they lived their disease (Session 1)

The first session of each patients' focus group involved the discussion of four main themes:

A. Knowledge of Lupus and the treatment you receive
B. Your involvement in your treatment
C. Communicating with others about Lupus
D. How does Lupus impact on your social life and relations with others?

A. Knowledge of Lupus and the treatment you receive

Are you well informed about the range of treatments available?

- 5 participants responded "no"
- 6 participants responded with a qualified "yes"
- 5 participants responded "yes"

Reasons for responding "no" ranged from lack of a real dialogue with their rheumatologist (due to lack of continuity of treatment by the same specialist), to total trust in their rheumatologist (and therefore feeling less need to question choice of treatment). Another reason was described as not knowing what questions to ask.

The main reason for responding with a qualified "yes" was insufficiency of information. They felt they did not receive enough information about new treatments or about treatments other than those already prescribed.

"Yes" responses were explained by experience of having lived with Lupus for some time, and in some cases motivated by the will to be involved in decisions about their treatment.

What would help you to be better informed?

Participants agreed that the usually brief consultation in the clinic was not the ideal place for getting information. Apart from limited time, there was the problem of not knowing what questions to ask, and the relationship with the clinician (as "God"). Several participants appreciated the role of specialised nurses as a more approachable source of information.

All respondents reported reliance on some form of self-help: websites (while aware of the risks these may pose), with mention of Lupus Europe and Lupus UK as valuable sources. For many patients, however, language was a barrier and they expressed a need for information translated into their own languages.

They said that different patients, at different times, needed different types and "levels" of information, and should know where to find them: medical-scientific information; information specific to the treatments they were on; lifestyle information.

Possible ways of improving access to information included patient/clinician forums (which take place in some patients' countries). Some participants felt that this could produce two-way benefits: helping patients to know what information is significant to their doctor, while helping doctors to understand better what patients need to know.

Do you know what medications you are on, and what they are for?

- 13 participants reported that they knew what medicines they were prescribed, and their indications;
- 1 participant responded that she knew their names but not what they all treated;
- 1 participant responded that she was on so many medications that it was difficult to keep track.

The majority of participants made an effort to search for further information about their medication (over and above what their rheumatologist told them), quoting websites, pharmacists and leaflets as sources. This was largely to find out more about side effects.

How do you rate your knowledge of side effects?

The majority of participants reported that they had a sufficiently good knowledge of the side effects their medication could provoke. A small number of participants was not sure which side effects were caused by which medicines. 3 participants said that early in their treatment they had suffered serious effects which they had not been warned about.

From what participants said, experience and long years in treatment brought advantages (accumulated knowledge of possible side effects) and disadvantages (the risk of becoming "hardened" and overlooking minor, but perhaps significant, symptoms).

The main source of information was the leaflet accompanying the medicine. Participants described the leaflet as "unfriendly": the small print, the language used and the scary nature of the counter-indications. Participants liked the practice in some countries (i.e. UK) of providing patients with a simpler, more colourful, additional leaflet designed specifically for Lupus patients by the patients' organisation.

B. Your involvement in your treatment

Do you know how to manage your disease by yourself?

Much of the discussion centred around the meaning of the question. The interpretations which participants settled on were:

- at a routine level, responsibly following the instructions and recommendations made by the clinician between one visit and another;
- learning to live with the disease, knowing what limits to accept and pacing oneself, in addition to adopting recommended lifestyle changes;
- going beyond mere compliance and actively seeking out complementary practices which could help to cope with pain, depression, fatigue, etc. Examples given were meditation, exercise, nutrition, counselling, and psychotherapy.

Words used recurrently in this conversation were "responsibility" and "making choices". There was a caveat, however: the ability to make choices was only possible in periods of low activity or remission.

Two participants recounted cases in which they had, in consultation with their rheumatologist, requested and obtained changes in their medication.

Some participants thought that managing the disease required tools designed to help them monitor and record their state. One participant demonstrated a watch which allowed her to record the number of steps taken daily and hours of sleep. This idea of a log was further explored in the second session, during which they discussed of a Lupus-dedicated App.

Do you have enough information about lifestyle choices?

About half the participants said that they did not receive adequate information about lifestyle choices from their rheumatologist, especially at the beginning of their treatment, or that they received it only if they asked.

Again, the point was raised that visits were short and there was limited time for questions about lifestyle. Support groups and specialised nurses were considered to be a more likely source of information.

In those countries or regions in which there were dedicated Lupus centres, patients reported that both the quality and the quantity of lifestyle advice they received were high.

What is your experience of the treatment you receive from your rheumatologist(s)?

Here responses were extremely varied, covering the whole range from poor to excellent. The main determining factor appeared to be the type of organisation of the national health service in the different countries. Even within countries there could be wide differences in the quality of care provided.

The negative responses were given for the following reasons:

- lack of continuity: "I never see the same rheumatologist. They never get to know me";
- lack of time: participants quoted 10-15 minutes as the average duration of visits;
- some national systems were overloaded, leading that one patient to go privately, as the only way to have timely access to a rheumatologist;
- lack of shared knowledge about Lupus between different areas of specialisation.

Highly positive responses came from those participants who had access to dedicated Lupus centres with multidisciplinary teams of specialists who exchange information about their patients (rheumatologists, neurologists, nephrologists and other specialists, all with experience of treating Lupus patients). The Lupus centre in France described by one participant was seen by the others as a model. Apart from receiving treatment from a multidisciplinary team, patients had access to whole-day sessions, during which physicians, nurses and other professionals gave advice and handled Q&A sessions on a wide range of topics. These included advice on nutrition and make-up.

This contrast in experience in treatment in different countries and systems was referred to recurrently throughout the focus group sessions.

C. Communicating with others about Lupus

How important to you is it to share your experience with other Lupus patients?

The answers given by participants, sometimes by the same participant, were mixed. Some felt a strong need to share experiences with other patients, for example in the context of support groups.

Very often, however, they found support group meetings tended to be rather negative affairs. Several participants found it upsetting, especially in the early stages, to listen to other patients describing how the disease affected them, especially cases of organ involvement ("Am I going to wind up like that?").

In some cases, the attitude to sharing with others changed over time. The word used several times by participants to describe their state upon being diagnosed with Lupus was "overwhelmed". Some reported that their initial reaction was a kind of denial, not wanting to find out more about the disease and not wanting to discuss it with others.

With time, most participants found value in the opportunity support groups gave to hear how other patients coped with the disease and overcame problems. They came to appreciate the level of knowledge other patients had acquired, and some went on to take an active role and to help others acquire knowledge. They found national associations particularly valuable as an environment where information could be trusted.

For some participants, support groups did not provide enough information about medical research, and they had to look elsewhere.

What about communication with others?

Discussion centred around the main obstacles to communication with others. These were identified as:

- lack of knowledge: because of its rarity and complexity; when patients informed others that they had Lupus it meant very little to their interlocutors. It was not like telling people that one had cancer;
- lack of belief: others (including some physicians) often underestimated the gravity of the fatigue that patients suffered and sometimes even interpreted it as laziness, lack of drive or hypochondria. Again, they made the comparison with cancer and treatment for it; everyone knows that chemotherapy produces debilitating effects;
- lack of visible symptoms: patients told of occasions when they were told, "You look fine", and of the difficulty they had explaining that they did not feel fine at all.

Participants generally found it more difficult to communicate about their condition with close friends and loved ones, rather than strangers. The group split roughly half and half on how open they were with friends about having Lupus and what it entailed.

Some simply avoided telling others that they had Lupus, since it posed the problem of either saying too little (and giving only a superficial understanding) or having to say a lot (and having to go into too much personal detail).

When participants discussed how to overcome these obstacles, in one group we heard of an interesting experiment in France in which a theatre director and actors interviewed patients about their experience of living with Lupus. On the basis of these interviews, they put on a theatrical production to an audience of doctors, patients and non-patients. Many saw patient/non-patient cooperation as the key to better understanding.

Despite the feeling that non-Lupus sufferers could never fully understand what it meant to live with the disease, all participants were passionately in favour of efforts to inform the general public, and to do so in layman's terms. The UK TV information campaign about arthritis was quoted as a possible model. Another approach proposed, to elicit public interest, was a testimonial, a well-known public figure with Lupus (Lady Gaga was quoted as an albeit flawed example).

One further aspect of communication that was discussed was how to communicate in an emergency (for example when they found themselves in an emergency unit when in flare). Participants mentioned two problems: a) difficulty in thinking clearly and remembering things, thus making it difficult to communicate with doctors and other staff, and b) the lack of access that emergency

personnel had to their medical records. Some participants made a point of carrying around with them some written information about their condition and the medication they were on.

D. How does Lupus impact on your social life and relations with others?

Many of the points made related to the obstacles to communication in the above section.

Relations were put under stress by not being able to respect commitments and having to cancel appointments at the last moment. Social life was impoverished by having to opt out of going to the theatre or going out with friends, and the fact that they could not drink alcohol or had to avoid sunlight.

We heard cases of extreme impact on relations with loved ones, from marriage break-up to choosing on occasions not to spend time with members of the family.

Strategies for dealing with this were very personal and varied widely. They included:

- choosing friends carefully and finding out who your real friends are;
- creating space and being clear about when one can be contacted ("never call me before lunch at the weekend");
- changing the context or timing in which you meet friends or family, to accommodate the lifestyle choices you have made;
- accepting, without any sense of guilt, that you may have to "break some rules" as far as family and social norms are concerned;
- at work, insisting firmly on manageable deadlines for completing tasks;
- avoiding planning too far ahead;
- lowering expectations of others' sympathy or understanding.

Features and capabilities that an ideal Lupus-dedicated App should have, and how it would help patients and clinicians (Session 2).

This session started with a brief discussion of how participants used the web in relation to SLE. With two exceptions, all participants used, or had used, the web to gather information about the disease itself, medication, side effects and other topics. This ranged from a few who consulted academic databases such as PubMed, to read articles and research abstracts, to others who regularly used sites such as Lupus Europe, to others still who used search engines such as Google to find information.

Some had searched for Lupus-dedicated Apps but had found few that they wanted to use.

All were aware of the risk of misinformation, and they felt it would be useful to have a list of trustworthy sites.

When it came to discussing what the ideal Lupus app would be able to do, participants had a clear of some of the features it should not have:

- no self-diagnosis
- no community
- no unvalidated data
- no advertising

What are the priority features would you like to see, and what would you use them for?

Working in subgroups, participants listed priority features and capabilities and explained what they would use them for. Results are summarized below (Table 20).

Table 20. Desired features and usefulness of the ideal Lupus-dedicated App.

Desired features and capabilities	Usefulness
Check-list created by the rheumatologist and sent to the patient's smartphone, with a list of the things to monitor before the next visit	To help the patient know what the rheumatologist needs to know
Periodic report (log of medication taken, pain, mood, sleep, etc.) sent by the patient to the rheumatologist before visits	To keep an accurate and complete record that can help the rheumatologist, and make for efficient use of time during the visit
Links to Lupus-related information	When travelling, for example, to be able to locate doctors with Lupus experience, hospitals, pharmacies, support groups
Reminder	To remind the patient to take medication
New medication database	To keep updated; to know what alternative treatments may be available
Statistics: the patient's own data and data related to the general Lupus population	To allow the patient to understand how her data relate to that of the wider population
Personalised patient profile, with medication prescribed	To have something portable that they can show to their rheumatologist, or to a doctor in an emergency
Real-time live chat function to dialogue with rheumatologists and/or specialised nurses	To be able to address concerns (symptoms, possible side effects) in dialogue with a trustworthy and experienced source ("a virtual Lupus team")
Progress diary, with evolution of test results and Log to record fatigue, joint pain, sleep, migraine, mood, temperature, skin condition	To have a picture of how the disease is evolving, for both the patient and the rheumatologist

All participants retained as essential these features:

- a simple, "friendly" user interface
- availability in different languages

- absolute security of personal data
- no charge for the App.

Clinicians' focus groups

Fifteen rheumatologists from seven European countries took part in the focus groups: Denmark France, Germany, Greece, Italy, Portugal and Romania. They were recruited among experts specialist for the treatment of SLE in Europe.

The aim of the focus groups was to build on the patients' survey results and to deepen and widen the findings in two main areas:

- clinicians' use of PROMs, involvement of patients in their treatment, their awareness of patients' need for information and education, their needs and expectations as clinicians;
- the features and capabilities that a projected Lupus-dedicated app should have, and how it would help patients and clinicians.

The first session of each clinicians' focus group involved the discussion of four main themes:

A. The importance of the use of PROMs
B. Education
C. Sharing the therapeutic strategy with your patients
D. Needs and expectations as clinicians

Clinicians' use of PROMs, involvement of patients in their treatment, their awareness of patients' needs for information and education, their needs and expectations as clinicians (Session 1)

A. The importance of the use of PROMs

Responses were varied, and this depended much on the role that participants attributed to PROMs. In some cases, participants saw them simply as a means to corroborate clinical or laboratory findings as to the patient's condition. In other cases, they were seen as a useful means of capturing information the rheumatologist might otherwise miss.

As in the survey results, the main obstacle to the use of PROMs was time. Most participants felt that it was not feasible to make use of PROMs in the limited time available during a visit, typically 20 minutes. A possible solution to this problem, already in operation in some treatment centres, was to have patients complete questionnaires in the waiting room before their visit.

Other reasons given for not using PROMs, again very much in line with the survey results, were lack of validated questionnaires, the subjective nature of some measures (i.e. of fatigue and pain) and discordance with the rheumatologist's own interpretation of the patient's condition.
On a scale ranging from 0 (no importance) to 5 (extreme importance), the clinicians evaluated "How important are PROMs in producing a change in treatment":

ranking	0	1	2	3	4	5
responses	**0**	**1**	**0**	**4**	**8**	**1**

Several participants expressed the view that PROMs were drivers for change in treatment only when the patient was in remission or when disease activity was low.
There was general agreement that PROMs could be especially useful when tracked over time. This depended on the provision of treatment by the same rheumatologist, or at least by the same team.

How important is it for you, as clinicians, to have information about your patients' social life?
The response from the two groups was almost unanimously affirmative:

ranking	0	1	2	3	4	5
responses					**2**	**13**

What aspects of patients' social life do you, as clinicians, need to know?
Responses in both groups were very similar and included the following aspects:

- availability of support (partners, family, friends) or whether the patient lived alone
- childbearing (planning or not to have children)
- major life events (births, deaths, marriage, divorce)
- work (job, employment status)
- financial situation
- leisure (sport, cultural activities)
- body image

There were unexplored areas, ones that clinicians did not necessarily ask about. One participant mentioned the question of patients' sexual activity, and how Lupus might impact on this. This is a clear match with one of the "topics not raised" identified in the patients' focus groups.
Both groups talked about the importance of trust. This was something that could only be built over time, in a situation in which the patient and clinician (or a team) established a relationship. As one

participant put it, “We grow up together”. This was possible in most, but not all, health provision systems.

Several participants made the point that they had not been specifically trained, either at medical school or subsequently, to deal with such matters. With experience, and the establishment of trust, they had learned how to do so. They noted that younger, less experienced colleagues tended not to ask patients questions about their social life.

On the question of how clinicians pose questions about social life, one participant drew a parallel with asking questions about adherence to prescribed treatment. Answers were not always truthful. Rather than closed questions, which might induce feelings of guilt (i.e. “Do you take your medication?”), the use of open questions which might encourage the patient to speak more openly (i.e. “How often do you take your medication?”).

There was also a danger of patients attributing to Lupus obstacles to their social life that had other causes. Similarly, patients might undertake activities in their social or working life which caused pain or fatigue, but which they attributed to the disease. These needed to be questioned and explored.

Some questions about patients’ social life might require the support of other specialists in the context of a multi-disciplinary team (i.e. psychologists). One suggestion was that specialised nurses could have a role to play in this. Patients might be more willing to discuss aspects of their social life (even delicate ones) with a nurse. This could take place in an informal setting before their consultation with the rheumatologist.

B. Education

Do you feel you do enough to educate patients about lifestyle choices?

Participants generally felt that they did not do enough to educate patients about lifestyle choices. These were identified as choices regarding nutrition, sun avoidance, monitoring of their condition, adherence to prescribed treatment, the importance of having periodic lab tests.

Two constraints already mentioned were given as reasons: lack of time and lack of specific training, either at medical school or later in the clinician’s career.

Because of the time constraint, it was felt that not enough could be done during normal consultations. Some Lupus centres held weekend sessions for patients, at which they received advice on lifestyle choices. However, to be effective, education and guidance needed to be repeated at regular intervals.

In addition to differences between patients as individuals, one participant remarked on cultural differences (in this case, between Greek and British patients), and the greater or lesser likelihood that patients would assiduously monitor their state.

C. Sharing the therapeutic strategy with your patients

What does "sharing the strategy" mean?

Just as in the patients' focus groups, the term "strategy" needed explaining. It was not the term clinicians used in discussing the way forward with patients.

In simple terms it was described as explaining "where we are, what we will do, what the goal is" for a period varying between three and six months. Immediately after diagnosis this also required explaining what Lupus was, how symptoms are treated and the possible effects of the disease in later life. It also required explaining the trade-off between the benefits of a treatment and possible risks.

Everyone agreed that the approach and type and quantity of information needed to be personalised, patient by patient. Some patients preferred not to know too much. Others, especially younger patients who had read about Lupus on the internet, were better informed and wanted to know more.

The very nature of the disease makes explanation of a strategy complex, as the number of possible scenarios over the medium term is wide.

How important is it to share the strategy with your patients?

Whatever the difficulties, participants were almost unanimous in responding that it was extremely important.

ranking	0	1	2	3	4	5
responses					**2**	**13**

Given this importance, the discussion turned to how best to share the strategy with patients. All agreed that they could do better and some admitted that, while they did indeed have a strategy in mind, they did not always share it with the patient. Again, a personalised approach was required. Apart from the question of how much patients wanted to know, there was the need to use different means to explain the disease and the strategy to different patients according to their learning style (preference for the written word, spoken word, graphics, etc.). For some it might be best to communicate the strategy through the internet, for others via a specialised nurse.

Some patients were in a nervous state during visits, and thus not able to absorb much information. They needed time to absorb the information they received and should be given something to take home to read and reflect on. There was, however, no standardised form this could take.

For the same reason, it was important not to stress patients with too much information. The clinician had to judge case by case how much information to give.

It was also vital to choose language carefully and to check that patients understood what was shared. This meant establishing a common language with patients from the beginning, ensuring that they understood recurrent terms and concepts (i.e. “remission”, “response”). A test carried out in one centre showed that some of the terms used by clinicians in interaction with patients were not understood. In fact, it was possible to explain even the more difficult concepts in everyday words (i.e. how the immune system worked, and the risk posed by suppressing immunity to infection).

Do you expect a high level of decision-making and self-determination in your patients?

There was no simple answer to this question. This was in part because there were differences of opinion among participants as to how much patients could realistically take decisions as to their treatment. There were greater differences, however, when it came to discussing the patients themselves. Their interest in taking an active part in taking decisions varied from zero (“you’re the doctor”) to wanting to take part in making an informed decision, to disputing the treatment recommended by the rheumatologist. This last category was deemed to be no more than 5% of the patient population.

If patients were motivated to take an active part (reckoned by one participant to be as much as 80% of the patient population) there could be some sharing of decisions. The clinician could explain, for example, two possible treatments, describe their respective benefits and risks and then support the patient in her choice. A well-informed patient with a long history of Lupus could be trusted to make adjustments to her dosage of steroids.

This decision-sharing process could be open to manipulation by the clinician as, however well informed the patient might be, there was still an enormous information and experience gap. “Information is power”, as one participant said. This raised the question about the type of information patients needed to be able to exercise some degree of self-determination. Participants listed some of the things patients needed to be able to have:

- an awareness of risks
- the ability to recognise and manage flares (estimated as 60% of patients by one participant)
- the ability to recognise symptoms
- an awareness of the importance of monitoring blood pressure, body temperature, etc.
- knowing in what circumstances they should call their doctor.

Self-determination was a challenging concept. It had to be based on a comprehensive understanding. On the negative side, patients could be said to exercise self-determination when they decided not to adhere to their prescribed treatment. This, however, was in many cases self-determination based on lack of knowledge. It could be the result of not receiving enough information about medication from

the rheumatologist. A patient who relied for information on reading the leaflet, surfing the web or talking to ill-informed fellow patients in Lupus groups might be scared into non-adherence.

As in the patients' groups, participants saw a need for other means, besides the leaflet, to inform patients about drugs and their side effects. Nurses and pharmacists were a valuable source, while in some countries more readable documentation was available, in books or produced by patient associations.

A final point was made about patient engagement. There was a risk of assuming that some patients were not interested in being involved in their treatment simply because they did not voluntarily say so, or because they did not ask any questions. Passivity or silence might be induced by inhibition in the presence of the doctor, or by simply not knowing what questions to ask.

D. Your needs and expectations as clinicians

Access to, and use of, second opinions through national or international reference centres.

