

OUTCOME MEASURES FOR CHILDHOOD-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS (cSLE).

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Non-Standard Abbreviations:

BILAG	British Isles Lupus Activity Group Index
CRVs	Core response variables
RIFLE	Response Index for Lupus Erythematosus
cSLE	Childhood-onset Systemic Lupus Erythematosus
ECLAM	European Consensus Lupus Activity Measurement
SELENA	Safety of Estrogens in Lupus Erythematosus – National Assessment
HRQOL	Health related quality of life
SLAM	Systemic Lupus Activity Measure
MCID	Minimal clinically important differences
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
OMERACT	Outcome Measure in Rheumatology Clinical Trials
SDI	SLE International Collaborating Clinics/ American College of Rheumatology Damage Index

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Introduction.

The goal of health care and medical interventions is to improve patient longevity and health. The classic outcome measure to verify the effects of medical interventions for chronic diseases is patient survival. As patient survival increases, this traditional outcome parameter of medical success is too insensitive to assess the effect of medical care. This is also true for children with systemic lupus erythematosus (1, 2). Since the introduction of steroids, and possibly the off-label use of newer medications for childhood-onset SLE (cSLE; also juvenile SLE, jSLE), the 5-year survival rate of children with cSLE has increased from 42% in the 1950s (3) to over 90% in the 1980s(4). Currently, 5-year survival is estimated at 97% (5) and, furthermore, the 10-year survival of children with cSLE is between 85 – 90% (6-10).

Decreases in patient mortality with cSLE necessitate the development of other outcome parameters to verify the response to current therapeutic regimens and test the efficacy of new, less toxic drugs for cSLE. High quality, easy to measure outcome parameters are needed to accurately and effectively capture changes in patient health.

This review summarizes the currently available outcome measures for children with cSLE and provides a brief overview of parameters that should be considered when assessing cSLE patients in daily practice and clinical research.

Children with cSLE are not miniature adults with SLE.

Although children and adults with SLE share many signs and symptoms of disease, they differ in the degree and frequency of clinical findings of disease activity and damage, as well as the treatment approaches used by their physicians (11, 12). Similarly, children remain more often serologically active compared to adults (13). All disease activity measures incorporate laboratory parameters, and some also include medication choices.

Because of the differences in the range of observed disease activity, damage, serologic abnormalities and treatments between cSLE and adult SLE, one cannot a priori assume that the disease measures developed for adults are suitable for cSLE. In addition, pediatric rheumatologists must consider long-term toxicity and the effects of drugs on growth and development in children with cSLE. Therefore, all outcome measures developed for adults have to be examined for their usefulness (measurement properties) in children. Unless specifically mentioned, all definitions and outcome measures presented in the following have only been tested for adults with SLE.

Surrogate & Biological Markers

Recent expert discussions at the National Institute of Health (NIH) and FDA-supported meetings have stressed the necessity of developing highly-responsive, easy to measure SLE outcome parameters to quantify the effects of new and better therapeutic interventions. Certain experts have pointed out that it is important to make a distinction between so-called *surrogate markers* of disease, such as disease activity indices and responder criteria versus true *biomarkers* of SLE, e.g. objectively measurable laboratory markers of the disease process and response to treatment. Currently available biological markers, including ESR, complement levels, and anti-ds-DNA antibody titers are all too insensitive to reliably measure a patient's response to therapy (14). Because this is more than likely due to the lack of suitable surrogate and biologic markers, there are only 3 medications (aspirin, hydroxychloroquine, glucocorticoids) that have ever been fully approved for adult SLE by the U.S. Food and Drug Administration (FDA), while there are none for cSLE.

Core Response Variables for cSLE for use in future definitions of clinical improvement.

While the search for high-quality biomarkers for cSLE continues, the development of *surrogate markers* has to be pursued. In pediatric rheumatology, surrogate markers of disease are often based on a set of *core response variables (CRVs)*. A set of CRVs constitutes a group of disease outcomes that capture all relevant health aspects of a patient with a certain disease. CRVs have been developed for juvenile arthritis and myositis (15, 16). In an international group effort, the Pediatric Rheumatology

International Trial Organization (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG) have developed CRVs for assessing short-term and long-term changes in children with cSLE(17) (**Table 1**).

PRINTO and PRCSG are currently in the process of developing *preliminary criteria for disease improvement or response to therapy for cSLE* based on the set of CRVs described above. The results of a 2nd International Consensus Conference in September 2003 will be published in the near future.

Disease Activity Measures.

Measures of absolute disease activity.

There are more than 50 disease activity measures for adult SLE (18). Likely, the most commonly used measure of absolute disease activity is the *SLE Disease Activity Index (SLEDAI)* (19). This is a concise measure of disease activity with excellent test-retest reliability and high responsiveness to clinically important changes (20, 21). Recently, the SLEDAI 2K has been introduced in order to increase the usefulness of the SLEDAI when performing serial assessments of disease activity (22). Another frequently used and widely validated disease activity instrument is the *Systemic Lupus Activity Measure (SLAM)*(18). Different from the SLEDAI, the SLAM includes not only objective signs and laboratory parameters but also subjective signs of disease. Thus, the SLAM is thought to be preferable to the SLEDAI in capturing patient-relevant disease changes (20). The European Consensus Lupus Activity Measurement (ECLAM) (23, 24) is a measure of absolute disease activity for adult SLE that resembles the SLEDAI, but uses a differential scoring system. The *British Isles Lupus Activity Group Index (BILAG)* (25) is yet another disease activity measure that has been widely validated. This measure is quite comprehensive. Although numeric scores were not intended by the authors initially, several conversion methods are now available to transform the alphabetic BILAG score into a numeric disease activity score (26).