Participants rated the importance of this very highly:

ranking	0	1	2	3	4	5
responses				**1**	**1**	**13**

As Lupus is a complex disease, producing many different manifestations, all participants had had at times to ask for second opinions. Many participants in the groups were also providers of second opinions. Over time, specialists built up their own networks and knew where to go to get authoritative opinions. In their early years, they might have to seek the opinions of specialists who had published papers about Lupus. Participants reported that they usually received the advice they sought.

They could count on support also from the European CPMS platform, which had a section devoted to rheumatic diseases (ReCONNNET), which allowed clinicians to upload cases for comment by experienced specialists.

Rheumatologists operating in some areas might find they had few local resources to rely on. They would be advised to contact centres of excellence in their own countries, especially if language was a barrier.

Networking with specialists from other disciplines (gynaecologists, neurologists, etc.).

Participants were unanimous in rating the importance of networking as extremely high. As Lupus is a multi-systemic disease, rheumatologists needed to develop networks with specialists in other areas and to interact with them very frequently.

ranking	0	1	2	3	4	5
responses						**15**

Despite this, there were some reservations. Specialists from other therapeutic areas did not necessarily have enough knowledge of Lupus, or experience of dealing with Lupus patients. Given that Lupus is a relatively rare disease, Lupus patients might make up only a small number of, for example, a nephrologist's patients, and thus make it more difficult to acquire experience.

It might also mean that rheumatologists became dependent on the support of a small number of specialists in other areas with sufficient experience of treating Lupus patients.

Working alongside other specialisations worked well in those cases where there were multi-disciplinary teams grouped together in Lupus centres. This was the context in which some, but not all, participants worked.

The possibility of delegating basic tasks for monitoring the disease and its treatment to General Practitioners.

Regarding on possibility of delegating basic tasks for monitoring the disease and its treatment to General Practitioners (GP), the clinicians responded as follows:

ranking	**0**	**1**	**2**	**3**	**4**	**5**
responses	**0**	**0**	**0**	**6**	**2**	**7**

Responses were very mixed. Most participants agreed that GPs could play a bigger role but did not always have the means to do so. The main obstacle was GPs' lack of knowledge of Lupus. Generally speaking, they did not know enough about the disease or its treatment. Many agreed, however, that GPs could play a much greater role and that this would be of benefit to both the patient and the rheumatologist. It would require GPs having more information about, for example, the values to look out for in lab tests.

Responses were mixed also because the system of communication in the patient / specialist / GP triangle was managed in different ways in different countries. Access to patients' information (medical records, medication, results of lab tests, etc.) was also managed in different ways. In some cases, as in Denmark and the Galicia region in Spain, digitalisation was advanced and access to, and exchange of, information was easier. Finally, rheumatologists realised they were competing for GPs'

attention, as Lupus patients were only a small number of their patients. Knowing more about Lupus might not be a priority for them.

The possibility of delegating basic tasks for monitoring the disease and its treatment to patients

Consolidated responses for the two groups were as follows:

ranking	**0**	**1**	**2**	**3**	**4**	**5**
responses				**1**	**4**	**9**

Discussion on this point returned to many of the topics explored in the section about patients' self-determination. First of all, the question of whether patients wanted to play an active part in their treatment. This time participants estimated that approximately 50% of patients did wish to take responsibility for monitoring their condition and taking some decisions as to their treatment. This had little to do with generational differences.

Since Lupus is a chronic disease, usually diagnosed in early adulthood, patients had time to learn about the disease and how to manage it. The question was: what could be delegated to them? One possible area was understanding of, and interpretation of, lab test results. In theory it should be possible for patients to understand if their condition as reported in test results was within the norms or not. They would then know whether or not they should consult their physician. Lab test reports, however, are not presented in a patient-friendly form. Adopting a format which was easier to interpret (i.e. using colour codes and graphics) would be helpful. Given that some monitoring of condition and tests could be delegated to patients, it would be possible for rheumatologists to have a checklist to use during visits. Had the patient tested for osteoporosis? Been to the ophthalmologist? Had the necessary vaccinations? This would make for more efficient use of time during consultations.

Participants were almost unanimous in believing that greater delegation, to those patients who wished to take responsibility, would be beneficial to both their patients and themselves.

Features and capabilities that a projected Lupus-dedicated App should have, and how it would help patients and clinicians (Session 2).

The second session explored priority features for clinicians that this group would like to see the App and expected benefits from them.

Priority features clinicians would like to see in a SLE App.

A summary of priority features suggested during focus groups is reported in the table below.

Table 21. Priority features and capabilities of an ideal SLE App.

Priority features	Capabilities
PROs (Patient Reported Outcomes)	Scores related to pain, fatigue, depression, self-evaluation of activity, etc. to be received before examinations.
Periodic measurements	I.e. blood pressure, weight, infections.
Assessment of adherence	
Alerts	I.e. activity level, lack of adherence-
File transfer	The ability to upload clinical files to the hospital system.
Cockpit or dashboard	An overview of the patient's present and past condition: treatments, lab results, PROs and previous scores, reminders (i.e. vaccinations).
Patient profile	"Starting data": classification criteria, time of diagnosis, ethnicity.
Events	I.e. Pregnancy, fractures-

Participants were unanimous in saying that an ideal App containing priority features they suggested would provide benefits to both clinicians and patients.

In details, from the clinicians' side that App will allow:

- being able to receive patient data before visits would make for more efficient use of time. Time saved could thus be used in productive ways;
- the rheumatologist would have a better, more compete overview of the patient's condition and its evolution;
- having all the patient's data at his/her fingertips would make a positive impression on the patient and instill confidence;
- used well, it could give clinician a wider vision of how the patient lives the disease;
- in general terms, it could improve the physician/patient relationship, drawing them closer to each other.

Mixed focus groups

Following the focus groups for separate groups of patients and clinicians, this was the final step in the process. It was designed to bring together not only patients and clinicians but also general practitioners, nurses and one caregiver.

Seventeen participants from European countries took part in the focus group: six specialists, six patients, 1 caregiver, 2 nurses and 2 general practitioners. The participants came from eight European countries: Denmark, France, Germany, Greece, Italy, Spain, Sweden and UK.

The aim was to identify practical, concrete actions that could lead to fulfilment of the objectives of the project.

Based on the earlier focus groups, the subjects for discussion were the following:

A. patients' involvement in the treatment they receive
B. self-management by patients of their disease
C. education of patients and of other players
D. communication
E. use of clinicians' questionnaires (PROMs)

Some of the topics which participants highlighted were:

- the very different conditions that patients, clinicians and GPs encountered, and operated under, according to country and region, affecting every aspect of Lupus care from continuity of treatment (by the same rheumatologist or team) to accessibility to medical records, to the role of GPs;
- the importance, where they existed, of multidisciplinary Lupus teams;
- the importance of the role of nurses in communication with patients;
- the individual nature of patients' needs as to the type and quantity of information they received about the disease and their treatment.

The two groups identified a number of best practices, especially as far as education, communication and GP/specialist interaction were concerned, and they also came up with a number of practical proposals which included:

- to provide patients with links to sources of reliable, certified information about Lupus, treatments and related information;
- to provide patients with a hotline, by which they can get answers when they have doubts or in times of distress;
- to provide patients with an electronic diary, in which they can record events and which they can bring to their consultation with the rheumatologist;
- to aid effective self-management, to provide a list of information patients need about medical, social and lifestyle issues and what they need to monitor;
- to provide a system into which patients can enter test results, and which generates alerts;
- to send clinicians' questionnaires (PROMs) to patients in advance of visits, and to have them sent back to the clinic before the consultation, to make more focused and efficient use of time.

The main themes emerged from focus groups are summarized below, reporting the phrases of participants.

Group 1 was composed of three patients, three clinicians and two nurses. They came from France, Greece, Italy, Spain and Sweden. Group 2 was composed of three patients, three clinicians, two general practitioners and one caregiver. They came from Germany, Italy, Spain, Sweden and the UK.

A. Patients' involvement in the treatment they receive

Group 1	Group 2
Recurrent concepts: awareness, relationship, trust, education, sharing, information and deal. A patient: *Involvement doesn't mean taking decisions. I'd like to be aware of what's going on.* A clinician: *It's a deal. There are things you can't negotiate. You reach a point and make a deal. The patient has to be compliant with the treatment you have chosen. The doctor has to be available if the patient comes back to you if not doing well.* A nurse: *Involvement is sharing information. What is the foundation for changing treatment? What are the patient's thoughts about change of treatment?* **What are the limits to involvement?** A clinician: *It depends on the doctor and it depends on the patient. There are doctors who don't want patients to say anything but "yes". There are patients who don't want to be involved.* A patient: *When you are young, you don't want to know. I went many years without knowing it was Lupus. Then I saw people with problems and I was scared. As time passes you know about symptoms, the treatment.* **In reality in how many cases are patients offered a choice between treatments?** A patient: *Zero!* A clinician: *Many times!*	**Qualities connected with involvement: educated, trustful, active, engaged, expert, empowered and social.** A patient: *I hear of patients just sitting there, getting information from the physician and not giving anything back. Involved for me is wanting to be part of your own treatment. At the beginning you are in the safe hands of the physician. As you learn more about yourself and the disease, you should become more involved in your treatment.* A clinician*: I want an active patient. A patient who gets to controlling at least part of the disease. To become active so that they can change things.* **What are the limits to involvement?** "White coat fear": patients who were active in social events often took a more passive attitude when interacting with physicians. Patients seeing other patients with disabilities and worrying that they too will become like them. Misinformation, either through Facebook or unreliable sources of information via internet ("miracle" cures or diets), or from other patients.

B. Self-management by patients - What can patients do for themselves?

Group 1	Group 2
A nurse: *I think a lot of patients can actually manage in some areas. To start, to reduce the delay. When it's something familiar, not a completely new thing, not a new symptom. It*	A patient: *We decide if we want to be healthy, to have positive attitude. So we decide. We are responsible for everything that goes on.*

shouldn't be the first time they've had oedemas, and they know how to manage it. The question is what is the limit? How long should I proceed? If you start something, you need to have some information. You have to follow up. You need to have the information that something is getting worse. A clinician: *No, nobody has told you how to do that. It's not your fault.* A patient: *Maybe they should. If I think about my experience, I'm not able to do it properly. When something new comes up. At the moment, for example, I don't know what to do and I feel helpless. As a new patient, I had only one problem. Others came up and I didn't know how to deal with them. Maybe it's because of my lack of experience.* A clinician: *Some things they can manage well. For example, the management of drugs for hypertension. I give a suggestion. During the summer, when the weather is hot, you have to reduce the dosage. When using diuretics, I give them a suggestion to write their weight every day and sign if their weight increases or decreases.*	A clinician: *Certain manifestations are symptomatic. With experience you can manage dosing corticosteroids, up and down.* A clinician: *Perhaps patients don't notice there is severe inflammation. You need blood samples. Lupus is complicated and you need to differentiate between different manifestations.* A patient: *The problem is some patients are left to their own devices.* Clinicians defined self-management as "self-adjustment" and "shared decisions". Patients insisted that shared decisions only made sense if clinicians clearly explained the pros and cons of the different treatments they proposed. A patient gave an example of a decision not shared. *A physician who unwittingly prescribed a medication to a painter, which made her hands tremble. He didn't know she was a painter, and was heartbroken when, sometime later, he was told of the effect on the patient. A gap in knowledge about the patient's life outside the consultation room.*

C. Education of patients and other players - What are the education needs of patients?

Group 1	Group 2
A clinician: *Of course, it's about medication, about the disease. But it's also about self-management and lifestyle habits and how these interact with wellbeing. It could be basic things. When you get the disease, you need all this information again. It's not just for Lupus patients, it's important for every human being. Exercise and not smoking is also important for Lupus.* A patient: *Doctors can't manage your life. They can say don't do this, don't do that. They can repeat the same things. But they're not your mother or father. They're just doctors.* A nurse: *It's a question of being ready to change. I can say we have support groups. Do you want to have support? Not just "Why don't you stop doing it?" It's the same with physiotherapy. You want to have support. That's why I ask the question. It's not to blame someone.*	A clinician: *It depends what you want to teach them. If it's about treatment, medication, it's definitely the physician who's the best one to teach. We have great experience of courses where patients have access to information from physicians. A slide show on this is Lupus in a nutshell, and then we have hundreds of questions. Maybe two hours. Outside the context of the consultation.* A patient: *Sometimes you need bite-size pieces of information, that you can access at home. When you don't want to go to a big event where you're going to be bombarded with all this information. You need access to both.*

A clinician: *Flyers with the ten most important points would be nice to have. You have to combine. The information you give orally the patient forgets. If you write five important things, the patient can remember.* A summary of what patient education should be, provided by a patient: *We need a leaflet or an app. Something where patients can get information at any time about basic topics. The disease, the main manifestations, information about lifestyle, about self-management, comorbidities.* Final comments in this section: A clinician: *Educated patients cope better. It's our responsibility to guide patients to the right sources of information. There is an important area of working for the future, where we can and provide accurate information for patients.* A nurse: *The education of people in other social areas. Social regulations, and there are so many people out there who don't know what Lupus is. Depending on how the system works in other countries. What kind of context do patients really have to have? The social security system or whatever. There are a lot of blank areas out there.*	

D. Communication - How should communication work in the patient/clinician/GP triangle?

Group 1	Group 2

Clinician-GP side Clinicians: *The GP gives you a patient and the problem is for you, everything.* *In the UK it's different. It's the GP who decides to send the patient to … to change the treatment and so on.* A patient: *I think they don't feel confident enough to go further. Lupus is such a complicated disease. My GP wanted to help me at the beginning. I've known him for many years. But, "I have to stop", he said to me because I cannot go that far. I understood him.*	**Sharing clinical data** A patient: *In Sweden–not with all GPs, but I think more than half in Stockholm–we have common medical files. This is an immense improvement. I can actually see how they discussed hypertension or treatment, and if they did X-rays I can see it also.* A patient: *In the UK we have a bad situation with the hospital trusts. Different hospital trusts in, say, London, within the same region, they can't see the MRI scan. And certainly the GPs can't see it either. They have to physically post it to them. But they won't actually see the visual of the scan, just the report from the person who has done it* A GP: *The GP needs to be in contact with the specialist. The red flags – fever is simple, pain is simple, but the patient isn't just a number on the thermometer. If a patient tells me they have a temperature of 40° it's easy for me to work. But if they tell me they have depression, I don't know if it's a red flag.*

E. Use of PROMs

Group 1	Group 2
Two clinicians reported that they did not use PROMs. One clinician and one nurse reported that they did administer them. No patient reported that their clinician used them. **Usefulness of PROMs** ***Pro-PROMs*** PROMs were useful, not only in studies but also in clinical practice; Patients could be asked to fill in questionnaires while in the waiting room, to make efficient use of time; The scores allowed the clinician to focus on specific areas. A clinician: *You can use it for assessing the situation. … It's not so time-consuming if it's well organised. It's not only the score, it's a free questionnaire. You can check each specific question. You can compare it with the previous visit.*	Two of the three clinicians reported that they did not use PROMs in routine clinical practice (as opposed to research). In one case, because the existing validated questionnaire they used was too long. One reported that he made limited use of them. 2 patients replied no, one reported regular use. Time was again seen as a major constraint. A clinician: *It is not good enough to spend the long time it requires. It doesn't capture enough things for the time that it requires.* A clinician: *I think that having these questionnaires for Lupus, having patients fill in the form on line before the visit, it would be a big help. You would see that this patient has problems with joints, has headache, has fatigue. Then you can go*

Cons-PROMS The clinician can get the information he/she needs about pain, fatigue, etc. during the interview; It is time-consuming. A clinician: *The medical interview is not just for the doctor to get information and for the patient to get information. There's something else there that can have a therapeutic effect. It's important that patients feel you are aware of them and you work in a team. … Is it (using PROMs) worth the time it consumes? I don't know whether this would change my clinical practice.*	*straight to those manifestations. And it would save time. The system incorporates a system of alarms, so if the patient scores really high on pain or on fatigue, you have a red mark even before the patient comes through the door and you can say, "Oh, there's a red flag." It allows you to ask the right questions during the consultation.*

F. Wrap-up questions

Group 1	Group 2
Can you each think of one feature or capability that an app should have to help in one of those areas? **Patient involvement** 2 patients and 1 nurse: electronic diary where the patient could record things of importance so it would be easier when you come to the consultation, to report what happened and to prepare for the consultation. Clinician: *a list of potential problems the patient needs explaining. It has to be simple, otherwise it won't work*. **Self-management** *-To give a simple list of important points, the things to monitor*. (Clinician) *-Yes, things to monitor. From sleep to physical exercise to medicines taken.* (Patient) *-Something I can come back to, when I want to, when I need information about this area.* (Nurse) **Education** *You could link the app to a video channel in which you have programmed. You can even listen to them in the tube, on the bus.* (Clinician) *The doctors don't take seriously the psychological effect on the patient. When you feel good you have a better chance to get better. Some of them think there is only the treatment. For me it is everything, the treatment, psychology and lifestyle. We have to talk about it more.* (Patient) **PROMs** There was general agreement that the app could play a useful role. This was expressed forcefully by a clinician who previously had been very skeptical about the use of PROMS: *Yes, you could fill it up in the app and send it. This could be a very good opportunity.*	**Can you each think of one thing that would allow us to take a step forward on any of them?** **Strengthening the links in the patient/specialist/GP triangle and also between specialists:** *If we make stronger the relationship between the corners of the triangle - patients, specialists and GPs - maybe the triangle is littler and people are closer.* (GP) *The team effort. The thing that GPs get closer to specialists. Specialists get closer to patients. A guy can't build a skyscraper alone. He has to have plumbers, carpenters, welders.* (Caregiver) *To establish parameters of the team so we keep talking together and have it all agreed between us. Keep talking, so we all have a contribution to make*. (Patient) *I think strengthening the network is essential. Also to focus on those things that are most important. I really see that we get overwhelmed by the information and the time that costs. The app needs to be there, but we need to be able to focus on the things that are most important.* (Clinician) **Possible uses and benefits of an app** *It can follow the disease over time, chronically. … It can make some statistics. It can be useful also to send a red flag, because you can enter the results of your analysis and it can say, "Pay attention. Maybe you are going to have an acute episode." An app, well made, would be a big help*. (GP)

	Something very practical. As a patient, I would like a hotline to the clinic, some way of always being able to communicate. It might be a chat, something online. Always being able to get an answer when you're in doubt. (Patient)

Two themes ran through all the focus groups sessions. The first one is related to differences in the health provision systems in different countries including: organizational differences, budget constraints, channels of communication and the different degrees of adoption of digitalization. The second one referred to the importance of education. In this regard, clinicians recognized that patients, GPs, nurses, and specialists in other therapeutic areas that came into contact with SLE patients, all needed more information and training but also that that they needed themselves training in communication skills to be able to handle exchanges with patients more effectively.

3.5 Discussion

This project has attempted to approach the important issue of "patient-physician discordance" in long-term care of SLE patients using the focus group methodology, getting doctors, patients and other actors potentially involved in disease management, to work side-by-side.

The patient-physician relationship takes the form of an ongoing negotiation through which to reach a consent: doctors and patients do have different visions and needs and it appears imperative to find a way of integrating these two viewpoints [73].

It is possible to summarize patients' and physicians' viewpoints as follows.

The patient's viewpoint.

All patients remarked on the difficulties they faced in communicating with others about different aspects of their disease, since it is complex and not widely known, because of lack of belief of the gravity of the disease and in particular of some non-visible symptoms (i.e. fatigue).

SLE patients declared that they have a real, shared hunger for information about the disease, therapies and their side-effects and about the life-style choices they should make. This is due to several reasons: lack of time; not know what to ask to the clinician; lack of dialogue with the rheumatologist. Therefore, near all patients had to resort to some form of self-help to fill the gaps in their knowledge, visiting web sites (not always reliable), reading the leaflets that accompany their medicines (usually pretty unfriendly) and so on.

Importantly, patients declared that information conveyed must be selected and customised.

Overall, a marked difference in the degree of satisfaction with the information and the treatment received seems to depend on the organization of the national health service and on the availability of specialized Lupus centers. In fact, highly positive responses came from those participants who had access to dedicated Lupus centers with multidisciplinary teams of specialists who exchange information about their patients.

The interpretation of the meaning of "self-management" of the disease was discussed at length during focus groups and a certain degree of variability emerged among patients. Patients declared that "manage" their disease means: following the doctor's advice, adopting life-style recommendations, knowing and accepting limitations, seeking out strategies for coping with symptoms, such as pain and fatigue. In addition to this, patients agreed on two further points. First of all, conscious management of the disease depends on having access to tools which can help them monitor their state of health. Patients were also aware that their ability to make choices is limited to those periods in which the disease is under control.

The clinician's viewpoint.

Overall, we found that doctors do not feel an urgent need for any new clinical tools for monitoring the disease. Existing tools are well known and used in clinical practice, even if doctors are aware of their limits and differences as far as organ involvement is concerned.