The SLEDAI, SLAM, BILAG and ECLAM have all been validated for use in cSLE(24, 26, 27). No single best disease activity measure for cSLE has been identified. In a clinical setting, the use of the SLEDAI may be preferable because it is concise and easy to complete. For research purposes, the choice of the disease activity measure will largely depend on the research question posed.

The American College of Rheumatology (ACR) organized a consensus building process to determine relevant changes of the scores of disease activity measures for adult SLE (**Table 2**)(28). These criteria have not been officially adopted by the ACR.

Measures of change in disease activity: flare and response to therapy.

There are several measures that aid the interpretation of *changes* in disease activity. Generally, these measures of change in disease activity are less well validated than the SLE measures of absolute disease activity. The *Selena Flare Tool* was developed for the SELENA study (29) to measure flares (**Table 3**). A minor flare is present if at least one of the 5 minor/moderate symptoms is present while a major flare is defined by the presence of at least 1 of the 6 major symptoms in the patient. The SELENA Flare-tool categorizes all patients without flares as being 'unchanged or better'.

Similarly, the *Response Index for Lupus Erythematosus (RIFLE)* has been developed to capture changes of disease activity (30, 31). The RIFLE is a 60–item measure where items are rated on a 5-point Likert scale (not present, present and unchanged, present and worse, partial response, resolution). This measure has not been used in children with cSLE.

Especially for observational studies, disease flares have been defined as the need for significant increases of the doses of corticosteroids and/ or the need for additional or more intensive immunosuppressive medications (26, 32).

Complete Response to Therapy and Remission. The OMERACT group and others have proposed various definitions to describe patients with quiescent disease. Often complete clinical response or remission is defined as the absence of signs or symptoms of active disease (SLEDAI score = '0')(33) for at least 3 months(34). It is unclear whether patients of with complete clinical response or in remission can be treated with drugs including immunosuppressives, or whether they should be off all medications.

Assessments for renal disease of adult SLE. Definitions of *renal flare* have been proposed for SLE trials by the OMERACT group and others. The most commonly used definition has been proposed by Moroni et al.(35) (**Table 4**).

Similarly, *renal improvement* is often defined as, 1) the stabilization of renal

function; 2) absence of casts; 3) decrease of hematuria by $\geq 50\%$ (max < 10 RBC/hpf);and, 4) a decrease of proteinuria by $\geq 50\%$ with a maximum absolute daily proteinuria of 3 gram or 1 gram in patients who presented with or without nephrotic syndrome, respectively (36).

There are several published definitions of *renal remission*. Often renal remission is defined as: 1) the stabilization or improvement in renal function; 2) the resolution of urine sediment abnormalities; 3) the absence of red blood cells and casts in the urinary sediment, and, 4) proteinuria < 1 gram/ day for at least 6 months, but preferably up to 3 years (36). Clarification is still required as to whether patients in renal remission can be maintained on immunosuppressives, ACE inhibitors or related drugs. Another issue to be clarified is whether concomitant complement levels should be within normal limits.

Health-related Quality of Life.

The Medical Outcomes Survey Short-form 36 (SF36)(37) or the SF20 are often used for adults with SLE(38). These questionnaires can be used for patients ages 16 years and older. HRQOL of children younger than 16 years of age has been measured by the PedsQL Inventory (39, 40) and the Child Health Questionnaire (17, 41, 42). It remains to be determined whether these tools adequately capture all of the relevant health domains of children with cSLE.

Disease Damage.

The Systemic Lupus Erythematosus SLE International Collaborating Clinics/ American College of Rheumatology Damage Index (SDI) is currently the only available measure of disease damage for both adults and children with SLE (43, 44). The SDI includes disease-specific and non-disease-specific damage occurring after the diagnosis with SLE. To be considered in the SDI, an SDI item has to be present for at least 6 continuous months since the diagnosis with SLE or cSLE. Damage scored by the SDI is grouped into 12 different domains (ocular, neuropsychiatric, renal, pulmonary, cardiovascular, peripheral vascular, gastrointestinal, musculoskeletal, skin, premature gonadal failure, diabetes mellitus, and malignancy). SDI scores correlate survival with disease activity over time (31, 45, 46). However, the use of SDI domain scores, rather than the overall SDI summary score, may be preferable in statistical analyses (47).

Summary.

Important advantages have been made to measure the level of health and the degree of disease activity and damage of children with cSLE. The development of the cSLE CRVs constitutes an important step towards the standardized assessment and reporting of cSLE. Nonetheless, many of the surrogate markers developed for adult SLE have yet to be assessed in cSLE. Additionally, there exists a lack of high-quality measures to evaluate neuropsychiatric involvement with cSLE in clinical practice and research. There is, however, ongoing intensive research in sensitive, specific and responsive SLE biomarkers. In the future, such superior disease markers may make the use of surrogate markers including global assessment, neuropsychiatric testing batteries, and disease indices unnecessary. Nevertheless, in the interim, standardized surrogate markers that capture clinically relevant changes in the patient are essential for improving the medical care of children with cSLE.