What does emerge is the need to be able to work in a specialist network, to be able to share experiences and information with expert rheumatologists belonging to centres of reference, and to be able to team up with specialists in other fields involved in the treatment of the disease (nephrologists, gynaecologists, cardiologists and so on) and to so provide a proper multidisciplinary approach to management of Lupus patients.

The role of PROMs in the management of the disease was the subject of much debate. Doctors declared that they find it difficult to interpret and use the results of these questionnaires, despite recognising their importance in theoretical terms as tools for understanding the patient's viewpoint, without the mediation of the physician or other healthcare professionals.

Physicians agreed on the importance of knowing those aspects of patients' lives which are not strictly related to the disease itself (quality of life, family, social and work settings, economic situation, etc.), the need for a patient-by-patient personalised approach and a patient-physician relationship built on trust which was often difficult to achieve.

Clinicians discussed about how possible it is in reality to take the patient's viewpoint into account, actively to involve them in their treatment, sharing therapeutic strategies and allowing them to "self-manage" some aspects of the disease itself. They all agreed that educating the patient on the disease,

therapies and life-style choices was a necessary condition for them to play an active role in management of the disease. When the patient is well-informed about the disease, it is then possible to delegate some "basic" tasks in its management.

The key elements for a new shared strategy

The project results lay the foundations for a new shared strategy for disease management, which may serve as a prototype for other chronic diseases.

According to the project results, the key elements for the development of a new paradigm for SLE management should include:

- **MULTIDISCIPLINARITY and NETWORKING**
- **PATIENT-PHYSICIAN COMMUNICATION**
- **PATIENT'S EDUCATION**
- **PATIENT'S EMPOWERMENT**

Thus, we can derive some fundamental aspects that should be part of the strategy for the daily management of SLE.

First of all, the ideal setting for the management of the disease is represented by a dedicated "Lupus clinic", where the patient can be in charge of a team of expert health care professionals and can receive support for all the health-related issues affected by the disease.

Working alongside other specializations work well in those cases where there are multi-disciplinary teams grouped together in Lupus centres. This kind of networking should be strongly encouraged; possible strategies could be to support the organization of local meetings and regular clinical case discussions between different specialists to share knowledge and experience on SLE.

Over time, specialists built up their own local networks and knew where to go to get authoritative opinions. However, this is not always possible, especially in small centres. A possible solution could be to favor the contact with regional or national centres of excellence, especially if language is a barrier. Alternatively, existing international networks, like ERN-ReCONNET, could provide the support.

From both the patients' and clinicians' perspective emerged that the communication between the parts is often inadequate in terms of both contents and means.

Patients remarked on the difficulties they faced in communicating with doctors, and doctors agreed on the importance of promoting a holistic approach to the patient by also considering non-clinical aspects of patient's life, although challenging. A specialized nurse, part of the Lupus clinic teams with a mediating role; websites with reliable medical information certified by verified association of clinicians or patient associations; educational activities organized through patients' associations;

patient's friendly, simple, leaflets designed specifically for SLE patients represent some of the possible strategies emerged to improve patient-clinician communication.

Moreover, any effort to improve health care professionals' communication skills should be done (i.e. training early during medical school and residency but also in further educational settings, meetings focused on the doctor-patient communication).

Some strategies should be put in place to optimize the use of time during visits: PROMs to be filled at home or in the waiting room; wearable devices or an electronic diary to record clinical and life-styles data collected during the daily routine may contribute to making more focused and efficient use of time during the visits; the improvement of the visiting environment may also be of help.

One of the most important issues emerged from the project is that patients have an urgent need to receive information about the disease and, on the other hand, clinicians think that only an educated patient can be really empowered to self-manage certain aspects of the disease. Information conveyed to patients should be customized by their doctor, considering that different patients, at different stages of life and of their disease, have different information needs. The doctor should find a way of choosing the appropriate language for each specific patient and select information on the basis of the current emotional state of the patient, the stage of disease and the patient's degree of acceptance of their disease. Therefore, from the time of diagnosis onwards a continuous, personalized process of patient education should be encouraged to favor patients' self-management.

Some instruments may be of help to make such an educational process to happen. Both clinicians and patients agreed on the fact that an ideal IT solution (an App for instance) would be of benefit in the management of the disease. It could provide a more complete picture of the patient's condition and its evolution; it could give to the doctor a wider vision of how the patient lives the disease, improving the physician/patient relationship, drawing them closer to each other. A dedicated SLE-specific App could allow a more efficient data collection before the visit (i.e. PROs) with a more efficient use of time during the outpatient visit. Moreover, it could represent a reliable source of educational material about the disease, and it could provide tools to help patients in the "self-management" of the disease (i.e.: lifestyle advice, reminder for adherence, exercise record, record of blood pressure or other values etc).

Self-management of simple tasks is important as one of the first steps towards patient's engagement and empowerment. According to what emerged from the project, possible areas of self-management and possible solutions should include for example: understanding of some important lab test results by the patient himself; regular reporting of symptoms, signs, medical consultations etc occurred between visits.

The process should be gradual and personalized according to the individual attitude, will and capacity. Patients recognized that being an active patient, involved in decisions about the disease, is a prerequisite for their empowerment.

In conclusion, several unmet needs seem to be present in the management of SLE, both from the patient's and the clinician's point of view. Patient-physician discordance still represents a complex subject, particularly relevant to chronic diseases.

The patients are called upon to take an active part in their treatment, aware of how important it is to comply with the doctor's advice but, at the same time, able and empowered to manage certain aspects of the disease autonomously. This can only happen if patients are educated about the disease, about treatments, appropriate lifestyles and those limits that have to be accepted. An educated patient can learn to live better with his/her condition and will be able to develop strategies for self-management. The clinician, on the other hand, has to provide the patient with the tools which will allow such an educational process to happen, and has to make a point of taking into account the non-clinical aspects of the patient's life. Bringing together clinical data and patient-driven data, providing access to educational material and monitoring tools will allow these two viewpoints to come together in a holistic, integrated picture.

Several possible solutions to work on emerged, including organizational strategies, educational activities and IT solutions. Therefore, the results of the project pointed out a path to follow in the management of Lupus patients and lay the foundations for a new shared strategy for disease management in clinical practice which may serve as a prototype for other chronic diseases.

Finally, the design of this new shared strategy for the management of chronic diseases acquires even more importance in the context of COVID-19 pandemic. This pandemic has indeed highlighted the need to know how to manage complex patients even at a distance, using tools that allow the monitoring of clinical conditions. The importance of having patients educated about their disease and able to self-manage and recognize the alarm signs related to their state of health has emerged.

Therefore, in this setting, the results of the project may be of importance towards building a patient-physician alliance that appears to be increasingly important in the monitoring of chronic diseases.

References

1. Sullivan M. The new subjective medicine: taking the patient's point of view on health care and health. *Soc Sci Med 1982* 2003;56(7):1595–1604.

2. Development of the World Health Organization WHOQOL-BREF quality of life assessment. The WHOQOL Group. *Psychol Med* 1998;28(3):551–558.

3. Cella DF. Quality of life: concepts and definition. *J Pain Symptom Manage* 1994;9(3):186–192.

4. Panopalis P, Clarke AE. Quality of life in systemic lupus erythematosus. *Clin Dev Immunol* 2006;13(2–4):321–324.

5. Post MWM. Definitions of quality of life: what has happened and how to move on. *Top Spinal Cord Inj Rehabil* 2014;20(3):167–180.

6. Elkinton JR. Medicine and the quality of life. *Ann Intern Med* 1966;64(3):711–714.

7. Guyatt GH, Naylor CD, Juniper E, Heyland DK, Jaeschke R, Cook DJ. Users' guides to the medical literature. XII. How to use articles about health-related quality of life. Evidence-Based Medicine Working Group. *JAMA* 1997;277(15):1232–1237.

8. Mahieu M, Yount S, Ramsey-Goldman R. Patient-Reported Outcomes in Systemic Lupus Erythematosus. *Rheum Dis Clin North Am* 2016;42(2):253–263.

9. Stamm TA, Bauernfeind B, Coenen M, et al. Concepts important to persons with systemic lupus erythematosus and their coverage by standard measures of disease activity and health status. *Arthritis Rheum* 2007;57(7):1287–1295.

10. U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. *Health Qual Life Outcomes* 2006;4:79.

11. Urowitz M, Gladman DD, Ibañez D, et al. Changes in quality of life in the first 5 years of disease in a multicenter cohort of patients with systemic lupus erythematosus. *Arthritis Care Res* 2014;66(9):1374–1379.

12. Kuriya B, Gladman DD, Ibañez D, Urowitz MB. Quality of life over time in patients with systemic lupus erythematosus. *Arthritis Rheum* 2008;59(2):181–185.

13. Lai J-S, 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(4):672–679.

14. Holloway L, Humphrey L, Heron L, et al. 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.

15. M C, J A, K M, Ls T. Comparison of the psychometric properties of health-related quality of life measures used in adults with systemic lupus erythematosus: a review of the literature. *Rheumatol*

Oxf Engl [Internet] 2013 [cited 2021 Aug 15];52(4). Available from: https://pubmed.ncbi.nlm.nih.gov/23264550/

16. McElhone K, Abbott J, Shelmerdine J, et al. Development and validation of a disease-specific health-related quality of life measure, the LupusQol, for adults with systemic lupus erythematosus. *Arthritis Rheum* 2007;57(6):972–979.

17. Leong KP, Kong KO, Thong BYH, et al. Development and preliminary validation of a systemic lupus erythematosus-specific quality-of-life instrument (SLEQOL). *Rheumatol Oxf Engl* 2005;44(10):1267–1276.

18. Doward LC, McKenna SP, Whalley D, et al. The development of the L-QoL: a quality-of-life instrument specific to systemic lupus erythematosus. *Ann Rheum Dis* 2009;68(2):196–200.

19. Yazdany J. Health-related quality of life measurement in adult systemic lupus erythematosus: Lupus Quality of Life (LupusQoL), Systemic Lupus Erythematosus-Specific Quality of Life Questionnaire (SLEQOL), and Systemic Lupus Erythematosus Quality of Life Questionnaire (L-QoL). *Arthritis Care Res* 2011;63 Suppl 11:S413-419.

20. Jolly M, Pickard AS, Block JA, et al. Disease-specific patient reported outcome tools for systemic lupus erythematosus. *Semin Arthritis Rheum* 2012;42(1):56–65.

21. Jolly M, Garris CP, Mikolaitis RA, et al. 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* 2014;66(10):1542–1550.

22. Schneider M, Mosca M, Pego-Reigosa J-M, et al. Cross-cultural validation of Lupus Impact Tracker in five European clinical practice settings. *Rheumatol Oxf Engl* 2017;56(5):818–828.

23. Urowitz MB, Gladman DD, Tom BDM, Ibañez D, Farewell VT. Changing patterns in mortality and disease outcomes for patients with systemic lupus erythematosus. *J Rheumatol* 2008;35(11):2152–2158.

24. Morgan C, Bland AR, Maker C, Dunnage J, Bruce IN. Individuals living with lupus: findings from the LUPUS UK Members Survey 2014. *Lupus* 2018;27(4):681–687.

25. T K, A D, D N, G B, D D. Burden of illness in systemic lupus erythematosus: results from a UK patient and carer online survey. *Lupus* [Internet] 2017 [cited 2021 Aug 15];26(10). Available from: https://pubmed.ncbi.nlm.nih.gov/28406053/

26. Gallop K, Nixon A, Swinburn P, Sterling KL, Naegeli AN, Silk MET. Development of a conceptual model of health-related quality of life for systemic lupus erythematosus from the patient's perspective. *Lupus* 2012;21(9):934–943.

27. Schmeding A, Schneider M. Fatigue, health-related quality of life and other patient-reported outcomes in systemic lupus erythematosus. *Best Pract Res Clin Rheumatol* 2013;27(3):363–375.

28. Jolly M. How does quality of life of patients with systemic lupus erythematosus compare with that of other common chronic illnesses? *J Rheumatol* 2005;32(9):1706–1708.

29. Chaigne B, Finckh A, Alpizar-Rodriguez D, et al. Differential impact of systemic lupus erythematosus and rheumatoid arthritis on health-related quality of life. *Qual Life Res Int J Qual Life Asp Treat Care Rehabil* 2017;26(7):1767–1775.

30. Wolfe F, Michaud K, Li T, Katz RS. EQ-5D and SF-36 quality of life measures in systemic lupus erythematosus: comparisons with rheumatoid arthritis, noninflammatory rheumatic disorders, and fibromyalgia. *J Rheumatol* 2010;37(2):296–304.

31. Doria A, Rinaldi S, Ermani M, et al. Health-related quality of life in Italian patients with systemic lupus erythematosus. II. Role of clinical, immunological and psychological determinants. *Rheumatol Oxf Engl* 2004;43(12):1580–1586.

32. Chaigne B, Chizzolini C, Perneger T, et al. Impact of disease activity on health-related quality of life in systemic lupus erythematosus - a cross-sectional analysis of the Swiss Systemic Lupus Erythematosus Cohort Study (SSCS). *BMC Immunol* 2017;18(1):17.

33. Appenzeller S, Clarke AE, Panopalis P, Joseph L, St Pierre Y, Li T. The relationship between renal activity and quality of life in systemic lupus erythematosus. *J Rheumatol* 2009;36(5):947–952.

34. Jolly M, Toloza S, Goker B, et al. Disease-specific quality of life in patients with lupus nephritis. *Lupus* 2018;27(2):257–264.

35. Magro-Checa C, Beaart-van de Voorde LJJ, Middelkoop H a. M, et al. Outcomes of neuropsychiatric events in systemic lupus erythematosus based on clinical phenotypes; prospective data from the Leiden NP SLE cohort. *Lupus* 2017;26(5):543–551.

36. Mok CC, Ho LY, Cheung MY, Yu KL, To CH. Effect of disease activity and damage on quality of life in patients with systemic lupus erythematosus: a 2-year prospective study. *Scand J Rheumatol* 2009;38(2):121–127.

37. Legge A, Doucette S, Hanly JG. Predictors of Organ Damage Progression and Effect on Health-related Quality of Life in Systemic Lupus Erythematosus. *J Rheumatol* 2016;43(6):1050–1056.

38. Hanly JG. Disease activity, cumulative damage and quality of life in systematic lupus erythematosus: results of a cross-sectional study. *Lupus* 1997;6(3):243–247.

39. Jolly M, Utset TO. Can disease specific measures for systemic lupus erythematosus predict patients health related quality of life? *Lupus* 2004;13(12):924–926.

40. McElhone K, Castelino M, Abbott J, et al. The LupusQoL and associations with demographics and clinical measurements in patients with systemic lupus erythematosus. *J Rheumatol* 2010;37(11):2273–2279.

41. Vordenbäumen S, Brinks R, Sander O, et al. [Determinants of health-related quality of life in systemic lupus erythematosus: a monocentric, retrospective long-term observational study in Germany]. *Z Rheumatol* 2019;78(9):813–819.

42. Shi Y, Li M, Liu L, et al. Relationship between disease activity, organ damage and health-related quality of life in patients with systemic lupus erythematosus: A systemic review and meta-analysis. *Autoimmun Rev* 2021;20(1):102691.

43. Kiani AN, Petri M. Quality-of-life measurements versus disease activity in systemic lupus erythematosus. *Curr Rheumatol Rep* 2010;12(4):250–258.

44. Tse KC, Tang CSO, Lio WI, Lam MF, Chan TM. Quality of life comparison between corticosteroid- and-mycofenolate mofetil and corticosteroid- and-oral cyclophosphamide in the treatment of severe lupus nephritis. *Lupus* 2006;15(6):371–379.

45. Choi ST, Kang JI, Park I-H, et al. Subscale analysis of quality of life in patients with systemic lupus erythematosus: association with depression, fatigue, disease activity and damage. *Clin Exp Rheumatol* 2012;30(5):665–672.

46. Thumboo J, Fong KY, Chan SP, et al. A prospective study of factors affecting quality of life in systemic lupus erythematosus. *J Rheumatol* 2000;27(6):1414–1420.

47. Almehed K, Carlsten H, Forsblad-d'Elia H. Health-related quality of life in systemic lupus erythematosus and its association with disease and work disability. *Scand J Rheumatol* 2010;39(1):58–62.

48. Mathias SD, Berry P, Pascoe K, et al. Treatment Satisfaction in Systemic Lupus Erythematosus: Development of a Patient-Reported Outcome Measure. *J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis* 2017;23(2):94–101.

49. Mathias SD, Berry P, De Vries J, et al. Development of the Systemic Lupus Erythematosus Steroid Questionnaire (SSQ): a novel patient-reported outcome tool to assess the impact of oral steroid treatment. *Health Qual Life Outcomes* 2017;15(1):43.

50. McElhone K, Abbott J, Teh LS. A review of health related quality of life in systemic lupus erythematosus. *Lupus* 2006;15(10):633–643.

51. Alarcón GS, McGwin G, Uribe A, et al. Systemic lupus erythematosus in a multiethnic lupus cohort (LUMINA). XVII. Predictors of self-reported health-related quality of life early in the disease course. *Arthritis Rheum* 2004;51(3):465–474.

52. Barbasio C, Vagelli R, Marengo D, et al. Illness perception in systemic lupus erythematosus patients: The roles of alexithymia and depression. *Compr Psychiatry* 2015;63:88–95.

53. Gladman DD, Urowitz MB, Gough J, MacKinnon A. Fibromyalgia is a major contributor to quality of life in lupus. *J Rheumatol* 1997;24(11):2145–2148.

54. Buskila D, Press J, Abu-Shakra M. Fibromyalgia in systemic lupus erythematosus: prevalence and clinical implications. *Clin Rev Allergy Immunol* 2003;25(1):25–28.

55. Akkasilpa S, Minor M, Goldman D, Magder LS, Petri M. Association of coping responses with fibromyalgia tender points in patients with systemic lupus erythematosus. *J Rheumatol* 2000;27(3):671–674.

56. Boström C, Elfving B, Dupré B, Opava CH, Lundberg IE, Jansson E. Effects of a one-year physical activity programme for women with systemic lupus erythematosus - a randomized controlled study. *Lupus* 2016;25(6):602–616.

57. Navarrete-Navarrete N, Peralta-Ramírez MI, Sabio JM, Martínez-Egea I, Santos-Ruiz A, Jiménez-Alonso J. Quality-of-life predictor factors in patients with SLE and their modification after cognitive behavioural therapy. *Lupus* 2010;19(14):1632–1639.

58. Haupt M, Millen S, Jänner M, Falagan D, Fischer-Betz R, Schneider M. Improvement of coping abilities in patients with systemic lupus erythematosus: a prospective study. *Ann Rheum Dis* 2005;64(11):1618–1623.

59. Mazzoni D, Cicognani E, Prati G. Health-related quality of life in systemic lupus erythematosus: a longitudinal study on the impact of problematic support and self-efficacy. *Lupus* 2017;26(2):125–131.

60. Vollenhoven RF van, Mosca M, Bertsias G, et al. Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. *Ann Rheum Dis* 2014;73(6):958–967.

61. Vollenhoven R van, Voskuyl A, Bertsias G, et al. A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). *Ann Rheum Dis* 2017;76(3):554–561.

62. Franklyn K, Lau CS, Navarra SV, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). *Ann Rheum Dis* 2016;75(9):1615–1621.

63. Piga M, Floris A, Cappellazzo G, et al. Failure to achieve lupus low disease activity state (LLDAS) six months after diagnosis is associated with early damage accrual in Caucasian patients with systemic lupus erythematosus. *Arthritis Res Ther* 2017;19(1):247.

64. Morand EF, Golder V. Treat-to-target Endpoint Definitions in Systemic Lupus Erythematosus: More Is Less? *J Rheumatol* 2019;46(10):1256–1258.

65. Ríos-Garcés R, Espinosa G, Vollenhoven R van, Cervera R. Treat-to-target in systemic lupus erythematosus: Where are we? *Eur J Intern Med* 2020;74:29–34.

66. Alarcón GS, Ugarte-Gil MF, Pons-Estel G, Vilá LM, Reveille JD, McGwin G. Remission and low disease activity state (LDAS) are protective of intermediate and long-term outcomes in SLE patients. Results from LUMINA (LXXVIII), a multiethnic, multicenter US cohort. *Lupus* 2019;28(3):423–426.

67. Floris A, Piga M, Perra D, et al. Treatment Target in Newly Diagnosed Systemic Lupus Erythematosus: The Association of Lupus Low Disease Activity State and Remission With Lower Accrual of Early Damage. *Arthritis Care Res* 2020;72(12):1794–1799.

68. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019;78(6):736–745.

69. Tsang-A-Sjoe MWP, Bultink IEM, Heslinga M, Tuyl LH van, Vollenhoven RF van, Voskuyl AE. The relationship between remission and health-related quality of life in a cohort of SLE patients. *Rheumatol Oxf Engl* 2019;58(4):628–635.

70. Ugarte-Gil MF, Gamboa-Cárdenas RV, Reátegui-Sokolova C, et al. Low Disease Activity State/Remission Predicts a Better Health-Related Quality of Life in Systemic Lupus Erythematosus Patients. *Arthritis Care Res* 2019;

71. Mok CC, Ho LY, Tse SM, Chan KL. Prevalence of remission and its effect on damage and quality of life in Chinese patients with systemic lupus erythematosus. *Ann Rheum Dis* 2017;76(8):1420–1425.

72. Margiotta DPE, Fasano S, Basta F, et al. The association between duration of remission, fatigue, depression and health-related quality of life in Italian patients with systemic lupus erythematosus. *Lupus* 2019;28(14):1705–1711.

73. Kernder A, Elefante E, Chehab G, Tani C, Mosca M, Schneider M. The patient's perspective: are quality of life and disease burden a possible treatment target in systemic lupus erythematosus? *Rheumatol Oxf Engl* 2020;59(Suppl5):v63–v68.

74. Furie R, Petri MA, Strand V, et al. 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(1):e000031.

75. Strand V, Berry P, Lin X, Asukai Y, Punwaney R, Ramachandran S. Long-Term Impact of Belimumab on Health-Related Quality of Life and Fatigue in Patients With Systemic Lupus Erythematosus: Six Years of Treatment. *Arthritis Care Res* 2019;71(6):829–838.

76. Petri MA, Martin RS, Scheinberg MA, Furie RA. Assessments of fatigue and disease activity in patients with systemic lupus erythematosus enrolled in the Phase 2 clinical trial with blisibimod. *Lupus* 2017;26(1):27–37.

77. Furie R, Wang L, Illei G, Drappa J. Systemic Lupus Erythematosus (SLE) Responder Index response is associated with global benefit for patients with SLE. *Lupus* 2018;27(6):955–962.

78. Tamayo T, Fischer-Betz R, Beer S, Winkler-Rohlfing B, Schneider M. Factors influencing the health related quality of life in patients with systemic lupus erythematosus: long-term results (2001--2005) of patients in the German Lupus Erythematosus Self-Help Organization (LULA Study). *Lupus* 2010;19(14):1606–1613.

79. Schmeding A, Schneider M. Fatigue, health-related quality of life and other patient-reported outcomes in systemic lupus erythematosus. *Best Pract Res Clin Rheumatol* 2013;27(3):363–375.

80. Baker K, Pope J. Employment and work disability in systemic lupus erythematosus: a systematic review. *Rheumatol Oxf Engl* 2009;48(3):281–284.

81. Palagini L, Mosca M, Tani C, Gemignani A, Mauri M, Bombardieri S. Depression and systemic lupus erythematosus: a systematic review. *Lupus* 2013;22(5):409–416.

82. Al Dhanhani AM, Gignac MAM, Su J, Fortin PR. Work disability in systemic lupus erythematosus. *Arthritis Rheum* 2009;61(3):378–385.

83. Cornet A, Andersen J, Myllys K, Edwards A, Arnaud L. Living with systemic lupus erythematosus in 2020: a European patient survey. *Lupus Sci Med* 2021;8(1):e000469.

84. Yen JC, Neville C, Fortin PR. Discordance between patients and their physicians in the assessment of lupus disease activity: relevance for clinical trials. *Lupus* 1999;8(8):660–670.

85. Georgopoulou S, Prothero L, D'Cruz DP. Physician-patient communication in rheumatology: a systematic review. *Rheumatol Int* 2018;38(5):763–775.

86. Alarcón GS, McGwin G, Brooks K, et al. Systemic lupus erythematosus in three ethnic groups. XI. Sources of discrepancy in perception of disease activity: a comparison of physician and patient visual analog scale scores. *Arthritis Rheum* 2002;47(4):408–413.

87. Leong KP, Chong EYY, Kong KO, et al. Discordant assessment of lupus activity between patients and their physicians: the Singapore experience. *Lupus* 2010;19(1):100–106.

88. Yen JC, Abrahamowicz M, Dobkin PL, Clarke AE, Battista RN, Fortin PR. Determinants of discordance between patients and physicians in their assessment of lupus disease activity. *J Rheumatol* 2003;30(9):1967–1976.

89. Neville C, Clarke AE, Joseph L, Belisle P, Ferland D, Fortin PR. Learning from discordance in patient and physician global assessments of systemic lupus erythematosus disease activity. *J Rheumatol* 2000;27(3):675–679.

90. T P, A W, K E, A R, If R. Patients' own ability to assess activity of their rheumatoid arthritis. *Rheumatol Oxf Engl* [Internet] 2006 [cited 2021 Aug 15];45(8). Available from: https://pubmed.ncbi.nlm.nih.gov/16717064/

91. Ua W, Rb M, Vk J, et al. Disease activity dynamics in rheumatoid arthritis: patients' self-assessment of disease activity via WebApp. *Rheumatol Oxf Engl* [Internet] 2017 [cited 2021 Aug 15];56(10). Available from: https://pubmed.ncbi.nlm.nih.gov/28957553/

92. Golder V, Ooi JJY, Antony AS, et al. Discordance of patient and physician health status concerns in systemic lupus erythematosus. *Lupus* 2018;27(3):501–506.

93. Piga M, Congia M, Gabba A, et al. Musculoskeletal manifestations as determinants of quality of life impairment in patients with systemic lupus erythematosus. *Lupus* 2018;27(2):190–198.

94. Chiara T, Linda C, Andrea DS, et al. Impact of Joint Involvement on Patients Reported Outcomes in Systemic Lupus Erythematosus. *Curr Rheumatol Rev* 2018;14(2):188–192.

95. Zhu TY, Tam L-S, Lee VWY, Lee KK, Li EK. Relationship between flare and health-related quality of life in patients with systemic lupus erythematosus. *J Rheumatol* 2010;37(3):568–573.

96. Birt JA, Hadi MA, Sargalo N, et al. Patient Experiences, Satisfaction, and Expectations with Current Systemic Lupus Erythematosus Treatment: Results of the SLE-UPDATE Survey. *Rheumatol Ther* 2021;

97. Tamirou F, Arnaud L, Talarico R, et al. Systemic lupus erythematosus: state of the art on clinical practice guidelines. *RMD Open* 2018;4(2):e000793.

98. Falasinnu T, Drenkard C, Bao G, Mackey S, Lim SS. The Problem of Pain in Systemic Lupus Erythematosus: An Explication of the Role of Biopsychosocial Mechanisms. *J Rheumatol* 2021;48(8):1279–1289.

99. Pettersson S, Möller S, Svenungsson E, Gunnarsson I, Welin Henriksson E. Women's experience of SLE-related fatigue: a focus group interview study. *Rheumatol Oxf Engl* 2010;49(10):1935–1942.

100. 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(5):811–819.

101. Wang B, Gladman DD, Urowitz MB. Fatigue in lupus is not correlated with disease activity. *J Rheumatol* 1998;25(5):892–895.

102. Moazzami M, Strand V, Su J, Touma Z. Dual trajectories of fatigue and disease activity in an inception cohort of adults with systemic lupus erythematosus over 10 years. *Lupus* 2021;30(4):578–586.

103. Monahan RC, Beaart-van de Voorde LJ, Eikenboom J, et al. Fatigue in patients with systemic lupus erythematosus and neuropsychiatric symptoms is associated with anxiety and depression rather than inflammatory disease activity. *Lupus* 2021;30(7):1124–1132.

104. Chehab G, Carnarius H, Schneider M. What matters for lupus patients? *Presse Medicale Paris Fr 1983* 2014;43(6 Pt 2):e197-207.

105. Bruce IN, Mak VC, Hallett DC, Gladman DD, Urowitz MB. Factors associated with fatigue in patients with systemic lupus erythematosus. *Ann Rheum Dis* 1999;58(6):379–381.

106. Pettersson S, Boström C, Eriksson K, Svenungsson E, Gunnarsson I, Henriksson EW. Lifestyle habits and fatigue among people with systemic lupus erythematosus and matched population controls. *Lupus* 2015;24(9):955–965.

107. Yilmaz-Oner S, Ilhan B, Can M, et al. Fatigue in systemic lupus erythematosus : Association with disease activity, quality of life and psychosocial factors. *Z Rheumatol* 2017;76(10):913–919.

108. Arnaud L, Mertz P, Amoura Z, et al. Patterns of fatigue and association with disease activity and clinical manifestations in systemic lupus erythematosus. *Rheumatol Oxf Engl* 2021;60(6):2672–2677.

109. Jump RL, Robinson ME, Armstrong AE, Barnes EV, Kilbourn KM, Richards HB. Fatigue in systemic lupus erythematosus: contributions of disease activity, pain, depression, and perceived social support. *J Rheumatol* 2005;32(9):1699–1705.

110. Mertz P, Schlencker A, Schneider M, Gavand P-E, Martin T, Arnaud L. Towards a practical management of fatigue in systemic lupus erythematosus. *Lupus Sci Med* 2020;7(1):e000441.

111. Elefante E, Tani C, Stagnaro C, et al. Impact of fatigue on health-related quality of life and illness perception in a monocentric cohort of patients with systemic lupus erythematosus. *RMD Open* 2020;6(1).

112. Cui C, Li Y, Wang L. The Association of Illness Uncertainty and Hope With Depression and Anxiety Symptoms in Women With Systemic Lupus Erythematosus: A Cross-sectional Study of Psychological Distress in Systemic Lupus Erythematosus Women. *J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis* 2020;

113. Jolly M, Kosinski M, Garris CP, Oglesby AK. Prospective Validation of the Lupus Impact Tracker: A Patient-Completed Tool for Clinical Practice to Evaluate the Impact of Systemic Lupus Erythematosus. *Arthritis Rheumatol Hoboken NJ* 2016;68(6):1422–1431.

114. Antony A, Kandane-Rathnayake RK, Ko T, et al. Validation of the Lupus Impact Tracker in an Australian patient cohort. *Lupus* 2017;26(1):98–105.

115. Ogunsanya ME, Kalb SJ, Kabaria A, Chen S. A systematic review of patient-reported outcomes in patients with cutaneous lupus erythematosus. *Br J Dermatol* 2017;176(1):52–61.

116. Bexelius C, Wachtmeister K, Skare P, Jönsson L, Vollenhoven R van. Drivers of cost and health-related quality of life in patients with systemic lupus erythematosus (SLE): a Swedish nationwide study based on patient reports. *Lupus* 2013;22(8):793–801.

117. Elefante E, Tani C, Stagnaro C, et al. Articular involvement, steroid treatment and fibromyalgia are the main determinants of patient-physician discordance in systemic lupus erythematosus. *Arthritis Res Ther* 2020;22(1):241.

118. Chambers SA, Raine R, Rahman A, Isenberg D. Why do patients with systemic lupus erythematosus take or fail to take their prescribed medications? A qualitative study in a UK cohort. *Rheumatol Oxf Engl* 2009;48(3):266–271.

119. Jolly M. Pitfalls and opportunities in measuring patient outcomes in lupus. *Curr Rheumatol Rep* 2010;12(4):229–236.

120. Acocella I. The focus groups in social research: advantages and disadvantages. *Qual Quant* 2012;46(4):1125–1136.

APPENDIX 1

Renal involvement recommendations	Year	Country	Indicator identified	Clinical use/significance	Grade of evidence	Strength of Rec	References
EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. G Bertsias et al., *Ann Rheum Dis* 2008;67:195–205.	2008	Europe	Renal biopsy Urinary sediment Proteinuria, serum creatinine, anti-dsDNA, C3	To evaluate disease activity, chronicity/damage. **Second renal biopsy**: to evaluate clinical response and outcome in LN. **Urine sediment analysis**: monitoring LN therapy. Changes in these parameters correlate with renal flares and outcome.	4	B	1,2,3,4,5,6,7,8,9,10
European consensus statement on the terminology used in the management of lupus glomerulonephritis. C Gordon et al., *Lupus*. 2009 Mar;18(3):257-63.	2009	Europe	Renal biopsy Proteinuria, renal function and urinary sediment	LN (ISN/RPS 2003 classification to assess segmental or global involvement of the glomeruli and a measure of chronicity). These parameters have to be monitored to assess clinical renal manifestations. **Def of complete response**: inactive urinary sediment, proteinuria ≤0.2 g/day and normal or stable renal function. **Def of partial response**: inactive urinary sediment, proteinuria ≤0.5 g/day and normal or stable renal function. A sustained response of at least 3 to 6 months can be regarded as a **remission** but cannot be judged to be a complete remission in the absence of a biopsy. **Def of proteinuric flare**: persistent increase in proteinuria to values higher than 0.5-1.0 g/day after a complete response is achieved or a doubling of proteinuria, with values higher than 1.0 g/day, after achieving a partial response. **Def of nephritic flare**: increase or recurrence of active urinary sediment (increased haematuria with or without reappearance of cellular casts) with or without a concomitant increase in proteinuria. Severe nephritic flare: increase or recurrence of active urinary sediment with an increase ≥25% in serum creatinine. **Def of extra-renal flare**: affects one or more extra-renal systems in patients with LN and may require a change in therapy.	N/A	N/A	48,70,61,72,21,72b
European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. Mosca M. et al., *Ann Rheum Dis*. 2010 July ; 69(7): 1269–1274.	2010	Europe	Serum creatinine, urine sediment analysis, proteinuria and blood pressure. Protein/creatinine ratio (or 24 h proteinuria) and immunological tests (C3, C4, anti-dsDNA), urine	Predictive value for renal flare. In patients with established nephropathy, repeat these exams at least	1b	B	29,30, 2, 31,21,22,23,24,25,16,27,28

			microscopy and blood pressure.	every 3 months for the first 2–3 years.			
Joint European League Against Rheumatism and European Renal Association–European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. G Bertsias et al., *Ann Rheum Dis* 2012;71:1771–1782.	2012	Europe	Serum creatinine and GFR, proteinuria, urinary microscopy, body weight and blood pressure measurement. Serum C3/C4, anti-dsDNA . Complete blood cell count and serum albumin. Anti-phospholipid antibodies and serum lipid. Serial changes in: serum creatinine and GFR, proteinuria, haemoglobin, blood pressure. Kidney biopsy Repeat renal biopsy UPCR <50 mg/mmol and normal or near-normal GFR ≥50% reduction in proteinuria and normal or near-normal GFR	To define activity and response to treatment. Diagnostic utility Diagnostic utility Prognostic value Prognostic value ISN/RPS 2003 classification system. To assess active and chronic glomerular; tubulointerstitial changes; vascular lesions associated with anti phospholipid antibodies/ syndrome In worsening or refractory disease or at relapse; strong prognostic value of renal biopsy findings. Definition of **complete renal response** →prognostic value Definition of **partial renal response** →prognostic value	2 3 2 1 (haemoglobin 2) 2 1 2 3 3 2 1 1	C B C B A (haemoglobin B) C A B C C B B B	34,8,2,35,36,37,38,39,40,41,42,43,44,45,46,47,7, 5,48,49,50,51,52,53,54,55,56
American College of Rheumatology Guidelines for Screening, Case Definition, Treatment and Management of Lupus Nephritis. Bevra H.Hahn et al., *Arthritis Care Res* (Hoboken). 2012 June; 64(6): 797–808.	2012	USA	Renal biopsy Blood pressure, urinalysis, Prot/Cr ratio, serum creatinine; C3/C4 levels anti-DNA	ISN/RPS classification: evaluation of activity and chronicity and tubular and vascular changes. To monitor every month in patients with active nephritis at onset of treatment (except complement level every 2 months); every 3 months in patients with previous active nephritis; every 6 months in patients with no prior or current nephritis (except blood pressure every 3 months). To monitor every 3 months in patients with active nephritis at onset of treatment; every 6 months in patients with previous active nephritis and in patients with no prior or current nephritis.		C C C	57,48,58
Dutch guidelines for diagnosis and therapy of proliferative lupus nephritis. A. van Tellingen et al., *Neth J Med*. 2012 May;70(4):199-207.	2012	Netherlands	Proteinuria/24h Serum creatinine	**Complete response**: proteinuria <0.5 g/24h and/or serum creatinine within 125% of the baseline value at 6 to 12 months after the start of induction therapy. **Partial response**: reduction of proteinuria of >50% (and at least <3 g/24 hours) and serum creatinine within 125% of the baseline value at 6 to 12 months after the start of the induction therapy. **Flare**: increase of ≥25% in the lowest		C	59,60,61,62,63,64,65, 21,10,8

				serum creatinine level measured during the period of induction therapy and/or the development of either a nephrotic syndrome or proteinuria >1.5 g/24 hours in a previous non-proteinuric patient. **Failure** of the induction therapy: doubling of serum creatinine compared with the baseline value at three months after the start of induction therapy. **Refractory LN**: progressive deterioration of renal function and/or proteinuria despite optimal immunosuppressive therapy and supportive treatment.			
Diagnosis and treatment of lupus nephritis. Consensus document from the systemic auto-immune disease group (GEAS) of the Spanish Society of Internal Medicine (SEMI) and the Spanish Society of Nephrology (S.E.N.). Ruiz-Irastorza G. et al., *Nefrologia*. 2012;32 Suppl 1:1-35.	2012	Spain	Renal biopsy Haemogram, glucose, urea, serum creatinine and GFR, proteinuria/24h or uPr/Cr ratio and urinary sediment. Albumin, anti-nDNA, C3/C4. Complete auto-Ab serology (aPL included)	Diagnostic and prognostic value, treatment decision. ISN/RPS classification. During follow up, monthly for the first 6 months, then every 3 months (till month 24) to monitor renal disease. During follow up, monthly for the first 3 months, then every 3 months (till month 24) to monitor immunological activity. At baseline and then every year **Def of partial response**: in patients with ≥3.5g/24h, decreased proteinuria <3.5g/24h. In patients with baseline proteinuria <3.5g/24h, >50% reduction in proteinuria as compared to initial values. In both situations, stabilization (±25%) or improvement in serum creatinine with regard to initial values. **Def of complete response**: serum creatinine <1.2mg/dl (or decrease to initial values or ±15% of baseline value in patients with creatinine ≥1.2mg/dl), proteinuria <0.5g/24h, inactive urinary sediment (<5 red blood cells, <5 leukocytes, 0 red blood cell casts) and serum albumin >3g/d. **Def of mild recurrence**: ↑RBC in sediment from <5 to >15, with ≥2 dimorphic RBC in high-power fields and/or ≥1 casts, leukocyte count (in the absence of urinary infection), or both. **Def of moderate recurrence**: If baseline creatinine is: <2 mg/dl →↑by 0.2-1mg/dl; >2 mg/dl →↑by 0.4-1.5mg/dl and/or If Pr/Cr ratio is: <0.5	NA	NA	66,67,68,69,37,38,40,70,71

				→↑by ≥1; 0.5-1 →↑by ≥2 but with an absolute increase less than 5. **Def of severe recurrence**: : If baseline creatinine is: <2 mg/dl →↑by 1 mg/dl; ≥2 mg/dl →↑by 1.5 mg/dl and/or a Pr/Cr ratio >5			
The KDIGO practice guideline on glomerulonephritis: reading between the (guide)lines— application to the individual patient. Radhakrishnan J, Cattran DC. *Kidney Int*. 2012 Oct;82(8):840-56.	2012	International	Serum creatinine, uPCR, complement level, anti-DNA	**Def of complete response**: return of SCr to previous baseline, plus a decline in the uPCR to <500 mg/g (<50 mg/mmol). **Def of partial response**: stabilization (±25%) or improvement of SCr, but not to normal, plus a >50% decrease in uPCR. If there was nephrotic-range proteinuria (uPCR >3000 mg/g (>300mg/mmol)), improvement requires a >50% reduction in uPCR and a uPCR of <3000 mg/g (<300 mg/mmol). **Def of deterioration**: a sustained 25% increase in SCr is widely used but has not been validated.	N/A	N/A	

1. **Korbet** SM, Lewis EJ, Schwartz MM, Reichlin M, Evans J, Rohde RD. Factors predictive of outcome in severe lupus nephritis. Lupus Nephritis Collaborative Study Group. Am J Kidney Dis 2000;35:904–14.

2. **Illei** GG, Takada K, Parkin D, Austin HA, Crane M, Yarboro CH, et al. Renal flares are common in patients with severe proliferative lupus nephritis treated with pulse immunosuppressive therapy: long-term followup of a cohort of 145 patients participating in randomized controlled studies. Arthritis Rheum 2002;46:995–1002.

3. **Baldwin** DS, Gluck MC, Lowenstein J, Gallo GR. Lupus nephritis. Clinical course as related to morphologic forms and their transitions. Am J Med 1977;62:12–30.

4. **Balow** JE, Austin HA 3rd, Muenz LR, Joyce KM, Antonovych TT, Klippel JH, et al. Effect of treatment on the evolution of renal abnormalities in lupus nephritis. N Engl J Med 1984;311:491–5.