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Table 1: Core Set of cSLE Response Variables.

CRVs for short-term changes in health	CRVs for long-term changes in health
<ul style="list-style-type: none"> • Physician global assessment of disease activity • Health Related Quality of Life • Parents or patients global assessment of disease activity • Anti-ds-DNA antibody titer • Protein excretion and serum creatinine • Validated disease activity measure 	<ul style="list-style-type: none"> • Disease damage measure: SDI† • Physician global assessment of disease damage • Growth and development : height, weight, menses, Tanner Sex Maturity Stages • Health Related Quality of Life

† SLE International Collaborating Clinics/ American College of Rheumatology Damage Index

Table 2: Minimal clinically important differences (MCID) in the scores of validated disease activity measures for adult SLE patients

Disease Activity Measure	MCID for improvement	MCID for worsening
BILAG	-7	+8
SLEDAI	-6	+8
ECLAM	-3	+4
SLAM	-7	+6
SELENA-FLARE TOOL	-7	+8
RIFLE	-4	+3

Table 3: Selena Flare Tool

NO CHANGE OR BETTER	MILD TO MODERATE FLARE	SEVERE FLARE
<ol style="list-style-type: none"> 1. Change in SLEDAI‡ scores: increase of decrease by ≤ 2 2. Symptoms (improved or none) 3. Prednisone dose: decrease or unchanged 4. Additional medications: none 5. PGA†: decrease in PGA or < 1.0 	<ol style="list-style-type: none"> 1. Change in SLEDAI scores: increase by ≥ 3 but not > 12 2. Symptoms: new or worsening of <i>mild to moderate symptoms</i> (see table below) 3. Prednisone dose: increase but not > 0.5 mg/kg/day 4. Additional medications: added NSAID or hydroxychloroquine for disease activity 5. PGA: increase in PGA to ≥ 1.0 and ≤ 2.5 	<ol style="list-style-type: none"> 1. Change in SLEDAI scores: increase to > 12 2. Symptoms: new or worsening <i>severe symptoms</i> (see table below) requiring hospitalization or increase in prednisone dose 3. Prednisone dose: > 0.5 mg/kg/day 4. Additional medications: new cyclophosphamide, azathioprine, methotrexate 5. PGA: increase to > 2.5 6. Hospitalization for SLE

MILD TO MODERATE SYMPTOMS	SEVERE SYMPTOMS
<ol style="list-style-type: none"> 1. Rash (discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus) 2. Nasopharyngeal ulcers 3. Pleuritis 4. Pericarditis 5. Arthritis 6. Fever due to SLE 	<ol style="list-style-type: none"> 1. Systemic vasculitis 2. Nephritis 3. Myositis 4. Thrombocytopenia (< 60 0 per μl) 5. Hemolytic anemia (hemoglobin < 7 g/dl or decrease by \leq 3 g/dl)

‡ SLEDAI: Systemic lupus erythematosus disease activity index.

† PGA: physician global assessment of disease activity (scale: 0 – 3)

Table 4: Definition of Renal flares for SLE.

Proteinuric flare	Nephritic Flare
<ul style="list-style-type: none"> ▪ Increase of proteinuria > 2 gram/ day <u>OR</u> doubling of proteinuria from baseline proteinuria > 3.5 gram/day ▪ plus inactive sediment 	<p>MILD</p> <ul style="list-style-type: none"> ▪ Reappearance of cellular casts <u>OR</u> 10 RBCs/hpf ▪ plus <30% increase of serum creatinine <p>MODERATE</p> <ul style="list-style-type: none"> ▪ Reappearance of cellular cast <u>OR</u> ▪ 10 RBCs/hpf ▪ plus <30% increase of serum creatinine ▪ plus increase of proteinuria > 2 gram/ day <p>SEVERE</p> <ul style="list-style-type: none"> ▪ Reappearance of cellular cast <u>OR</u> ▪ 10 RBCs/hpf ▪ plus \geq30% increase of serum creatinine ▪ irrespective of any increase of proteinuria

APPENDIX.

- App 1. SLEDAI
- App 2. SLAM
- App 3. ECLAM
- App 4. BILAG
- App 5. SELENA Flare Tool
- App 6. RIFLE
- App 7. SDI

App. 1: SYSTEMIC LUPUS ERYTHEMATOSUS DISEASE ACTIVITY INDEX

ITEMS PRESENT DURING THE PRECEDING 10 DAYS TO THE VISIT ARE:

Weight	SLEDAI Score	Descriptor	Definition
8	_____	Seizures	Recent <u>onset</u> , exclude metabolic, infectious, or other drug causes.
8	_____	Psychosis	Altered ability to function in normal activity due to severe disturbance in the associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia, and drug causes.
8	_____	Organic Brain Syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuation clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	_____	Visual disturbances	Retinal changes of SLE. Include Cytoid bodies, retinal hemorrhages, serous exudates or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	_____	Cranial nerve disorder	<u>New onset</u> of sensory or motor neuropathy involving cranial nerves.
8	_____	Lupus headaches	Severe, persistent headaches; may be migrainous, but must be non-responsive to narcotics.
8	_____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	_____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	_____	Arthritis	>2 joints with pain and signs of inflammation (i.e. tenderness, swelling, or effusion).
4	_____	Myositis	Proximal muscle aching/ weakness, associated with elevated creatine, phospho kinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	_____	Urinary casts	Heme-granular casts or red cell casts.
4	_____	Hematuria	> 5 red blood cells/ high power field. Exclude stone, infection, or other cause.
4	_____	Proteinuria	> 0.5 gram/24 hours (children: > 30mg/kg/24 hours). New onset or recent increase by > 0.5 gram/24 hours.
4	_____	Pyuria	> 5 white blood cells/ high power field. Exclude infection.

2	_____	New rash	<u>New onset or recurrence</u> of inflammatory type rash.
2	_____	Alopecia	<u>New onset or recurrence</u> of abnormal, patchy, or diffuse loss of hair.
2	_____	Mucosal ulcers	<u>New onset or recurrence</u> of oral or nasal ulcerations.
2	_____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, EKG or ECHO.
2	_____	Low complement	Decrease in CH50, C3, C4, below the lower limit of normal for testing laboratory.
2	_____	Increased DNA binding	> 25% binding by Farr assay or above normal range for testing laboratory.
1	_____	Fever	> 38°C. Exclude infectious cause.
1	_____	Thrombocytopenia	< 100,000 platelets/ mm ³ .
1	_____	Leukopenia	< 3000 white blood cells/ mm ³
=====		Total SLEDAI Score	

App. 2: SYSTEMIC LUPUS ACTIVITY MEASURE

ITEMS PRESENT DURING THE PRECEEDING 1 MONTH TO THE VISIT ARE:

	Absent or Normal	Mild	Moderate	Severe	Not recorded
Constitutional					
1. Weight loss	0	1 < 1-% body weight		3 > 10%	
2. Fatigue	0	1 No limits on activity		3 Functional limitation	
3. Fever	0	1 37.5-38.5 ° C		3 > 38.5 ° C	
Integument					
4. Oral/nasal ulcers or periungual erythema, or major rash, or photosensitive rash, or nailfold infarct	0	1			
5. Alopecia	0	1 Hair loss with trauma	2 Spontaneous hair loss		
6. Erythematous, maculopapular rash, or discoid lupus, or lupus profundus, or bilious lesions	0	1 < 20% total body surface (TBS)	2 20-50% TBS	3 > 50% TBS	
7. Vasculitis (leukocytoclastic vasculitis, urticaria, palpable purpura, livedo reticularis, ulcer or panniculitis)	0	1 < 20% TBS	2 20-50% TBS	3 > 50% TBS or necrosis	
Eye					
8. Cytoid bodies	0	1 Present		3 Visual acuity < 20/200	
9. Hemorrhages (retinal or choroidal) or episcleritis	0	1 Present		3 Visual acuity < 20/200	

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	Absent or Normal	Mild	Moderate	Severe	Not recorded
10. Papillitis or pseudotumor cerebri	0	1 Present		3 Visual acuity < 20/200 or field cut	
Reticuloendothelial					
11. Diffuse lymphadenopathy (cervical, axillary, epitrochlear)	0	1 Shoddy	2 > 1 cm x 1.5 cm		
12. Hepato- or splenomegaly	0	1 Palpable only with inspiration	2 Palpable without inspiration		

Pulmonary				
13. Pleural effusion/pleurisy	0	1	2	3
		Shortness of breath or pain with prompt- inge. Exam normal or near normal.	Shortness of breath or pain with exercise, decreased breath sounds and dull lower lobe(s).	Shortness of breath or pain at rest, decreased breath sounds, and dull middle and lower lobes.
14. Pneumonitis	0	1	2	3
		X-ray infiltrates only	Shortness of breath with exercise	Shortness of breath at rest
Cardiovascular				
15. Raynaud's	0	1		
		Present		
16. Hypertension	0	1	2	3
		Diast. 90-105	Diast. 105-115	Diast. >115
17. Carditis	0	1	2	3
		Pericarditis by EKG &/or RUB &/or effusions by echo; no sx	Chest pain or arrhythmia	Myocarditis with hemo-dynamic compromise &/or arrhythmia
Gastrointestinal				
18. Abdominal pain (serositis, pancreatitis, ischemic bowel, etc.)	0	1	2	3
		Com-plaint	Limiting pain	Peritoneal signs/ ascites
Neuromotor				
19. Stroke syndrome (includes mononeuritis multiplex, transient ischemic attack (TIA), reversible ischemic neurologic deficit (RIND), cerebrovascular accident (CVA), retinal vascular thrombosis)	0	1	2	3
		Single TIA	Multiple TIA/RIND or mono-neuritis multiplex or cranial neuro- pathy or chorea	CVA/myelitis, retinal vascular occlusion
20. Seizure	0	1	2	3

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		1-2/ month	> 2/month	Status epilepticus
21. Cortical dysfunction	0	1 Mild depression /personality disorder or cog- nitive deficit	2 Δ in sensorium or severe depression or limiting cognitive impair- ment	3 Psychosis or dementia or coma
22. Headache (including migraine equivalents)	0	1 Complaint	2 Limits some activity	3 Incapacitating