5. **Hill** GS, Delahousse M, Nochy D, Thervet E, Vrtovsnik F, Remy P, et al. Outcome of relapse in lupus nephritis: roles of reversal of renal fibrosis and response of inflammation to therapy. Kidney Int 2002;61:2176–86.

6. **Rahman** A, Gladman D, Ibanez D, Urowitz M. Significance of isolated hematuria and isolated puyria in systemic lupus erythematosus. J Rheumatol 2000;10:418–23.

7. **Hebert** LA, Dillon JJ, Middendorf DF, Lewis EJ, Peter JB. Relationship between appearance of urinary red blood cell/white blood cell casts and the onset of renal relapse in systemic lupus erythematosus. Am J Kidney Dis 1995;26:432–8.

8. **Houssiau** FA, Vasconcelos C, D'Cruz D, Sebastiani GD, de Ramon Garrido E, Danieli MG, et al. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: lessons from long-term followup of patients in the Euro- Lupus Nephritis Trial. Arthritis Rheum 2004;50:3934–40.

9. **Cortes-Hernandez** J, Ordi-Ros J, Labrador M, Segarra A, Tovar JL, Balada E, et al. Predictors of poor renal outcome in patients with lupus nephritis treated with combined pulses of cyclophosphamide and methylprednisolone. Lupus 2003;12:287–96.

10. **Gourley** MF, Austin HA 3rd, Scott D, Yarboro CH, Vaughan EM, Muir J, et al. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. A randomized, controlled trial. Ann Intern Med 1996;125:549–57.

30. **Ciruelo** E, de la Cruz J, López I, et al. Cumulative rate of relapse of lupus nephritis after successful treatment with cyclophosphamide. Arthritis Rheum 1996;39:2028–2034.

31. **Moroni** G, Quaglini S, Maccario M, et al. "Nephritic flares" are predictors of bad long-term renal outcome in lupus nephritis. Kidney Int 1996;50:2047–2053.

34. **Reich** HN, Gladman DD, Urowitz MB, et al. Persistent proteinuria and dyslipidemia increase the risk of progressive chronic kidney disease in lupus erythematosus. Kidney Int 2011;79:914–20.
35. **Mok** CC, Ying KY, Ng WL, et al. Long-term outcome of diffuse proliferative lupus glomerulonephritis treated with cyclophosphamide. Am J Med 2006;119:355e25–33.
36. **Mosca** M, Tani C, Aringer M, et al. European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. Ann Rheum Dis 2010;69:1269–74.
37. **Fine** DM, Ziegenbein M, Petri M, et al. A prospective study of protein excretion using short-interval timed urine collections in patients with lupus nephritis. Kidney Int 2009;76:1284–8.
38. **Hebert** LA, Birmingham DJ, Shidham G, et al. Random spot urine protein/ creatinine ratio is unreliable for estimating 24-hour proteinuria in individual systemic lupus erythematosus nephritis patients. Nephron Clin Pract 2009;113:c177–82.
39. **Leung** YY, Szeto CC, Tam LS, et al. Urine protein-to-creatinine ratio in an untimed urine collection is a reliable measure of proteinuria in lupus nephritis. Rheumatology (Oxford) 2007;46:649–52.
40. **Moroni** G, Radice A, Giammarresi G, et al. Are laboratory tests useful for monitoring the activity of lupus nephritis? A 6-year prospective study in a cohort of 228 patients with lupus nephritis. Ann Rheum Dis 2009;68:234–7.
41. **Birmingham** DJ, Irshaid F, Nagaraja HN, et al. The complex nature of serum C3 and C4 as biomarkers of lupus renal flare. Lupus 2010;19:1272–80.
42. **Esdaile** JM, Abrahamowicz M, Joseph L, et al. Laboratory tests as predictors of disease exacerbations in systemic lupus erythematosus. Why some tests fail. Arthritis Rheum 1996;39:370–8.
43. **Ghirardello** A, Villalta D, Morozzi G, et al. Diagnostic accuracy of currently available anti-double-stranded DNA antibody assays. An Italian multicentre study. Clin Exp Rheumatol 2011;29:50–6.
44. **Jaekell** HP, Trabandt A, Grobe N, et al. Anti-dsDNA antibody subtypes and anti-C1q antibodies: toward a more reliable diagnosis and monitoring of systemic lupus erythematosus and lupus nephritis. Lupus 2006;15:335–45.
45. **Steinberg** AD, Decker JL. A double-blind controlled trial comparing cyclophosphamide, azathioprine and placebo in the treatment of lupus
glomerulonephritis. Arthritis Rheum 1974;17:923–37.
46. **Hill** GS, Delahousse M, Nochy D, et al. Predictive power of the second renal biopsy in lupus nephritis: significance of macrophages. Kidney Int 2001;59:304–16.

47. **Moroni** G, Pasquali S, Quaglini S, et al. Clinical and prognostic value of serial renal biopsies in lupus nephritis. Am J Kidney Dis 1999;34:530–9.

48. **Weening** JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. J Am Soc Nephrol 2004;15:241–50.

49. **Furness** PN, Taub N. Interobserver reproducibility and application of the ISN/RPS classification of lupus nephritis-a UK-wide study. Am J Surg Pathol 2006;30:1030–5.

50. **Grootscholten** C, Bajema IM, Florquin S, et al. Interobserver agreement of scoring of histopathological characteristics and classification of lupus nephritis. Nephrol Dial Transplant 2008;23:223–30.

51. **O'Dell** JR, Hays RC, Guggenheim SJ, et al. Tubulointerstitial renal disease in systemic lupus erythematosus. Arch Intern Med 1985;145:1996–9.

52. **Esdaile** JM, Federgreen W, Quintal H, et al. Predictors of one year outcome in lupus nephritis: the importance of renal biopsy. Q J Med 1991;81:907–18.

53. **Austin** HA III, Boumpas DT, Vaughan EM, et al. High-risk features of lupus nephritis: importance of race and clinical and histological factors in 166 patients. Nephrol Dial Transplant 1995;10:1620–8.

54. **Hill** GS, Delahousse M, Nochy D, et al. A new morphologic index for the evaluation of renal biopsies in lupus nephritis. Kidney Int 2000;58:
1160–73.

55. **Ogawa** H, Kameda H, Nagasawa H, et al. Prospective study of low-dose cyclosporine A in patients with refractory lupus nephritis. Mod Rheumatol 2007;17:92–7.

56. **Descombes** E, Droz D, Drouet L, et al. Renal vascular lesions in lupus nephritis. Medicine (Baltimore) 1997;76:355–68.

57. **Weening** JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, Balow JE, Bruijn JA, Cook T, Ferrario F, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int. 2004; 65(2):521–530.

58. **Markowitz** GS, D'Agati VD. The ISN/RPS 2003 classification of lupus nephritis: an assessment at 3 years. Kidney Int. 2007; 71(6):491–495.

59. **Singh** JA, Solomon DH, Dougados M, et al. Development of classification and response criteria for rheumatic diseases. Arthritis Rheum.
2006;55:348-52.

60. **Bertsias** G, Gordon C, Boumpas DT. Clinical trial in systemic lupus erythematosus (SLE): lessons from the past as we proceed to the future

— the EULAR recommendations for the management of SLE and the use of end-points in clinical trials. Lupus. 2008;17:437-42.

61. **Gordon** C, Bertsias G, Ioannidis JPA, et al. EULAR points to consider for conducting clinical trials in systemic lupus erythematosus. Ann Rheum Dis. 2009;68:470-6.

62. **Steinberg** AD, Steinberg SC. Long-term preservation of renal function in patients with lupus nephritis receiving treatment that includes
cyclophosphamide versus those treated with prednisone only. Arthritis Rheum. 1991;605-7.

63. **Chen** YE, Korbet SM, Katz RS, et al. Value of complete or partial remission in severe lupus nephritis. Clin J Am Soc Nephrol. 2008;3:46-53.

64. **Chan** TM, Tse KC, Tang CS, Lai KN, Li FK. Long-term outcome of patients with diffuse proliferative lupus nephritis treated with prednisolone. Lupus. 2005;14:265-72.

65. **Ioannidis** JP, Boki KA, Katsorida ME, et al. Remission, relapse, and re-remission of proliferative lupus nephritis treated with cyclophophamide. Kidney Int. 2000;57:258-64.

66. **Falk** RJ, Schur PH, Appel GB. Indications for renal biopsy in patients with lupus nephritis. UpToDate. In: Basow DS (ed.). UpToDate, Waltham, MA, 2011. UpToDate 2011.

67. **Mittal** B, Rennke H, Singh AK. The role of kidney biopsy in the management of lupus nephrit is. Curr Opin Nephrol Hypertens 2005;14:1-8.

68. **Daleboudt** GM, Bajema IM, Goemaere NN, et al. The clinical relevance of a repeat biopsy in lupus nephritis flares. Nephrol Dial Transplant 2009;24:3712-7.

69. **Bajaj** S, Albert L, Gladman DD, et al. Serial renal biopsy in systemic lupus erythematosus. J Rheumatol 2000;27:2822-6.

70. Renal Disease Subcommittee of the American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria. The American College of Rheumatology response criteria for proliferative and membranous renal disease in systemic lupus erythematosus clinical trials. Arthritis Rheum 2006;54:421-32.

71. **Appel** GB, Contreras G, Dooley MA, et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. J Am Soc Nephrol 2009;20:1103-12.

72. **Bertsias** GK, Ioannidis JP, Boletis J, et al. Evidence for selection of end-points for clinical trials in systemic lupus erythematosus (SLE): a systematic literature review. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2008.

72b. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. Guidelines for referral and management of systemic lupus erythematosus in adults. Arthritis Rheum 1999; 42: 1785–1796.

Skin involvement recommendations	Year	Country	Indicator identified	Clinical use/significance	Grade of evidence	Strength of Rec	References
European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. Mosca M. et al., *Ann Rheum Dis*. 2010 July ; 69(7): 1269–1274.	2010	Europe	Classification skin lesions: LE specific and LE-non specific lesions, LE mimickers, drug-related Skin biopsy CLASI	**Repeated skin biopsy** during follow up if there is a change in clinical morphology of the lesion or lack of response to treatment. **CLASI** to monitor activity and damage.	5	D	11,12
Development of a Core Set Questionnaire by the European Society of Cutaneous Lupus Erythematosus (EUSCLE). A. Kuhn et al., *Autoimmunity Reviews* 8 (2009) 702 – 712.	2009	Europe	Development of a Core Set Questionnaire for the assessment of cutaneous lupus. The questionnaire includes the classification of skin lesions and the assessment of disease activity and damage.	**Classification skin lesions**: LE specific lesions: • Acute (malar rash or generalized) • Subacute (annular or papulosquamous) • Chronic (discoid, panniculitis or childblain) • Intermittent (lupus tumidus) LE non-specific lesions Evaluation of histology and direct immunofluorescence **Activity and damage of disease**: CLASI			136,137,138,139,140,141,142,143

11. **Rothfield** N, Sontheimer RD, Bernstein M. Lupus erythematosus: systemic and cutaneous manifestations. Clin Dermatol 2006;24:348–362.
12. **Krathen** MS, Dunham J, Gaines E, et al. The Cutaneous Lupus Erythematosus Disease Activity and Severity Index: expansion for rheumatology and dermatology. Arthritis Rheum 2008;59:338–344.

136. **Gilliam** JN. The cutaneous signs of lupus erythematosus. Cont Educ Fam Phys 1977;6:34–70.
137. **Gilliam** JN, Sontheimer RD. Distinctive cutaneous subsets in the spectrum of lupus erythematosus. J Am Acad Dermatol 1981;4:471–5.
138. **Gilliam** JN, Sontheimer RD. Skin manifestations of SLE. Clin Rheum Dis 1982;8:207–18.
139. **Kuhn** A, Ruzicka T. Classification of cutaneous lupus erythematosus. In: Kuhn A, Lehmann P, Ruzicka T, editors. Cutaneous Lupus Erythematosus. Heidelberg: Springer; 2004. p. 53–8.
140. **Baltaci** M, Fritsch P. Histologic features of cutaneous lupus erythematosus. Autoimmun Rev 2009;8:467–73.
141. **Provost** TT. Nonspecific cutaneous manifestations of systemic lupus erythematosus. In: Kuhn A, Lehmann P, Ruzicka T, editors. Cutaneous Lupus Erythematosus. Heidelberg: Springer; 2004. p. 93–106.
142. **Albrecht** J, Taylor L, Berlin JA,Dulay S, AngG, Fakharzadeh S, et al. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. J InvestDermatol 2005;125:889–94.
143. **Albrecht** J,Werth VP. Development of the CLASI as an outcome instrument for cutaneous lupus erythematosus. Dermatol Ther 2007;20:93–101.

Global disease activity recommendations	Year	Country	Indicator identified	Clinical use/significance	Grade of evidence	Strength of Rec	References
EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. G Bertsias et al., Ann Rheum Dis 2008;67:195 – 205.	2008	Europe	Skin lesions, anaemia, lymphopenia, or thrombocytopenia, low serum C3 and/or C4, anti-dsDNA and anti-C1q titres. Disease activity indices (BILAG, SLEDAI, ECLAM)	These parameters correlate with disease severity and can predict future flares. Use of at least one of the disease activity indices for monitoring of disease activity. They are also good predictors of damage and mortality.	Rashes 5 Anemia 4 Lymphopenia 4 Thrombocytopenia 5 C3/C4 4 anti-C1q 4 anti-dsDNA 4 N/A	Rashes C Anemia B Lymphopenia B Thrombocytopenia C C3/C4 B anti-C1q B anti-dsDNA B N/A	13,14,15,16,17,18
European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. Mosca M. et al., *Ann Rheum Dis*. 2010 July ; 69(7): 1269–1274.	2010	Europe	**Auto-Ab and complement** (ANA, anti-dsDNA, anti-Ro, anti-La, anti-RNP, anti-Sm, anti-phospholipid, C3,C4) **Other laboratory assessment** (complete blood count, erythrocyte sedimentation rate, C reactive protein, serum albumin, serum creatinine (or eGFR), urinalysis and urine protein/creatinine ratio) Validated disease activity indices	**Auto-Ab and complement**: at baseline. **Re-evaluation** in previously negative patients of: **anti-phospholipid antibodies** prior to pregnancy, surgery, transplant and use of oestrogen-containing treatments, or in the presence of a new neurological or vascular event; **anti-Ro and anti-La antibodies** before pregnancy; **anti-dsDNA, C3/C4** may support evidence of disease activity/remission. **Other laboratory assessment**: at 6-12 months interval in patients with inactive disease. Evaluation of disease activity by a validated index at each visit and organ damage annually.	Auto-Ab and complement 2b Other laboratory assessment 5 5	Auto-Ab and complement C Other laboratory assessment D D	16,19,20,21,22,23,24,25,26,27,28,29
EULAR points to consider for conducting clinical trials in systemic lupus erythematosus: literature based evidence for the selection of	2009	Europe	Renal function measures Disease activity indices Serum complement level Anti-dsDNA titers	No single intermediate outcome measure as surrogate marker of therapeutic success in SLE. Response of renal function measures (doubling of serum creatinine,	N/A 4 4	D B B	144-168 8,127,80,78,10,9,29,2,91,18

endpoints. G K Bertsias et al., *Ann Rheum Dis* 2009;68:477–483.				proteinuria) to treatment correlate with renal outcome in RCTs. Disease activity indices (SLEDAI, BILAG, SLAM, ECLAM, SIS) predictors of mortality and damage in observational cohorts. Improvement in SLEDAI correlate with remission of neuropsychiatric lupus and lupus nephritis. Normalization of serum C3and/or C4 associated with renal remission and favorable renal outcome. Reduction of anti-dsDNA titers is associated with induction of remission (renal, general). Serum creatinine levels correlate with induction/maintenance of renal remission and outcome. Proteinuria is a determinant for induction of renal remission, renal flares and outcome. The is concordance between early (6 months) and late response in the following intermediate outcome measures: serum creatinine, proteinuria, anti-dsDNA titers, serum C3, prednisone dose, SLEDAI, ECLAM. No direct evidence for the definition of minimum clinically meaningful effect in any of the outcome measures considered.	4 4 4 4 4 4 N/A	B B B B B B D	
Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. Ronald F van Vollenhoven et al, *Ann Rheum Dis*	2014	International	Validated lupus activity indices (SELENA-SLEDAI, SLEDAI-2K, SLAM, BILAG) and/or organ specific markers (e.g. complete renal response)	Treatment target of SLE should be remission of systemic symptoms and organ manifestations or the lowest possible disease activity measured by a validated lupus activity index and/or by organ	3 (SLE) / 1(LN) 2	C(SLE) / A(LN) B	73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91,92,93,94,95,96,97,98, 34,2, 29,16,17,14,41

2014;73:958 – 967.			Anti-dsDNA titer and serum complement levels SLICC damage Index (SDI)	specific markers. It is not recommended that the treatment in clinically asymptomatic patients be escalated based solely on stable or persistent serological activity. Since damage predicts subsequent damage and death, prevention of damage accrual should be a major therapeutic goal in SLE. Damage is reliably measured by the SDI.	1	A	
The British Society for Rheumatology guideline for the management of systemic lupus erythematosus in adults. C. Gordon et al., *Rheumatology* 2018;57: e1-e45.	2018	UK	SLEDAI-2K (or SELENA-SLEDAI) and BILAG SLICC/ACR Damage Index Vital signs (blood pressure, body weight, heart rate), urinalysis, renal function Anti-dsDNA Ab Complement levels, CRP, Full blood count, Liver function test aPLs anti-Ro/La	To regularly assess disease activity. If active disease, every 1-3 months; in stable disease, annually. Disease activity is categorized into mild, moderate and severe, with the occurrence of flares. To assess disease damage. If active disease, every 1-3 months; in stable disease, annually. All these clinical and laboratory parameters to monitor disease activity, every 1-3 months in case of active disease and every 6-12 months in case of stable disease. If previously negative, re-evaluate prior to pregnancy or surgery or in the presence of a new severe manifestation or vascular event. Check prior to pregnancy.	2 2 2 1 2 2 3 4 4 1	B C B A B C C D D A	36,99,100,101,102,103,104,105,106,107,108,109,110,111,44,87,16,2,92,112,113,114,115,116,117,118,119,120,14,86,88,91,17,93,21,42,7, 27,121,122,123,124,125,126

13. **Zecevic** RD, Vojvodic D, Ristic B, Pavlovic MD, Stefanovic D, Karadaglic D. Skin lesions—an indicator of disease activity in systemic lupus erythematosus? Lupus 2001;10:364–7.

14. **Mirzayan** MJ, Schmidt RE, Witte T. Prognostic parameters for flare in systemic lupus erythematosus. Rheumatology (Oxford) 2000;39:1316–9.

15. **Ziakas** PD, Giannouli S, Zintzaras E, Tzioufas AG, Voulgarelis M. Lupus thrombocytopenia: clinical implications and prognostic significance. Ann Rheum Dis 2005;64:1366–9

16. **Ho** A, Barr SG, Magder LS, Petri M. A decrease in complement is associated with increased renal and hematologic activity in patients with systemic lupus erythematosus. Arthritis Rheum 2001;44:2350–7.

17. **Ho** A, Magder LS, Barr SG, Petri M. Decreases in anti-double-stranded DNA levels are associated with concurrent flares in patients with systemic lupus erythematosus. Arthritis Rheum 2001;44:2342–9.

18. **Urowitz** MB, Feletar M, Bruce IN, Ibanez D, Gladman DD. Prolonged remission in systemic lupus erythematosus. J Rheumatol 2005;32:1467–72

19. **Hoffman** IE, Peene I, Meheus L, et al. Specific antinuclear antibodies are associated with clinical features in systemic lupus erythematosus. Ann Rheum Dis 2004;63:1155–1158

20. **Kavanaugh** AF, Solomon DH. American College of Rheumatology Ad Hoc Committee on Immunologic Testing Guidelines. Guidelines for immunologic laboratory testing in the rheumatic diseases: anti-DNA antibody tests. Arthritis Rheum 2002;47:546–555.

21. **Bertsias** G, Ioannidis JP, Boletis J, et al. Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. EULAR recommendations for the management of systemic lupus erythematosus. Report of a Task Force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics. Ann Rheum Dis 2008;67:195–205.

22. **Miyakis** S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306.

23. **Ruiz-Irastorza** G, Egurbide MV, Martinez-Berriotxoa A, et al. Antiphospholipid antibodies predict early damage in patients with systemic lupus erythematosus. Lupus 2004;13:900–905.

24. **Moroni** G, Ventura D, Riva P, et al. Antiphospholipid antibodies are associated with an increased risk for chronic renal insufficiency in patients with lupus nephritis. Am J Kidney Dis 2004;43:28–36.

25. **Stone** JH, Amend WJ, Criswell LA. Outcome of renal transplantation in systemic lupus erythematosus. Semin Arthritis Rheum 1997;27:17–26.

26. **Ng** WL, Chu CM, Wu AK, et al. Lymphopenia at presentation is associated with increased risk of infections in patients with systemic lupus erythematosus. QJM 2006;99:37–47.

27. **Gordon** C, Jayne D, Pusey C, et al. European consensus statement on the terminology used in the management of lupus glomerulonephritis. Lupus 2009;18:257–263.
28. **Mok** CC, Ho CT, Chan KW, et al. Outcome and prognostic indicators of diffuse proliferative lupus glomerulonephritis treated with sequential oral cyclophosphamide and azathioprine. Arthritis Rheum 2002;46:1003–1013.
29. **Mok** CC, Ying KY, Tang S, et al. Predictors and outcome of renal flares after successful cyclophosphamide treatment for diffuse proliferative lupus glomerulonephritis. Arthritis Rheum 2004;50:2559–2568.

73. **Petri** M, Purvey S, Fang H, et al. Predictors of organ damage in systemic lupus erythematosus: The Hopkins Lupus Cohort. Arthritis Rheum 2012;64:4021–8.
74. **Ibanez** D, Urowitz MB, Gladman DD. Summarizing disease features over time: I. Adjusted mean SLEDAI derivation and application to an index of disease activity in lupus. J Rheumatol 2003;30:1977–82.
75. **Andrade** RM, Alarcon GS, Fernandez M, et al. Accelerated damage accrual among men with systemic lupus erythematosus: XLIV. Results from a multiethnic US cohort. Arthritis Rheum 2007;56:622–30.
76. **Lopez** R, Davidson JE, Beeby MD, et al. Lupus disease activity and the risk of subsequent organ damage and mortality in a large lupus cohort. Rheumatology (Oxford) 2012;51:491–8.
77. **Bertoli** AM, Vila LM, Apte M, et al. Systemic lupus erythematosus in a multiethnic US cohort LUMINA LI: anaemia as a predictor of disease activity and damage accrual. Rheumatology (Oxford) 2007;46:1471–6.
78. **Stoll** T, Sutcliffe N, Mach J, et al. Analysis of the relationship between disease activity and damage in patients with systemic lupus erythematosus—a 5-yr prospective study. Rheumatology (Oxford) 2004;43:1039–44.
79. **Andrade** RM, Alarcon GS, Gonzalez LA, et al. Seizures in patients with systemic lupus erythematosus: data from LUMINA, a multiethnic cohort (LUMINA LIV). Ann Rheum Dis 2008;67:829–34.
80. **Manger** K, Manger B, Repp R, et al. Definition of risk factors for death, end stage renal disease, and thromboembolic events in a monocentric cohort of 338 patients with systemic lupus erythematosus. Ann Rheum Dis 2002;61:1065–70.
81. **Arends** S, Grootscholten C, Derksen RH, et al. Long-term follow-up of a randomised controlled trial of azathioprine/methylprednisolone versus
cyclophosphamide in patients with proliferative lupus nephritis. Ann Rheum Dis 2012;71:966–73.

82. **Tisseverasinghe** A, Lim S, Greenwood C, et al. Association between serum total cholesterol level and renal outcome in systemic lupus erythematosus. Arthritis Rheum 2006;54:2211–19.
83. **Drenkard** C, Villa AR, Garcia-Padilla C, et al. Remission of systematic lupus erythematosus. Medicine 1996;75:88–98.
84. **Nossent** J, Kiss E, Rozman B, et al. Disease activity and damage accrual during the early disease course in a multinational inception cohort of patients with systemic lupus erythematosus. Lupus 2010;19:949–56.
85. **Moroni** G, Quaglini S, Gravellone L, et al. Membranous nephropathy in systemic lupus erythematosus: long-term outcome and prognostic factors of 103 patients. Semin Arthritis Rheum 2012;41:642–51.
86. **Petri** M, Singh S, Tesfasyone H, et al. Prevalence of flare and influence of demographic and serologic factors on flare risk in systemic lupus erythematosus: a prospective study. J Rheumatol 2009;36:2476–80.
87. **Swaak** AJ, Groenwold J, Bronsveld W. Predictive value of complement profiles and anti-dsDNA in systemic lupus erythematosus. Ann Rheum Dis 1986;45:359–66.
88. **ter Borg** EJ, Horst G, Hummel EJ, et al. Measurement of increases in anti-double-stranded DNA antibody levels as a predictor of disease exacerbation in systemic lupus erythematosus. A long-term, prospective study. Arthritis Rheum 1990;33:634–43.
89. **Ng** KP, Manson JJ, Rahman A, et al. Association of antinucleosome antibodies with disease flare in serologically active clinically quiescent patients with systemic lupus erythematosus. Arthritis Rheum 2006;55:900–4.
90. **Bijl** M, Dijstelbloem HM, Oost WW, et al. IgG subclass distribution of autoantibodies differs between renal and extra-renal relapses in patients with systemic lupus erythematosus. Rheumatology (Oxford) 2002;41:62–7.
91. **Bootsma** H, Spronk P, Derksen R, et al. Prevention of relapses in systemic lupus erythematosus. Lancet 1995;345:1595–9.
92. **Tseng** CE, Buyon JP, Kim M, et al. The effect of moderate-dose corticosteroids in preventing severe flares in patients with serologically active, but clinically stable, systemic lupus erythematosus: findings of a prospective, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2006;54:3623–32.
93. **Steiman** AJ, Gladman DD, Ibanez D, et al. Prolonged serologically active clinically quiescent systemic lupus erythematosus: frequency and outcome. J Rheumatol 2010;37:1822–7.

94. **Steiman** AJ, Gladman DD, Ibanez D, et al. Outcomes in patients with systemic lupus erythematosus with and without a prolonged serologically active clinically quiescent period. Arthritis Care Res 2012;64:511–18.
95. **Chambers** SA, Allen E, Rahman A, et al. Damage and mortality in a group of British patients with systemic lupus erythematosus followed up for over 10 years. Rheumatology (Oxford) 2009;48:673–5.
96. **Hanly** JG, Urowitz MB, Su L, et al. Seizure disorders in systemic lupus erythematosus results from an international, prospective, inception cohort study. Ann Rheum Dis 2012;71:1502–9.
97. **Mak** A, Cheung MW, Chiew HJ, et al. Global trend of survival and damage of systemic lupus erythematosus: meta-analysis and meta-regression of observational studies from the 1950s to 2000s. Semin Arthritis Rheum 2012;41:830–9.
98. **Ramsey-Goldman** R, Alarcon GS, McGwin G, et al. Time to seizure occurrence and damage in PROFILE, a multi-ethnic systemic lupus erythematosus cohort. Lupus 2008;17:177–84.

99. **Nuttall** A, Isenberg DA. Assessment of disease activity, damage and quality of life in systemic lupus erythematosus: new aspects. Best Pract Res Clin Rheumatol 2013;27:309-18.
100. **Rao** V, Gordon C. Advances in the assessment of lupus disease activity and damage. Curr Opin Rheumatol 2014;26:510-9.
101. NHS England. Interim Clinical Commissioning Policy Statement: rituximab for the treatment of systemic lupus erythematosus in adults (reference NHS England A13/ PS/a).
102. **Yee** CS, Farewell V, Isenberg DA et al. The BILAG-2004 index is sensitive to change for assessment of SLE disease activity. Rheumatology 2009;48:691-5.
103. **Yee** CS, Cresswell L, Farewell V et al. Numerical scoring for the BILAG-2004 index. Rheumatology 2010;49:1665-9.
104. **Gladman** DD, Ibanez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29:288-91.
105. **Buyon** JP, Petri MA, Kim MY et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Ann Intern Med 2005;142(12 Pt 1):953-62.
106. The SELENA-SLEDAI index, (Appendix B). In: Tsokos G, Gordon C, Smolen J, eds. Systemic lupus erythematosus: a companion to rheumatology, 1st edn. Elsevier Science and Technology Journals, 2007: 525.

107. **Gladman** DD, Urowitz MB, Goldsmith CH et al. The reliability of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index in patients with systemic lupus erythematosus. Arthritis Rheum 1997;40:809-13.
108. **Mosca** M, Tani C, Aringer M et al. Development of quality indicators to evaluate the monitoring of SLE patients in routine clinical practice. Autoimmun Rev 2011;10:383-8.
109. **Ruperto** N, Hanrahan LM, Alarcon GS et al. International consensus for a definition of disease flare in lupus. Lupus 2011;20:453-62.
110. **Isenberg** DA, Allen E, Farewell V et al. An assessment of disease flare in patients with systemic lupus erythematosus: a comparison of BILAG 2004 and the flare version of SELENA. Ann Rheum Dis 2011;70:54-9.
111. **Riboldi** P, Gerosa M, Moroni G et al. Anti-DNA antibodies: a diagnostic and prognostic tool for systemic lupus erythematosus? Autoimmunity 2005;38:39-45.
112. **Bertsias** GK, Tektonidou M, Amoura Z et al. Joint European League Against Rheumatism and European Renal AssociationEuropean Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of adult and paediatric lupus nephritis. Ann Rheum Dis 2012;71:1771-82.
113. **van Vollenhoven** RF, Mosca M, Bertsias G et al. Treat-to target in systemic lupus erythematosus: recommendations from an international task force. Ann Rheum Dis 2014;73:958-67.
114. **Ishizaki** J, Saito K, Nawata M et al. Low complements and high titre of anti-Sm antibody as predictors of histopathologically proven silent lupus nephritis without abnormal urinalysis in patients with systemic lupus erythematosus. Rheumatology 2015;54:405-12.
115**. Walz LeBlanc** BA, Gladman DD, Urowitz MB. Serologically active clinically quiescent systemic lupus erythematosus— predictors of clinical flares. J Rheumatol 1994;21:2239-41.
116. **Mok** CC, Ho LY, Leung HW, Wong LG. Performance of anti-C1q, antinucleosome, and anti-dsDNA antibodies for detecting concurrent disease activity of systemic lupus erythematosus. Transl Res 2010;156:320-5.
117. **Danowski** A, de Azevedo MN, de Souza Papi JA, Petri M. Determinants of risk for venous and arterial thrombosis in primary antiphospholipid syndrome and in antiphospholipid syndrome with systemic lupus erythematosus. J Rheumatol 2009;36:1195-9.
118. **Ruiz-Irastorza** G, Cuadrado MJ, Ruiz-Arruza I et al. Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: report of a task force at the 13th International Congress on antiphospholipid antibodies. Lupus 2011;20:206-18.

119. **Pierangeli** SS, de Groot PG, Dlott J et al. 'Criteria' aPL tests: report of a task force and preconference workshop at the 13th International Congress on Antiphospholipid Antibodies, Galveston, Texas, April 2010. Lupus 2011;20:182-90.
120. **Cervera** R, Serrano R, Pons-Estel GJ et al. Morbidity and mortality in the antiphospholipid syndrome during a 10- year period: a multicentre prospective study of 1000 patients. Ann Rheum Dis 2015;74:1011-8.
121. **Vila** LM, Alarcon GS, McGwin G Jr et al. Systemic lupus erythematosus in a multiethnic US cohort, XXXVII: association of lymphopenia with clinical manifestations, serologic abnormalities, disease activity, and damage accrual. Arthritis Rheum 2006;55:799-806.
122. **Zhao** H, Li S, Yang R. Thrombocytopenia in patients with systemic lupus erythematosus: significant in the clinical implication and prognosis. Platelets 2010;21:380-5.
123. **Barnes** EV, Narain S, Naranjo A et al. High sensitivity Creactive protein in systemic lupus erythematosus: relation to disease activity, clinical presentation and implications for cardiovascular risk. Lupus 2005;14:576-82.
124. **O'Neill** SG, Giles I, Lambrianides A et al. Antibodies to apolipoprotein A-I, high-density lipoprotein, and C-reactive protein are associated with disease activity in patients with systemic lupus erythematosus. Arthritis Rheum 2010;62:845-54.
125. **Rezaieyazdi** Z, Sahebari M, Hatef MR et al. Is there any correlation between high sensitive CRP and disease activity in systemic lupus erythematosus? Lupus 2011;20:1494-500.
126. **Vila** LM, Alarcon GS, McGwin G Jr et al. Systemic lupus erythematosus in a multiethnic cohort (LUMINA): XXIX. Elevation of erythrocyte sedimentation rate is associated with disease activity and damage accrual. J Rheumatol 2005;32:2150-5.

144. **Carette** S, Klippel JH, Decker JL, Austin HA, Plotz PH, Steinberg AD, et al. Controlled studies of oral immunosuppressive drugs in lupus nephritis. A long-term follow-up. Ann Intern Med 1983;99:1–8.
145. **Boumpas** DT, Austin HA 3rd, Vaughn EM, Klippel JH, Steinberg AD, Yarboro CH, et al. Controlled trial of pulse methylprednisolone versus two regimens of pulse cyclophosphamide in severe lupus nephritis. Lancet 1992;340:741–5.
146. **Illei** GG, Austin HA, Crane M, Collins L, Gourley MF, Yarboro CH, et al. Combination therapy with pulse cyclophosphamide plus pulse methylprednisolone improves longterm renal outcome without adding toxicity in patients with lupus nephritis. Ann Intern Med 2001;135:248–57.

147. **Levey** AS, Lan SP, Corwin HL, Kasinath BS, Lachin J, Neilson EG, et al. Progression and remission of renal disease in the Lupus Nephritis Collaborative Study. Results of treatment with prednisone and short-term oral cyclophosphamide. Ann Intern Med 1992;116:114–23.

148. **Fraenkel** L, MacKenzie T, Joseph L, Kashgarian M, Hayslett JP, Esdaile JM. Response to treatment as a predictor of longterm outcome in patients with lupus nephritis. J Rheumatol 1994;21:2052–7.

149. **Abu-Shakra** M, Urowitz MB, Gladman DD, Gough J. Mortality studies in systemic lupus erythematosus. Results from a single center. II. Predictor variables for mortality. J Rheumatol 1995;22:1265–70.

150. **Cook** RJ, Gladman DD, Pericak D, Urowitz MB. Prediction of short term mortality in systemic lupus erythematosus with time dependent measures of disease activity. J Rheumatol 2000;27:1892–5.

151. **McLaughlin** JR, Bombardier C, Farewell VT, Gladman DD, Urowitz MB. Kidney biopsy in systemic lupus erythematosus. III. Survival analysis controlling for clinical and laboratory variables. Arthritis Rheum 1994;37:559–67.

152. **Nossent** JC. Course and prognostic value of Systemic Lupus Erythematosus Disease Activity Index in black Caribbean patients. Semin Arthritis Rheum 1993;23:16–21.

153. **Swaak** AJ, van den Brink HG, Smeenk RJ, Manger K, Kalden JR, Tosi S, et al. Systemic lupus erythematosus: clinical features in patients with a disease duration of over 10 years, first evaluation. Rheumatology 1999;38:953–8.

154. **Taccari** E, Sili Scavalli A, Spadaro A, Riccieri V, Trasimeni G, Di Biasi C, et al. Magnetic resonance imaging (MRI) of the brain in SLE: ECLAM and SLEDAI correlations. Clin Exp Rheumatol 1994;12:23–8.

155. **Ibanez** D, Gladman DD, Urowitz MB. Adjusted mean Systemic Lupus Erythematosus Disease Activity Index-2K is a predictor of outcome in SLE. J Rheumatol 2005;32:824–7.

156. **Mosca** M, Bencivelli W, Neri R, Pasquariello A, Batini V, Puccini R, et al. Renal flares in 91 SLE patients with diffuse proliferative glomerulonephritis. Kidney Int 2002;61:1502–9.

157. **Mosca** M, Bencivelli W, Vitali C, Carrai P, Neri R, Bombardieri S. The validity of the ECLAM index for the retrospective evaluation of disease activity in systemic lupus erythematosus. Lupus 2000;9:445–50.

158. **Stoll** T, Stucki G, Malik J, Pyke S, Isenberg DA. Association of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index with measures of disease activity and health status in patients with systemic lupus erythematosus. J Rheumatol 1997;24:309–13.

159. **Stummvoll** GH, Aringer M, Smolen JS, Schmaldienst S, Jimenez-Boj E, Horl WH, et al. IgG immunoadsorption reduces systemic lupus erythematosus activity and proteinuria: a long term observational study. Ann Rheum Dis 2005;64:1015–21.

160. **Barile-Fabris** L, Ariza-Andraca R, Olguin-Ortega L, Jara LJ, Fraga-Mouret A, Miranda-Limon JM, et al. Controlled clinical trial of IV cyclophosphamide versus IV methylprednisolone in severe neurological manifestations in systemic lupus erythematosus. Ann Rheum Dis 2005;64:620–5.

161. **Ong** LM, Hooi LS, Lim TO, Goh BL, Ahmad G, Ghazalli R, et al. Randomized controlled trial of pulse intravenous cyclophosphamide versus mycophenolate mofetil in the induction therapy of proliferative lupus nephritis. Nephrology (Carlton) 2005;10:504–10.

162. **Chan** TM, Li FK, Tang CS, Wong RW, Fang GX, Ji YL, et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. N Engl J Med 2000;343:1156–62.

163. **Mok** CC, Ho CT, Siu YP, Chan KW, Kwan TH, Lau CS, et al. Treatment of diffuse proliferative lupus glomerulonephritis: a comparison of two cyclophosphamide containing regimens. Am J Kidney Dis 2001;38:256–64.

164. **Sinico** RA, Radice A, Ikehata M, Giammarresi G, Corace C, Arrigo G, et al. Anti–C1q autoantibodies in lupus nephritis: prevalence and clinical significance. Ann N Y Acad Sci 2005;1050:193–200.

165. **Linnik** MD, Hu JZ, Heilbrunn KR, Strand V, Hurley FL, Joh T. Relationship between anti-double-stranded DNA antibodies and exacerbation of renal disease in patients with systemic lupus erythematosus. Arthritis Rheum 2005;52:1129–37.

166. **Lim** CS, Chin HJ, Jung YC, Kim YS, Ahn C, Han JS, et al. Prognostic factors of diffuse proliferative lupus nephritis. Clin Nephrol 1999;52:139–47.

167. **Decker** JL, Klippel JH, Plotz PH, Steinberg AD. Cyclophosphamide or azathioprine in lupus glomerulonephritis. A controlled trial: results at 28 months. Ann Intern Med 1975;83:606–15.

168. **Houssiau** FA, Vasconcelos C, D'Cruz D, Sebastiani GD, Garrido Ed Ede R, Danieli MG, et al. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis Trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. Arthritis Rheum 2002;46:2121–31.

NPS involvement recommendations	Year	Country	Indicator identified	Clinical use/significance	Grade of evidence	Strength of Rec	References
European League Against Rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. Mosca M. et al., *Ann Rheum Dis*. 2010 July ; 69(7): 1269–1274.	2010	Europe	Clinical monitoring of neuropsychological symptoms and cognitive impairment		2b	D	32,33
EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. G K Bertsias et al., *Ann Rheum Dis* 2010;69:2074–2082.	2010	Europe	Evaluate if the patient presents: generalized disease activity, previous NPSLE manifestations and aPL positivity.	These are strong risk factors for NPSLE.	2	B	79,127,128,129,130,131,132,133,134,135
			CSF analysis	Primarily to exclude CNS infection (e.g. in case of acute confusional state and mielopathy)	3	D	
			EEG	In case of seizure disorder. In the absence of definite epileptic abnormalities on EEG following recovery from the seizure, withholding of anti-epilectic drug after a single seizure should be considered.	2 3	D D	
			Neuropsychological assessment of cognitive function,	In patients with cognitive impairment.	2	B	
			Electromyography and nerve conduction studies	In case of peripheral neuropathy. To exclude alternative diagnosis.	3	D	
			MRI →recommended protocol (1A): T1/T2, FLAIR, DWI, gadolinium-enhanced T1 sequences	To assesses the degree of brain injury and identify the vascular lesion in case of **CVD**; in patients with history of head trauma or malignancies who present with acute confusional state or fever; in case of unexplained or moderate-to-severe cognitive decline; to identify structural lesions causally related to **seizure** disorder. Contrast-enhanced spinal cord MRI is useful to exclude cord compression and to detect T2-weighted hyperintense lesions and to monitor response to treatment in case of **myelitis**. MRI shows optic nerve enhancement in case of **optic neuritis** (the diagnostic work up for optic neuritis also includes: complete ophthalmological evaluation - including funduscopy and fluoroangiography- and visual evoked potentials.	2 2 3	D D D	

32. **Denburg** SD, Stewart KE, Hart LE, et al. How “soft” are soft neurological signs? The relationship of subjective neuropsychiatric complaints to cognitive function in systemic lupus erythematosus. J Rheumatol 2003;30:1006–1010.
33. **Hanly** JG, Urowitz MB, Sanchez-Guerrero J, et al. Systemic Lupus International Collaborating Clinics. Neuropsychiatric events at the time of diagnosis of systemic lupus erythematosus: an international inception cohort study. Arthritis Rheum 2007;56:265–273.