Joints				
24. Joint pain from synovitis and/or tenosynovitis	0	1 Arthralgia only	2 Objective inflammation	3 Limited function
Laboratory				
25. Hematocrit	0 > 35	1 30-35	2 25-29.9	3 < 25
26. WBC	0 > 3500	1 3500-2000	2 2000-1000	3 < 1000
27. Lymphocyte count	0 1500-4000	1 1499-1000	2 999-500	3 < 499
28. Platelet count	0 > 150T	1 100-150T	2 99-50T	3 < 50T
29. ESR (Westergren)	0 < 25	1 25-50	2 51-75	3 > 75
30. Serum creatinine or creatinine clearance	0 0.5-1.3 mg/dl or 80-100% CrCl	1 1-4 mg/dl or 79-60% CrCl	2 2.1-4 mg/dl or 30-60% CrCl	3 > 4 mg/dl or < 30% CrCl
31. Urine sediment	0	1 > 5 RCB &/or WBC/hpf &/or 0 to 1-3 granular &/or cellular casts/hpf &/or 1-2+ proteinuria &/or < 500 mg/L 24° urine protein	2 > 10 RCB &/or WBC/hpf or > 3 granular &/or cellular casts/hpf &/or 3 or 4+ &/or 500 mg/L-3.5 g/L 25° urine protein	3 > 25 RCB or WCB/hpf &/or red cell cast &/or > 4+ proteinuria &/or > 3.5 g/L 24° urine protein

App. 3:EUROPEAN CONSENSUS LUPUS ACTIVITY MEASUREMENT (ECLAM)

	MANIFESTATION	DEFINITION OF RESPONSE	
1.	<u>Generalized</u> Fever Fatigue	Any of the following: Documented basal morning temperature of 37.5° not due to an infective process A subjective feeling of extraordinary tiredness	0.5
2.	<u>Articular</u> Arthritis Evolving Arthralgia	Any of the following: Nonerosive arthritis involving at least 2 peripheral joints (wrist, metacarpophalangeal or proximal, interphalangeal joints) New onset or worsening of specific localized pain without objective symptoms in at least two peripheral joints	1
3a.	<u>Active</u> <u>Mucocutaneous</u> Malar rash Generalized rash Discoid rash Skin vasculitis Oral ulcers	Any of the following: Fixed erythema, flat or raised over the malar eminences, tending to spare the nasolabial folds A maculopapular rash not induced by drugs, that may be located anywhere on the body, and that is not strictly dependent on sun exposure Erythematous, raised patches with adherent keratotic scaling and follicular plugging Including digital ulcers, purpura, urticaria, bullous lesions Oral or nasopharyngeal ulcers, usually painless, observed by a physician	0.5
3b.	<u>Evolving</u> <u>mucocutaneous</u>	If any of the above mucocutaneous manifestations are new or have worsened since the last observation, add 1 point	1
4.	<u>Myositis</u>	Confirmed by raised muscle enzymes and/or EMG examination and/or histology	2
5.	<u>Pericarditis</u>	Documented by ECG or rub or evidence of pericardial effusion on ultrasound	1
6.	<u>Intestinal</u> Intestinal vasculitis Sterile peritonitis	Any of the following: Evidence of acute intestinal vasculitis Evidence of abdominal effusion in the absence of infective processes	2
7.	<u>Pulmonary</u> Pleurisy	Any of the following: Clinical or radiological evidence of pleural effusion in the absence of infective	1

	MANIFESTATION	DEFINITION OF RESPONSE	
	Pneumonitis Ingravescent dyspnea	processes Single or multiple lung opacities on chest x-ray thought to reflect active disease not due to an infective process Due to an evolving interstitial involvement	
8.	<u>Evolving Neuropsychiatric</u> [*] Headache/migraine Seizures Stroke Organic brain disease Psychosis	New appearance or worsening of any of the following: Recently developed, persistent, or recurrent. Poorly responsive to the most commonly used drugs, but partially or totally responsive to corticosteroids Grand mal or petit mal seizures, Jacksonian fits, temporal lobe seizures, or choreic syndrome, in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance Cerebral infarction or hemorrhage, instrumentally confirmed Impairment of memory, orientation, perception, and ability to calculate Dissociative features in the absence of offending drugs or known metabolic derangements, e.g., uremia, ketoacidosis, or electrolyte imbalance	2
9a.	<u>Renal</u> ⁺ Proteinuria Urinary casts Hematuria Raised serum creatinine or reduced creatinine clearance	Any of the following: At least 500 mg/day Red cells, hemoglobin, granular, tubular, or mixed casts Microscopic or macroscopic	0.5
9b.	<u>Evolving Renal</u>	If any of the above renal manifestations are new or have worsened since the last observation, add 2 points	2
10.	<u>Hematologic</u> Nonhemolytic anemia Hemolytic anemia [*]	Any of the following: A Coombs-negative normocytic hypochromic or normochromic anemia without reticulocytosis A Coombs-positive hemolytic anemia, with reticulocytosis and elevated LDH, in the absence of offending drugs	1

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	MANIFESTATION	DEFINITION OF RESPONSE	
	Leukopenia (or lymphopenia) Thrombocytopenia	<3,500/mm ³ WBC (or 1,500/mm ³ lymphocytes) in the absence of offending drugs <100,000/mm ³ in the absence of offending drugs	
11.	<u>Erythrocyte Sedimentation Rate</u> Raised ESR	>25 mm/h by Westergren or comparable methods, not due to other concomitant pathological process	1
12.	<u>Hypocomplementemia</u> C3 CH50	Reduced plasma level of any of the following: By radial immunodiffusion or laser nephelometer By standardized hemolytic methods	1
12b.	<u>Evolving Hypocomplementemia</u>	Significantly reduced level of any of the items mentioned above (plus C4) with respect to the last observation	1
		FINAL SCORE #	

*If this system (or manifestation) is the only one involved among items 1-20, add 2 more points.