127. **Mikdashi** J , Handwerger B. Predictors of neuropsychiatric damage in systemic lupus erythematosus: data from the Maryland lupus cohort. Rheumatology (Oxford) 2004; 43 : 1555 – 60.
128. **Tomietto** P, Annese V, D’Agostini S, et al General and specifi c factors associated with severity of cognitive impairment in systemic lupus erythematosus. Arthritis Rheum 2007; 57 : 1461 – 72.
129. **Appenzeller** S, Cendes F, Costallat LT. Epileptic seizures in systemic lupus erythematosus. Neurology 2004; 63 : 1808 – 12.
130. **Buján** S, Ordi-Ros J, Paredes J, et al Contribution of the initial features of systemic lupus erythematosus to the clinical evolution and survival of a cohort of Mediterranean patients. Ann Rheum Dis 2003; 62 : 859 – 65.
131. **Mikdashi** J, Krumholz A, Handwerger B. Factors at diagnosis predict subsequent occurrence of seizures in systemic lupus erythematosus. Neurology 2005; 64 : 2102 – 7.
132. **Sanna** G, Bertolaccini ML, Cuadrado MJ, et al Neuropsychiatric manifestations in systemic lupus erythematosus: prevalence and association with antiphospholipid antibodies. J Rheumatol 2003; 30 : 985 – 92.
133. **Mok** MY, Chan EY, Fong DY, et al Antiphospholipid antibody profi les and their clinical associations in Chinese patients with systemic lupus erythematosus. J Rheumatol 2005; 32 : 622 – 8.
134. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999; 42 : 599 – 608.
135. **González-Duarte** A, Cantú-Brito CG, Ruano-Calderón L, et al Clinical description of seizures in patients with systemic lupus erythematosus. Eur Neurol 2008; 59 : 320 – 3.

APPENDIX 2.1

Integrating patient-reported outcomes, clinical data and quality indicators to physician-driven data in clinical management of chronic rheumatic diseases: the paradigm of Systemic Lupus Erythematosus

Questionnaires for patients

Knowledge, practice, needs and expectations

1. Date of birth (dd/mm/yyyy) |__|__| / |__|__| / |__|__|__|__|

2. Country |__|__|__|__|__|__|__|__|

3. Gender

- ☐ Female
- ☐ Male
- ☐ Other

4. Highest grade or level of education

- ☐ Less than high school diploma
- ☐ High school graduate diploma
- ☐ Bachelors' degree
- ☐ Masters' degree
- ☐ Prefer not to answer

5. Employment status

- ☐ Employed/self-employed
- ☐ Temporarily not employed (non-medical reasons)
- ☐ Temporarily not employed due to SLE
- ☐ Temporarily not employed due to other medical conditions
- ☐ Unemployed (non-medical reasons)
- ☐ Unable to work because of SLE
- ☐ Unable to work because of other medical conditions
- ☐ Homemaker
- ☐ Retired
- ☐ Prefer not to answer

if he/she answers 'Employed' then continue else jump to question 7

6. Your job is

- ☐ Full time
- ☐ Part-time (non-medical reasons)
- ☐ Part-time due to SLE
- ☐ Part-time due to other health conditions
- ☐ Prefer not to answer

7. Marital status

- ☐ Single
- ☐ Married or in a civil or registered partnership
- ☐ Separated/Divorced
- ☐ Widowed
- ☐ Prefer not to answer

8. Living with

- ☐ Alone
- ☐ With family members
- ☐ With others

if he/she answers 'live alone' then he jumps to question 10 otherwise he continues

9. If living with family members/others please provide overall household size (including you) |__|__|

10. Household income

- ☐ Very low
- ☐ Low
- ☐ Medium
- ☐ High
- ☐ Very high
- ☐ Prefer not to answer

11. What is your diagnosis?

- ☐ Systemic Lupus Erythematosus
- ☐ Cutaneous Lupus
- ☐ Undifferentiated Connective Tissue Disease
- ☐ Mixed Connective Tissue Disease
- ☐ Primary Antiphospholipid Syndrome
- ☐ Other, please specify

12. Year of first symptoms /__/__/__/__/

13. Year of diagnosis /__/__/__/__/

14. What is your major organ involvement?

- ☐ Renal
- ☐ Articular
- ☐ Cutaneous
- ☐ Haematological
- ☐ Neuro-psychiatric
- ☐ Serositis
- ☐ Other, please specify

15. Are your family member/friends involved in your medical decisions?

- ☐ Yes

- No

16. Are you member of a patients' association?

- Yes
- No

if he/she answers 'no' then he jumps to question 18 otherwise he continues

17. Please specify the associations

---

18. What is your knowledge about available treatments for SLE?

- Very poor
- Poor
- Fair
- Good
- Very good
- I don't understand the question

19. Do you understand why it is important for you to take prescribed medications?

- Very poor
- Poor
- Fair
- Good
- Very good
- I don't understand the question

20. Do you know what each of your prescribed medications is used for?

- Very poor
- Poor
- Fair
- Good
- Very good
- I don't understand the question

21. What is your knowledge about the side effects of treatments?

- Very poor
- Poor
- Fair
- Good
- Very good

- I don't understand the question

22. Do you know how to manage your disease by yourself?

- Very poor
- Poor
- Fair
- Good
- Very good
- I don't understand the question

23. Do you know practical lifestyle options to cope with SLE?

- Very poor
- Poor
- Fair
- Good
- Very good
- I don't understand the question

24. Do you know your care pathway (treatment plan, periodic visits etc.)?

- Very poor
- Poor
- Fair
- Good
- Very good
- I don't understand the question

25. Do you feel the need to talk with someone with similar experience?

- No need
- Low need
- Moderate need
- High need
- Extreme need

26. Do you feel the need to maintain a relationship with friends?

- No need
- Low need
- Moderate need
- High need
- Extreme need

27. Do you feel the need to improve participation in social activities (i.e. going out with friends, going to the cinema, etc.)?

- No need

- Low need
- Moderate need
- High need
- Extreme need

28. Do you feel the need to have help with physical problems due to SLE?

- No need
- Low need
- Moderate need
- High need
- Extreme need

29. Do you feel the need to have help with emotional problems due to SLE?

- No need
- Low need
- Moderate need
- High need
- Extreme need

30. Do you feel the need to learn how to explain to people what it means to have SLE?

- No need
- Low need
- Moderate need
- High need
- Extreme need

31. Do you feel the need to have assistance for activities of daily life?

- No need
- Low need
- Moderate need
- High need
- Extreme need

32. Do you feel the need to be involved in the decisions about your treatment?

- No need
- Low need
- Moderate need
- High need
- Extreme need

33. Do you feel the need to have or increase coverage for payment of drugs and/or examinations?

- No need
- Low need
- Moderate need
- High need
- Extreme need

34. Are you a woman in childbearing age?

- Yes
- No

if she answers 'no' then he jumps to question 38 otherwise he continues

35. Do you feel the need to have information about treatment before pregnancy?

- No need
- Low need
- Moderate need
- High need
- Extreme need

36. Do you feel/felt the need to find out how to get help with child care?

- No need
- Low need
- Moderate need
- High need
- Extreme need
- Not applicable

37. Would you be interested to share with others how to involve partners in child care?

- No need
- Low need
- Moderate need
- High need
- Extreme need

38. The rheumatologist/physician treats me with respect and dignity

- Strongly disagree
- Disagree
- Neither agree nor disagree
- Agree
- Strongly agree

39. The rheumatologist/physician clearly explains to me my condition

- ☐ Strongly disagree
- ☐ Disagree
- ☐ Neither agree nor disagree
- ☐ Agree
- ☐ Strongly agree

40. The rheumatologist/physician clearly explains to me how to manage my disease

- ☐ Strongly disagree
- ☐ Disagree
- ☐ Neither agree nor disagree
- ☐ Agree
- ☐ Strongly agree

41. The rheumatologist/physician clearly explains to me how to manage my pain

- ☐ Strongly disagree
- ☐ Disagree
- ☐ Neither agree nor disagree
- ☐ Agree
- ☐ Strongly agree

42. The rheumatologist/physician clearly explains to me the side effects of my treatments

- ☐ Strongly disagree
- ☐ Disagree
- ☐ Neither agree nor disagree
- ☐ Agree
- ☐ Strongly agree

43. The rheumatologist/physician clearly explains to me the consequences of not following prescribed treatment or recommended lifestyle

- ☐ Strongly disagree
- ☐ Disagree
- ☐ Neither agree nor disagree
- ☐ Agree
- ☐ Strongly agree

44. The rheumatologist/physician gives me the opportunity to discuss my doubts

- ☐ Strongly disagree
- ☐ Disagree
- ☐ Neither agree nor disagree
- ☐ Agree

- Strongly agree

45. The rheumatologist/physician understands my health related issues

- Strongly disagree
- Disagree
- Neither agree nor disagree
- Agree
- Strongly agree

APPENDIX 2.2

Integrating patient-reported outcomes, clinical data and quality indicators to physician-driven data in clinical management of chronic rheumatic diseases: the paradigm of Systemic Lupus Erythematosus

Questionnaires for patients

Knowledge, practice, needs and expectations related to Information and Communication Technology (ICT) systems

1. Do you usually have access to the Web?

- Yes
- No

If you answer 'no' then you jump to question 6, otherwise you continue.

2. How often do you use the Web for business?

- Daily, several time
- Once a day
- 2-3 times a week
- Once a week
- Once a month
- Less than once a month
- Never

3. How often do you use the Web for private?

- Daily, several time
- Once a day
- 2-3 times a week
- Once a week
- Once a month
- Less than once a month
- Never

4. Where do you usually access the Web?

- Work
- Home
- School/University
- Web café/Library/Friends' house
- Other, please specify

5. Which device do you usually use to access the Web?

- Personal computer
- Tablet
- Smartphone

6. Do you usually access the Web to find information about SLE?

If you answer 'no' then you jump to question 10, otherwise you continue.

- Yes
- No, I don’t believe the Web provide reliable information about SLE
- No, I don’t need other information
- No, other reasons
- No, prefer not to specify reasons

7. Please choose just one of the following options

- The web is my primary source to find information about SLE

- I use both the web and paper or other source of information

8. How often during a week

- <1 hour/week
- 1-5 hours/week
- 6-10 hours/week
- >10 hour/week

9. Why do you use the Web to find information about SLE? (it is possible to choose more than one option)

- To find general information about SLE
- To find information about a disease manifestation and possible complications
- To find information about the effect of drugs
- To find information about available treatments
- To find information about the impact of lifestyle on SLE
- To find explanations about test results/advice from my clinician
- To find patients like me (e.g. in chats, online forums, self-help communities)
- To find help from specialists
- To find available clinical studies (and/or results from) or initiatives (initiative separate)
- To find patient education material
- To find there is a patients' Lupus group close to me
- Other, please specify

10. Do you know or use any of the Apps list below? (please tick which application you know and/or use)

If you answer "I don't use any of the Apps" continue else jump to 14

	Known	Used
The Lupus App	☐	☐
Lupus Disease	☐	☐
Lupus (SLE)	☐	☐
Lupus Support	☐	☐
Voyage Through Lupus	☐	☐
Lupus Symptoms Treatment	☐	☐
We Can Beat Lupus	☐	☐
LupusMinder	☐	☐
Lupus Diary	☐	☐
Lupus Rash Symptoms Treatments	☐	☐
Treating and Curing Lupus	☐	☐
Other, please specify……	☐	☐
Other, please specify……	☐	☐

I don't use any of the Apps above (even known)

11. Why don't you use any Apps for SLE? Please, among statements below choose the answer that apply.

I don’t see any usefulness in them

- ☐ I completely disagree
- ☐ I disagree
- ☐ I'm neither in disagreement nor in agreement
- ☐ I agree
- ☐ I completely agree

I’m not confident about privacy when using Apps

- ☐ I completely disagree
- ☐ I disagree
- ☐ I'm neither in disagreement nor in agreement
- ☐ I agree
- ☐ I completely agree

I don’t like the Apps currently available

- ☐ I completely disagree
- ☐ I disagree
- ☐ I'm neither in disagreement nor in agreement
- ☐ I agree
- ☐ I completely agree

There are no Apps available in my language

- ☐ I completely disagree
- ☐ I disagree
- ☐ I'm neither in disagreement nor in agreement
- ☐ I agree
- ☐ I completely agree

Other reason, please explain

- ☐ I completely disagree
- ☐ I disagree
- ☐ I'm neither in disagreement nor in agreement
- ☐ I agree
- ☐ I completely agree

12. Are there any factors that would drive the use of Apps for SLE?

- ☐ No other features

Explain desired feature that will let You use the App

……

……

……

……

13. Please check the more important reasons for using Apps

- ☐ To find general information about SLE
- ☐ To find information about a disease manifestation and possible complications
- ☐ To find information about the effects of drugs
- ☐ To find information about available treatments
- ☐ To find information about the impact of a lifestyle on SLE
- ☐ To find explanations about test results/advice of my clinician
- ☐ To find patients like me (e.g. in chats, online forums, self-help communities)
- ☐ To find help from specialists
- ☐ To find available clinical studies (and/or results from) or initiatives
- ☐ To find patient's education material
- ☐ To find a patients' Lupus group close to me
- ☐ Other, please specify

14. Please, rate your experience (with Apps) with respect to ENGAGEMENT (a quality of user experience, the ability of the user to attend and become involved in the experience)

The Lupus App

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Disease

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus (SLE)

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Support

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Voyage Through Lupus

- ☐ Very poor
- ☐ Poor

- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Symptoms Treatment

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

We Can Beat Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

LupusMinder

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Diary

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Rash Symptoms Treatments

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Treating and Curing Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

15. Please rate your experience (with Apps) with respect to FUNCTIONALITY (ON-LINE)

The Lupus App

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Disease

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus (SLE)

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Support

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Voyage Through Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Symptoms Treatment

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

We Can Beat Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good

- ☐ Very good

LupusMinder

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Diary

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Rash Symptoms Treatments

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Treating and Curing Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

16. Please, rate your experience (with Apps) with respect to FUNCTIONALITY (OFF-LINE)

The Lupus App

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Disease

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus (SLE)

- ☐ Very poor
- ☐ Poor

- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Support

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Voyage Through Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Symptoms Treatment

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

We Can Beat Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

LupusMinder

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Diary

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Rash Symptoms Treatments

- ☐ Very poor

- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Treating and Curing Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

17. Please, rate your experience (with Apps) with respect to AESTHETIC/VISUAL IMAGERY

The Lupus App

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Disease

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus (SLE)

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Support

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Voyage Through Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Symptoms Treatment

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

We Can Beat Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

LupusMinder

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Diary

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Rash Symptoms Treatments

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Treating and Curing Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

18. Please, rate your experience (with Apps) with respect to INFORMATION OBTAINED from the App

The Lupus App

- ☐ Very poor

- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Disease

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus (SLE)

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Support

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Voyage Through Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Symptoms Treatment

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

We Can Beat Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

LupusMinder

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Diary

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Rash Symptoms Treatments

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Treating and Curing Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

19. Please, rate your experience (with Apps) with respect to COST

The Lupus App

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Disease

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus (SLE)

- ☐ Very poor
- ☐ Poor
- ☐ Fair

- ☐ Good
- ☐ Very good

Lupus Support

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Voyage Through Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Symptoms Treatment

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

We Can Beat Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

LupusMinder

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Diary

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Rash Symptoms Treatments

- ☐ Very poor
- ☐ Poor

- ☐ Fair
- ☐ Good
- ☐ Very good

Treating and Curing Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

20. Please, rate your experience (with Apps) with respect to EASY OF USE

The Lupus App

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Disease

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus (SLE)

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Support

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Voyage Through Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Symptoms Treatment

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

We Can Beat Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

LupusMinder

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Diary

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Rash Symptoms Treatments

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Treating and Curing Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

21. What is your overall SATISFACTION with the App/s you usually use?

The Lupus App

- ☐ Very poor
- ☐ Poor

- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Disease

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus (SLE)

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Support

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Voyage Through Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Symptoms Treatment

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

We Can Beat Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

LupusMinder

- ☐ Very poor

- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Diary

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Lupus Rash Symptoms Treatments

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

Treating and Curing Lupus

- ☐ Very poor
- ☐ Poor
- ☐ Fair
- ☐ Good
- ☐ Very good

22. Would you recommend the Apps you usually use?

- ☐ The Lupus App
- ☐ Lupus Disease
- ☐ Lupus (SLE)
- ☐ Lupus Support
- ☐ Voyage Through Lupus
- ☐ Lupus Symptoms Treatment
- ☐ We Can Beat Lupus
- ☐ LupusMinder
- ☐ Lupus Diary
- ☐ Lupus Rash Symptoms Treatments
- ☐ Treating and Curing Lupus
- ☐ Other, please specify
- ☐ Other, please specify
- ☐ None of these

23. If you were able to provide recommendations/feedback for improving these Apps which suggestions would you give to developers?

- ☐ No suggestion

Please provide suggestions or leave blank

……

……

……

APPENDIX 2.3

Integrating patient-reported outcomes, clinical data and quality indicators to physician-driven data in clinical management of chronic rheumatic diseases: the paradigm of Systemic Lupus Erythematosus

Questionnaires for physicians

Socio-demographic and clinical section

Physician code: /__/__/__/__/__/__/__/__/

1. ***Country*** /__/__/__/__/__/__/__/__/

2. **Gender**

   □ Female □ Male

3. **Age (years)**

   □≤ 30 □ 31-40 □ 41-50 □ 51-60 □ 61-70 □ >70

4. **How many years have you been licensed as a physician?**

   □0-5 □ 6-10 □ 11-15 □ 16-25 □ >25

5. **How many years have you been licensed as a rheumatologist?**

   □0-5 □ 6-10 □ 11-15 □ 16-25 □ >25

6. **How many years have you been treating patients with SLE?**

   □0-5 □ 6-10 □ 11-15 □ 16-25 □ >25

7. **Approximately how many individual patients with SLE do you personally treat each year?**

   □0-30 □ 31-60 □ 61-90 □ >90

8. **Are you a representative of a regional of national reference centre for SLE?**

   □ No □ Yes

A. Physician assessment

I. Global assessment

1. **How often do you use at least one of the disease activity indices (SLEDAI, ECLAM, BILAG, SLAM) to monitor disease activity in your SLE patients?**

- ☐ At each visit
- ☐ Every three/six months
- ☐ Not regularly
- ☐ Only in case of flare

2. **Do you use, at least once a year, SLICC-damage index to assess and monitor organ damage accrual in your SLE patients?**

- ☐ No
- ☐ Yes

3. **Do you assess, at each visit, complement levels and anti-dsDNA antibodies as serological parameters to monitor disease activity in your SLE patients?**

- ☐ No
- ☐ Yes, always in presence of renal involvement
- ☐ In selected cases

4. **Do you assess, at each visit, ESR and/or CRP to monitor disease activity in your SLE patients?**

- ☐ No
- ☐ Yes, both of them
- ☐ Yes, only ESR
- ☐ Yes, only CRP

5. **Do you use, at each visit, anti-C1q antibodies to monitor disease activity in your SLE patients?**

- ☐ No
- ☐ Yes
- ☐ Only, in selected cases

6. **In your clinical practice, do you assess ENA as diagnostic and prognostic parameters in SLE patients?**

- ☐ No

- ☐ Yes
- ☐ Only, in selected cases

7. In your clinical practice, do you assess aPL antibodies as diagnostic and prognostic parameters in SLE patients?

- ☐ No
- ☐ Yes
- ☐ In selected cases, but always in presence of renal involvement

8. Please rate the utility of the above mentioned indicators in your clinical practice to monitor your patients AT FIRST VISIT.

	Not at all useful	Of little use	Somewhat useful	Useful	Very useful
Activity index					
SLICC-DI					
ESR and CRP					
Anti-dsDNA,					
C3 and C4					
Anti-C1q					
ENA					
aPL					

9. Please rate the utility of the above mentioned indicators in your clinical practice to monitor your patients during FOLLOW UP ASSESSMENT.

	Not at all useful	Of little use	Somewhat useful	Useful	Very useful
Activity index					
SLICC-DI					
ESR and CRP					
Anti-dsDNA,					
C3 and C4					
Anti-C1q					
ENA					
aPL					

II. Renal involvement/assessment

1. Do you perform or order renal biopsy in your SLE patients with a suspected renal involvement?

- ☐ No
- ☐ Yes
- ☐ Not routinely, only in selected cases

2. **Do you monitor renal function (serum creatinine and/or eGFR), at each visit, in your SLE patients with renal involvement?**

- ☐ No
- ☐ Yes

3. **Do you use proteinuria/24h or uPCr, at each visit, to monitor disease activity in your SLE patients (with renal involvement)?**

- ☐ No
- ☐ Yes

4. **Do you use urinary sediment, at each visit, to monitor disease activity in your SLE patients (with renal involvement)?**

- ☐ No
- ☐ Yes

5. **In your clinical practice, do you assess dyslipidemia in SLE patients with renal involvement at least once a year?**

- ☐ No
- ☐ Yes
- ☐ Not routinely, only in selected cases

6. **Please rate the utility of the above mentioned indicators in your clinical practice for monitoring lupus nephritis:**

	Not at all useful	**Of little use**	**Somewhat useful**	**Useful**	**Very useful**
Renal biopsy					
Serum creatinine and/or eGFR					
24h proteinuria or uPCR					
Urinary sediment					
C3 and C4, anti-dsDNA					
CBC					
aPL					
Lipids					

7. **Please rate your agreement with the following statements**:

	I completely disagree	**I disagree**	**I'm neither in disagreement nor in agreement**	**I agree**	**I completely agree**
SLICC-DI has a prognostic value for SLE patients					

Blood pressure has a prognostic value in all SLE patients					

8. Please rate your agreement with the statements in SLE patients with renal involvement:

Renal biopsy is useful for my therapeutic decision					
Renal function has a prognostic value					
Proteinuria/24h (or uPCr) has a prognostic value					
Blood pressure has a prognostic value					
aPL positivity has a prognostic value					
Dyslipidemia has a prognostic value					

III. Skin involvement/assessment

1. Do you perform or order a skin biopsy in a SLE patient with suspected cutaneous involvement?

- ☐ No
- ☐ Yes
- ☐ Not routinely, only in selected cases

2. Do you use, at each visit, CLASI to monitor disease activity and damage in your SLE patients with cutaneous involvement?

- ☐ No
- ☐ Yes
- ☐ Not routinely, only in selected cases

3. Please rate the utility of the above mentioned indicators in your clinical practice in monitoring SLE patients:

	Not at all useful	**Of little use**	**Somewhat useful**	**Useful**	**Very useful**
Skin biopsy					
CLASI					

IV. Neuropsychiatric involvement/assessement

1. **Do you perform MRI to diagnose neuropsychiatric involvement in your SLE patients?**

- No
- Yes
- Not routinely, only in selected cases

2. **Do you order EEG in your SLE patients, presenting with seizures, to diagnose neuropsychiatric involvement?**

- No
- Yes
- Not routinely, only in selected cases

3. **Do you perform, at each visit, neuropsychological assessments of cognitive function in your SLE patients with neuropsychiatric involvement?**

- No
- Yes, with neuropsychological tests
- Yes, just asking to the patient

4. **Do you assess aPL antibodies in your SLE patients at the onset of neuropsychiatric manifestations?**

- No
- Yes
- In selected cases

5. **Do you order CSF analysis, for differential diagnosis, in your SLE patients with a suspected neuropsychiatric involvement?**

- No
- Yes
- Only, in selected cases

6. Do you perform electromyography and nerve conduction studies in your SLE patients to diagnose peripheral nervous system involvement?

- No
- Yes
- Not routinely, only in selected cases

7. Please rate the utility of the above mentioned indicators in your clinical practice to explore clinical suspect neuropsychiatric involvement:

	Not at all useful	Of little use	Somewhat useful	Useful	Very useful
Brain MRI					
EEG					
Neuropsychological tests					
EMG and nerve conduction studies					
Disease activity indices					
aPL					
CSF analysis					

V. Cardiovascular risk assessment

1. Do you assess cardiovascular risk factors (dyslipidemia, glucose, blood pressure, BMI, smoking, lifestyle) in your SLE patients, at least once a year?

- ☐ No
- ☐ Yes, routinely
- ☐ Not routinely, only in selected cases

VI. Osteoporosis

1. Do you use 25(OH)-vitamine D level to screen all your SLE patients for vitD deficiency?

- ☐ No
- ☐ Yes

2. Do you use BMD assessment to screen and monitor your SLE patients for osteoporosis?

- ☐ No
- ☐ Yes, in all patients
- ☐ Only, in selected cases

3. Do you use FRAX score to estimate fracture risk in your SLE patients?

- ☐ No
- ☐ Yes
- ☐ In selected cases

4. Please rate the utility of FRAX to estimate the fracture risk in your clinical practice:

	Not at all useful	Of little use	Somewhat useful	Useful	Very useful
FRAX					

5. **Do you perform spine X-ray to assess vertebral fractures in your SLE patients?**

- ☐ No
- ☐ Yes, routinely
- ☐ Not routinely, only in selected cases

VII Infections

1. **Please rate the utility of the following parameters to assess infectious risk in your SLE patients:**

	Not at all useful	Of little use	Somewhat useful	Useful	Very useful
Neutrophils count					
Lymphocytes count					
IgG levels					

B. Quality indicators

1. **Do you educate all your SLE patients about sun avoidance?**

   - ☐ No
   - ☐ Yes, all patients
   - ☐ Only in selected cases

2. **Do you prescribe or suggest recommended vaccinations (e.g. influenza and pneumococcal vaccinations) to all your SLE patients on immunosuppressive therapy?**

   - ☐ No
   - ☐ Yes to all patients
   - ☐ Only in selected cases

3. **Do you prescribe anti-resorptive or anabolic treatment for osteoporosis to all your SLE patients under steroid therapy?**

   - ☐ No
   - ☐ Yes
   - ☐ In selected cases

4. **Do you screen all your SLE patients for HBV, HCV and tuberculosis before high doses corticosteroids and/or immunosuppressive therapy?**

   - ☐ No
   - ☐ Yes
   - ☐ Only in selected cases

5. **Do you recommend ophthalmologic evaluation, at least once a year, in all your SLE patients treated with Hydroxychloroquine?**

   - ☐ Yes, before or right after treatment initiation
   - ☐ Yes, after 5 years of therapy
   - ☐ No

6. **Do you recommend ophthalmologic evaluation in your SLE patients treated with glucocorticoids?**

   - ☐ No
   - ☐ Yes

- Only in selected cases

7. Please rate to what extent you think that sharing with the patient the diagnostic and therapeutic strategy is useful:

	Not at all useful	**Of little use**	**Somewhat useful**	**Useful**	**Very useful**
Sharing diagnostic & therapeutic choices					

C. Pregnancy

1. **Do you usually counsel your SLE patients before pregnancy?**

   - No
   - Yes, routinely in all patient in childbearing age
   - Only, in case of patient's request

2. **Do you check anti-SSA/SSB antibodies, before pregnancy, to perform risk stratification in the preconception counseling in all your SLE patients?**

   - No
   - Yes

3. **Do you check aPL antibodies, before pregnancy, to perform risk stratification in the preconception counseling in all your SLE patients?**

   - No
   - Yes

4. **Do you use low dose aspirin and heparin during subsequent pregnancies, if the patient has already had pregnancy complications as a result of the anti-phospholipid antibodies syndrome in your SLE patients?**

   - No
   - Yes
   - In selected cases

5. **Do you usually cooperate with a specialized gynecologist to perform supplementary fetal surveillance with Doppler ultrasonography and biometric parameters (placental insufficiency and small for gestational age fetuses) during pregnancy in your SLE patients during pregnancy?**

   - No
   - Yes, for all patients
   - Only, in selected cases

6. **In your clinical practice, do you cooperate with a specialized gynecologist to perform fetal echocardiography in patients with positive anti-Ro/SSA and/or anti-La/SSB antibodies for the diagnosis of CHB?**

   - No
   - Yes, for all SSA/SSB+ patients
   - Only, in selected cases

D. Needs and expectations

I. General needs

How do you rate the importance of the following unmet needs for the care of your lupus patients?

1. **Discussions and/or exchange of experiences with other SLE experts or opinion leaders regarding difficult cases**

- ☐ Not at all important
- ☐ Not very important
- ☐ Somewhat important
- ☐ Important
- ☐ Very important

2. **Improvement of the provision and utilization of second opinions through national and international reference centres?**

- ☐ Not at all important
- ☐ Not very important
- ☐ Somewhat important
- ☐ Important
- ☐ Very important

3. **Enhanced national or regional networking with Lupus-experienced specialists from <u>OTHER disciplines</u> (e.g. gynaecology, neurology)**

- ☐ Not at all important
- ☐ Not very important
- ☐ Somewhat important
- ☐ Important
- ☐ Very important

4. **Comparison of own patient management with aggregated data on the diagnostic and therapeutic procedures on well-defined cases (benchmarking)**

- ☐ Not at all important
- ☐ Not very important
- ☐ Somewhat important
- ☐ Important
- ☐ Very important

5. **Standardized documentation (e.g. laboratory findings, symptoms, pre-existing conditions, medication) also for referral purposes**

- ☐ Not at all important
- ☐ Not very important
- ☐ Somewhat important
- ☐ Important
- ☐ Very important

6. **Individualized recommendations or guidelines for the use of specific drugs based upon clinical manifestations, disease severity, and comorbidities**

- ☐ Not at all important
- ☐ Not very important
- ☐ Somewhat important
- ☐ Important
- ☐ Very important

7. **Enhanced methods (e.g. lab values, scoring systems) for physician-based assessments of disease activity or flares**

- ☐ Not at all important
- ☐ Not very important
- ☐ Somewhat important
- ☐ Important
- ☐ Very important

8. **Improved methods (e.g. by PROMS) for patient-based assessment of disease activity or flares**

- ☐ Not at all important
- ☐ Not very important
- ☐ Somewhat important
- ☐ Important
- ☐ Very important

9. **Possibility to delegate basic tasks for monitoring the disease and its treatment <u>to the general practitioner</u>:**

- ☐ Not at all important
- ☐ Not very important
- ☐ Somewhat important
- ☐ Important
- ☐ Very important

<u>to a trained nurse</u>:

- ☐ Not at all important
- ☐ Not very important
- ☐ Somewhat important
- ☐ Important
- ☐ Very important

<u>to the patient or their informal carers</u>:

- ☐ Not at all important
- ☐ Not very important
- ☐ Somewhat important
- ☐ Important
- ☐ Very important

10. What other unmet general needs can you identify when looking after your patients?

a. _____
b. _____
c. _____
d. _____
e. _____

II. Needs concerning physician-patient relationship

How do you assess the importance of the following information/strategies in the care of lupus patients compared to other disease?

1. Physician's knowledge of patient's social activities and participation

- ☐ Not at all important
- ☐ Not very important
- ☐ Somewhat important
- ☐ Important
- ☐ Very important

2. Physician's knowledge of patient's family conditions and social support

- ☐ Not at all important
- ☐ Not very important
- ☐ Somewhat important
- ☐ Important
- ☐ Very important

3. Physician's knowledge of patient's education level

- ☐ Not at all important
- ☐ Not very important
- ☐ Somewhat important
- ☐ Important
- ☐ Very important

4. Physician's knowledge of patient's knowledge, beliefs and perception of his lupus disease

- ☐ Not at all important
- ☐ Not very important
- ☐ Somewhat important
- ☐ Important
- ☐ Very important

5. Physician's knowledge of patient's future plans (incl. family planning)

- ☐ Not at all important
- ☐ Not very important
- ☐ Somewhat important
- ☐ Important
- ☐ Very important

6. Better informed patients to encourage shared decision making

- ☐ Not at all important
- ☐ Not very important
- ☐ Somewhat important
- ☐ Important
- ☐ Very important

7. Involvement of relatives, informal carers, or other patient representatives to simplify the shared decision making process

- ☐ Not at all important
- ☐ Not very important
- ☐ Somewhat important
- ☐ Important
- ☐ Very important

8. What other unmet needs for the physician-patient relationship in care of your lupus patients can you identify?

a. _____
b. _____
c. _____
d. _____

e. _____

III. Expectations

To what extent do you agree with the following potential expectations for the long-term care of lupus patients?

1. **I expect high level of shared decision making and self-determination by SLE patients**
   - ☐ I completely disagree
   - ☐ I disagree
   - ☐ I'm neither in disagreement nor in agreement
   - ☐ I agree
   - ☐ I completely agree

2. **Patients should comply with agreed treatment strategies**
   - ☐ I completely disagree
   - ☐ I disagree
   - ☐ I'm neither in disagreement nor in agreement
   - ☐ I agree
   - ☐ I completely agree

3. **Patients should adhere to their medication**
   - ☐ I completely disagree
   - ☐ I disagree
   - ☐ I'm neither in disagreement nor in agreement
   - ☐ I agree
   - ☐ I completely agree

4. **Patient is able to recognise and communicate a lupus flare on her/his own**
   - ☐ I completely disagree
   - ☐ I disagree
   - ☐ I'm neither in disagreement nor in agreement
   - ☐ I agree
   - ☐ I completely agree

5. **Comprehensive care in relation to problems not directly related to lupus (e.g. treatment of comorbidities, vaccinations) is provided by the general practitioner**
   - ☐ I completely disagree
   - ☐ I disagree
   - ☐ I'm neither in disagreement nor in agreement
   - ☐ I agree
   - ☐ I completely agree

6. **My lupus patient recognises me as the primary contact for all health problems**
   - ☐ I completely disagree
   - ☐ I disagree
   - ☐ I'm neither in disagreement nor in agreement
   - ☐ I agree
   - ☐ I completely agree

7. **My lupus patient informs me comprehensively about all health-relevant events (incl. comorbidities, concomitant medications, social security events)**
   - ☐ I completely disagree
   - ☐ I disagree
   - ☐ I'm neither in disagreement nor in agreement
   - ☐ I agree
   - ☐ I completely agree

8. **Patients acknowledge me because of my knowledge and effort**
   - ☐ I completely disagree
   - ☐ I disagree
   - ☐ I'm neither in disagreement nor in agreement
   - ☐ I agree
   - ☐ I completely agree

9. **Referring physicians acknowledge me because of my knowledge**
   - ☐ I completely disagree
   - ☐ I disagree
   - ☐ I'm neither in disagreement nor in agreement
   - ☐ I agree
   - ☐ I completely agree

10. **Society acknowledges me for my contribution to health care**
    - ☐ I completely disagree
    - ☐ I disagree
    - ☐ I'm neither in disagreement nor in agreement
    - ☐ I agree
    - ☐ I completely agree

11. **What other expectations do you have for the long-term care of lupus patients?**
    - **a.** _____
    - **b.** _____
    - **c.** _____
    - **d.** _____

e. _____

E. Patient Reported Outcome Measures (PROMS)

I. Global assessment

1. How would you rate your overall experience regarding the following potential patient-reported outcome domains for the care of SLE patients?

	Experience…				
	Very poor	Poor	Fair	Good	Very good
Adherence					
Anxiety					
Body Image / Self Image					
Depression					
Disease activity					
Disease damage					
Exercise, Physical Activity					
Fatigue					
(Health-related) Quality of Life					
Sexual functioning					
Sleep disorders					
Social support / participation					
Uncertainty / Lupus education					
Work productivity / Occupational problems					

2. How do you rate the importance of patient-reported outcome domains for the care of SLE patients?

	Important…				
	Not at all important	Not very important	Somewhat important	Important	Very important
Adherence					
Anxiety					
Body Image / Self Image					
Depression					
Disease activity					
Disease damage					
Exercise, Physical Activity					
Fatigue					
(Health-related) Quality of Life					
Sexual functioning					
Sleep disorders					
Social support / participation					

Uncertainty / Lupus education					
Work productivity / Occupational problems					

II. Routine care

1. Do you use patient reported outcome measures (PROs, PROMS) to monitor disease outcome in your SLE patients in routine care?

- ☐ No (go to section "Constraints")
- ☐ Yes (continue with question 2)

2. a. Do you use patient reported outcome measures (PROs, PROMS) to assess (health-related) quality of life in your SLE patients?

- ☐ Yes
- ☐ No

  Why do you refrain from using (health-related) quality of life PROs/PROMs in your patients? (Please select all that apply)

  - ☐ Lack of time
  - ☐ Not of interest to me
  - ☐ No use for my decision making
  - ☐ Lack of specific treatment options
  - ☐ Lack of validated questionnaires (esp. linguistically)
  - ☐ Other, (please specify) _____

b. Which (health-related) quality of life questionnaire do you use in your SLE patients and how frequently?

		Never	Once	Occasionally	Regularly	Each visit
European Quality of Life – 5D	EQ-5D					
Health Assessment Questionnaire	HAQ					
Lupus Impact Tracker	LIT					
Lupus Patient-Reported Outcome tool	LupusPRO					
Lupus quality of life	LupusQoL					
Medical Outcomes Study Short Form 12-Item	SF-12					
Medical Outcomes Study Short Form 36-Item	SF-36					
Modified Health Assessment Questionnaire	MHAQ					
Multidimensional Health Assessment Questionnaire	MD-HAQ					

Patient Reported Outcomes Measurement Information System - instruments	PROMIS					
Simple Measure of Impact of Illness in Youngsters	SMILEY					
SLE quality of life questionnaire	L-QoL					
Systemic Lupus Erythematosus Questionnaire on Family Role Functioning	SLE-FAMILY					
Systemic Lupus Erythematosus-Specific Quality of Life	SLEQOL					
Other (please specify) _____						

c. What is your <u>main reason</u> for assessing (<u>health-related) quality of life</u> in your SLE patients?

- ☐ Clinical decision making
- ☐ Scientific interest
- ☐ Quality assurance / Compliance with guidelines
- ☐ Requirement for administrative and billing reasons
- ☐ Other reason, (please specify) _____

3. a. Do you use <u>patient reported outcome measures</u> (PROs, PROMS) to monitor <u>fatigue</u> in your SLE patients in routine care?

- ☐ Yes
- ☐ No

Why do you refrain from questioning your patients about fatigue? (Please select all that apply)

- ☐ Lack of time
- ☐ Not of interest to me
- ☐ No use for my decision making
- ☐ Lack of specific treatment options
- ☐ Lack of validated questionnaires (esp. linguistically)
- ☐ Other, (please specify) _____

b. Which <u>fatigue</u> questionnaire do you use in your SLE patients and how frequently?

		Never	Once	Occasionally	Regularly	Each visit
Fatigue Severity Scale	FSS					
Functional Assessment Chronic Illness Therapy – Fatigue	FACIT					
Multidimensional Assessment of Fatigue	MAF					
Multidimensional Fatigue Inventory	MFI					
Other (please specify) _____						

c. What are your <u>main reason</u> for assessing <u>fatigue</u> in your SLE patients?

- ☐ Clinical decision making
- ☐ Scientific interest
- ☐ Quality assurance / Compliance with guidelines
- ☐ Requirement for the administrative and billing reasons
- ☐ Other reasons, (please specify) _____

4. a. For which other domains of disease outcome do you use <u>patient reported measures</u> to monitor your SLE patients in routine care?

	Never	Once	Occasionally	Regularly	Each visit
Adherence					
Anxiety					
Body Image / Self Image					
Depression					
Exercise, Physical Activity					
Disease activity					
Disease damage					
Sexual functioning					
Sleep disorders					
Social support/participation					
Uncertainty / Lupus education					
Work productivity / Occupational problems					
Other (please specify) _____					
Other (please specify) _____					
Other (please specify) _____					

b. Please name the specific PRO/PROM you use for the assessment of the selected domains

Adherence	
Anxiety	
Body Image/Self Image	
Depression	
Exercise, Physical Activity	
Disease activity	
Disease damage	
Sexual functioning	
Sleep disorders	
Social support	
Uncertainty / Lupus education	
Work productivity / Occupational problems	

Other (please specify) _____	
Other (please specify) _____	
Other (please specify) _____	

c. What are your <u>main reason</u> for assessing the selected patient-reported measure in your SLE patients?

	Clinical decision making	Scientific interest/Research purpose	Quality assurance / Guidelines	Administrative and billing reasons	Do not know
Adherence					
Anxiety					
Body Image / Self Image					
Depression					
Exercise, Physical Activity					
Disease activity					
Disease damage					
Sexual functioning					
Sleep disorders					
Social support					
Uncertainty / Lupus education					
Work productivity / Occupational problems					
Other (please specify) _____					
Other (please specify) _____					
Other (please specify) _____					

5. a. Do you assess other patient characteristics for medical treatment and care in your SLE patients?

	Never	**Once**	**Occasionally**	**Regularly**	**Each visit**
Education level					
Ethnicity					
Self-responsibility / Autonomy					
Socioeconomic factors (income, residence…)					
Other (please specify) _____					

Other (please specify) _____					
Other (please specify) _____					

b. What are your <u>main reason</u> for assessing the selected patient (reported) characteristics in your SLE patients?

	Clinical decision making	Scientific interest/Research	Quality assurance / Guidelines	Administrative and billing reasons	Do not know
Education level					
Ethnicity					
Self-responsibility / Autonomy					
Socioeconomic factors (income, residence…)					
Other (please specify) _____					
Other (please specify) _____					
Other (please specify) _____					

III. Constraints

1. What are the constraints that prevent you from using <u>patient reported outcome measures</u> (PROs, PROMS)? (please select all that apply)

- ☐ Lack of time
- ☐ Not of interest to me
- ☐ No use for my decision making
- ☐ Lack of validated questionnaires
- ☐ Lack of linguistically validated questionnaires
- ☐ Poor credibility of the results
- ☐ Discordance with my assessment / impression
- ☐ Other, (please specify) _____