+Excluding patients with end stage chronic renal disease.

#If the final total score is not an integer number, round off to the lower integer for values <6 and to the higher integer for values >6.

If final total score is >10, round off to 10.

APP 4: BILAG ASSESSMENT FORM (version 3)

(All events refer to the previous month unless noted otherwise.)

Patient:

Maximum dose in last month or since last visit

GENERAL

Answer: 1) Improving 2) Same 3) Worse 4) New

1.	Pyrexia (documented)	()
2.	Weight loss – unintentional > 5%	()
3.	Lymphadenopathy/splenomegaly	()
4.	Fatigue/malaise/lethargy	()
5.	Anorexia/nausea/vomiting	()

MUCOCUTANEOUS

Answer: 1) Improving 2) Same 3) Worse 4) New

6.	Maculopapular rash – severe, active (discoïd/bullous)	()
7.	Maculopapular eruption – mild	()
8.	Active discoïd lesions – generalized, extensive	()
9.	Active discoïd lesions – local, inc. lupus profundus	()
10.	Alopecia – severe, active	()
11.	Alopecia – mild	()
12.	Severe panniculitis	()
13.	Angioedema	()
14.	Extensive mucosal ulceration	()
15.	Small mucosal ulcers	()
16.	Malar erythema	()
17.	Subcutaneous nodules	()
18.	Perniotic skin lesions	()
19.	Periungual erythema	()
20.	Swollen fingers	Y/N
21.	Sclerodactyly	Y/N
22.	Calcinosis	Y/N
23.	Telangiectasia	Y/N

NEUROLOGICAL

Answer: 1) Improving 2) Same 3) Worse 4) New

24.	Deteriorating level of consciousness	()
25.	Acute psychosis or delirium or confusional state	()
26.	Seizures	()
27.	Stroke or stroke syndrome	()
28.	Aseptic meningitis	()
29.	Mononeuritis multiplex	()
30.	Ascending or transverse myelitis	()
31.	Peripheral or cranial neuropathy	()
32.	Disc swelling/cytoid bodies	()
33.	Chorea	()
34.	Cerebellar ataxia	()
35.	Headaches – severe unremitting	()
36.	Organic depressive illness	()
37.	Organic brain syndrome inc. pseudotumor cerebri	()
38.	Episodic migrainous headaches	()

MUSCULOSKELETAL

Answer: 1) Improving 2) Same 3) Worse 4) New

39.	Definite myositis (Bohan and Peter)	()
40.	Severe polyarthritis – with loss of function	()
41.	Arthritis	()
42.	Tendonitis	()
43.	Mild chronic myositis	()
44.	Arthralgia	()
45.	Myalgia	()
46.	Tendon contractures and fixed deformity	()
47.	Aseptic necrosis	()

CARDIOVASCULAR AND RESPIRATORY

Answer: 1) Improving 2) Same 3) Worse 4) New

48.	Pleuropericardial pain	()
49.	Dyspnea	()
50.	Cardiac failure	()
51.	Friction rub	()
52.	Effusion (pericardial or pleural)	()
53.	Mild or intermittent chest pain	()
54.	Progressive CXR changes – lungs	Y/N
		Y/N

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55. Progressive CSR changes – heart	Y/N
56. ECG evidence of pericarditis or myocarditis	()
57. Cardiac arrhythmias including tachycardia > 100 in absence of fever	Y/N ()
58. Pulmonary function fall by > 20%	
59. Cyto-histological evidence of inflammatory lung disease	

79. Hemoglobin (g/dl)	()
80. Total white cell count x 10 ⁹ /l	()
81. Neutrophils x 10 ⁹ /l	()
82. Lymphocytes x 10 ⁹ /l	()
83. Platelets x 10 ⁹ /l	()
84. Evidence of active hemolysis	()
85. Coombs test positive	()
86. Evidence of circulating anticoagulant	()

VASCULITIS

Answer: 1) Improving 2) Same 3) Worse 4) New

60. Major cutaneous vasculitis including ulcers	()
61. Major abdominal crisis due to vasculitis	() ()
62. Recurrent thromboembolism (excluding stroke)	()
63. Raynaud's	()
64. Livedo reticularis	()
65. Superficial phlebitis	()
66. Minor cutaneous vasculitis (nailfold, digital, purpura, ulcers)	() ()
67. Thromboembolism (excluding stroke) 1 st episode	

RENAL

Answer with number (value) or Y/N

68. Systolic BP mmHg	()
69. Diastolic BP (5 th phase)	()
70. Accelerated hypertension	Y/N
71. Dipstick (- = 1, ++ = 2, +++ = 3)	()
72. 24 h urine protein (g)	()
73. Newly documented proteinuria of > 1 g/24 h	() ()
74. Nephrotic syndrome	Y/N
75. Creatinine (plasma/serum)	()
76. Creatinine clearance/GFR (ml/min)	() Y/N
77. Active urinary sediment	()
78. Histological evidence of active nephritis (within 3 months)	

HEMATOLOGY

Answer with number (value) or Y/N

SCORE

Gen Muc NS Msk Car Vas Ren Hae

Scoring system for the BILAG index (version 3)

It is implicit in this scoring system that all features scored are thought to be due to active lupus. The questionnaire asks whether features are improving, the same, worse, or new. If a new feature has developed in the last month (or since the last assessment if less than a month ago) it should be scored as new (i.e. 4), even if it has subsequently improved or resolved. For the first assessment any response will register the feature as a criterion. For subsequent assessments, features will only contribute to the score if they are the same, worse, or new. These different grades have been used so that BILAG can be used to identify all patients who have developed a particular feature for the first time and also to document the response of particular features to treatment. In the renal and hematological assessments (which include laboratory tests) they must confirm that abnormal results are due to active lupus (rather than drug side-effects for example).

When assessing a patient for the first time there may be no data to enter for a particular system. In this circumstance the patient should be assigned to either category D or E for that particular system. "D" should be entered if the patient has ever had any involvement of that system and "E" if there has never been previous involvement. Once a patient has scored an A, B, C, or D in a particular system they will always score at least a D in the future. The score E implies no involvement of the system ever.

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1. General non-specific manifestations

1. Pyrexia
2. Weight loss – unintentional > 5% in 1 month
3. Lymphadenopathy
4. Fatigue/malaise/weakness
5. Anorexia/nausea/vomiting

Category A

Pyrexia plus 2 other

Category B

Pyrexia or 2 other

Category C

Any other criterion

Category D

Previous involvement

Category E

No involvement

2. Mucocutaneous

Category A

Any one of:

1. Severe maculopapular, discoid, or bullous eruption; i.e. active facial and/or extensive (> 2/9 body surface), scarring or causing disability.
2. Angioedema
3. Extensive mucosal ulceration

Category B

Any one of:

1. Malar erythema
2. Mild maculopapular eruption
3. Panniculitis
4. Localized active discoid lesions including lupus profundus
5. Severe active alopecia
6. Subcutaneous nodules
7. Pernotic skin lesions

Category C

Any one of:

1. Periungual erythema
2. Swollen fingers
3. Sclerodactyly
4. Calcinosis
5. Telangiectasia
6. Mild alopecia
7. Small mucosal ulceration

Category D

Previous involvement

Category E

No previous involvement

3. Nervous system (first assessment)

Category A

Any one of:

1. Impaired level of consciousness
2. Psychosis or delirium or confusional state
3. Grand mal seizure
4. Stroke or stroke syndrome
5. Aseptic meningitis
6. Mononeuritis multiplex
7. Ascending or transverse myelitis
8. Peripheral or cranial neuropathy
9. Chorea
10. Cerebellar ataxia

Category B

Any one of:

1. Headache (severe unremitting)
2. Organic depressive illness
3. Chronic brain syndrome including pseudotumor cerebri
4. Disc swelling or cytooid bodies

Category C

Episodic migrainous headaches

Category D

Previous involvement

Category E

No previous involvement

NS disease (subsequent assessments)

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Category A

Any one of the following scored "worse" or "new":

1. Impaired level of consciousness
2. Psychosis or delirium or confusional state
3. Grand mal seizure
4. Stroke or stroke syndrome
5. Aseptic meningitis
6. Mononeuritis multiplex
7. Ascending or transverse myelitis
8. Peripheral or cranial neuropathy
9. Chorea
10. Cerebellar ataxia

Category B

Any one of the following scored "new" or worse":

1. Headache (severe unremitting)
2. Organic depressive illness
3. Chronic brain syndrome including pseudotumor cerebri
4. Disc swelling or cytoid bodies

Or any one of the following scored "new" or "worse":

5. Impaired level of consciousness
6. Psychosis, delirium, or confusional state
7. Grand mal seizure

Category C

1. Episodic migrainous headaches, or "A" 4-10 or "B" 1-4 scored "same" or "improving"

Category D

Previous involvement

Category E

No previous involvement

4. Musculoskeletal

Category A

One or more of:

1. Myositis
2. Severe polyarthritis with loss of function (not responsive to steroids < 20 mg/day, antimalarials, NSAIDS)

Category B

1. Arthritis (definite synovitis)
2. Tendonitis

Category C

1. Arthralgia
2. Myalgia
3. Tendon contractures and fixed deformity
4. Aseptic necrosis
5. Mild chronic myositis

Category D

Previous involvement

Category E

No previous involvement

5. Cardiovascular/respiratory

Category A

Cardiac failure or symptomatic effusion plus two other criteria or four from:

1. Pleuropericardial pain
2. Dyspnea
3. Friction rub
4. Progressive CXR changes – lung fields
5. Progressive CSR changes – heart size
6. ECG evidence of pericarditis or myocarditis
7. Cardiac arrhythmias including tachycardia > 100 in absence of fever
8. Deteriorating lung function: < 20% of expected or > 20% fall
9. Cyto-histological evidence of inflammatory lung disease

Category B

Any two criteria listed under A

Category C

Mild intermittent chest pain or one other criterion

Category D

Previous involvement

Category E

No previous involvement

6. Vasculitis

Category A

Any one of the following:

1. Major cutaneous vasculitis (including ulcers) accompanied by infarction occurring in previous month
2. Major abdominal crisis due to vasculitis
3. Recurrent thromboembolism (excluding strokes)

Category B

Any one of the following:

1. Minor cutaneous vasculitis (nailfold vasculitis, digital vasculitis, purpura, urticaria)
2. Superficial phlebitis
3. Thromboembolism (excluding strokes) – first episode

Category C

Any one of the following:

1. Raynaud's phenomenon
2. Livedo reticularis

Category D

Previous involvement

Category E

No involvement

7. Renal (first assessment)

Category A

Two or more of the following provided at 1, 4, or 5 is included:

1. Proteinuria, defined as > 1 g/24 h or 3+ or 4+ dipstick
2. Accelerated hypertension
3. Creatinine clearance < 50 mg/min
4. Active urinary sediment (on an uncentrifuged specimen): pyuria (> 5 wc/hpf); hematuria (> 5 rcb/hpf) or red cell casts in the absence of infection
5. Histological evidence of active nephritis within the last 3 months (or since the previous assessment if seen less than 3 months ago)

Category B

One of the following

1. One of the category A criteria
2. Urinary dipstick 2+ or more
3. 24 h urinary protein > 0.5 g but < 1 g

Category C

1. Urinary dipstick +

2. Blood pressure > 140/90 (5th phase)
3. Creatinine > 130 mmol/l

Category D

Previous renal involvement

Category E

No previous involvement

Renal (subsequent assessments)

Category A

Two or more of the following providing 1, 4, or 5 is included:

1. Proteinuria, defined as a) urinary dipstick increased by 2 or more levels; or b) 24 h urinary protein rising from > 0.20 g to > 1 g; or c) 24 h urinary protein rising from > 1 g by 100%; or d) newly documented proteinuria of > 1 g
2. Accelerated hypertension
3. Deteriorating renal function, defined as a) plasma creatinine > 130 µM/l and having risen to > 130% of previous value; or b) creatinine clearance having fallen to < 67% of previous value; or c) creatinine clearance < 50 ml/min, and last time was > 50 ml/min or was not measured
4. Active urinary sediments (as defined above)
5. Histological evidence of active nephritis (as defined above)

Category B

One of the following:

1. One of the category A criteria
2. a) urinary dipstick of 2+ or more or b) 24 h urinary protein rising from > 1 g by > 50% but < 100%

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3. Plasma creatinine > 130 µM/l or having risen to 115% of previous value

Category C

One of the following:

1. 24 h urinary protein > 0.25 g
2. Urinary dipstick 1+ or more
3. Rising blood pressure, defined as 1) systolic rise of ≥ 30 mm or b) diastolic rise of ≥ 15 mm (providing the recorded values are > 140/90)

Category D

Previous renal disease

Category E

No previous renal disease

8. Hematological

Category A

One of the following:

1. wbc < 1000
2. platelet count < 25
3. hemoglobin < 8

Category B

One of the following:

1. wbc < 2500
2. platelet count < 100
3. hemoglobin < 11
4. evidence of active hemolysis (raised bilirubin +/- reticulocytes and positive Coombs test)

Category C

One of the following:

1. wbc < 4000
2. lymphocyte count < 1500
3. platelet count < 150
4. Coombs test positive but no evidence of active hemolysis
5. evidence of circulating lupus anti-coagulant detected by functional assays

Category D

Previous involvement

Category E

No previous involvement

Glossary

General

1. Pyrexia: temperature > 37.5° documented.
3. Lymphadenopathy: palpable LNs more than 1 cm in diameter.

Mucocutaneous

6. Maculopapular eruption – severe: active discoid, bullous, or maculopapular eruption; severe, facial, and/or extensive (> 2/9 or body surface area), scarring or causing disability.
8. Lupus profundus: erythematous elevated plaques with an overlying discoid skin lesion.
9. Alopecia – severe, active: abnormal diffuse hair loss which is clinically detectable with scalp inflammation.
12. Panniculitis: extensive, painful, erythematous subcutaneous nodules associated with fat necrosis which resolve with scarring.
13. Angio-edema: with stridor, or affecting tongue or lips
14. Extensive mucosal ulceration: severe, deep, disabling ulcers.

Neurological

25. Acute psychosis or delirium or confusional state: severe disturbance in the perception of reality characterized by: delusions, hallucinations, incoherence, marked illogical thinking, bizarre or catatonic behavior.
35. Headache severe, unremitting: continuous headache not relieved by non-narcotic analgesia.
36. Organic depressive illness: associated with somatic symptoms and severe enough to merit treatment with anti-depressive medication.
37. Organic brain syndrome: impaired orientation, memory, or other intellectual function in the absence of metabolic, psychiatric, or pharmacological causes. Clinical features develop over a short period (usually hours to days) and tend to fluctuate over the course of the day:

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- (a) clouding of consciousness with reduced capacity to focus and sustain attention to environment;
- (b)
 - i. perceptual disturbance: misinterpretations, illusions, or hallucinations
 - ii. incoherent speech
 - iii. insomnia or daytime drowsiness
 - iv. increased or decreased psychomotor activity;
- (c) disorientation and recent memory impairment.

- 77. Active urinary sediment: on uncentrifuged specimen. Pyuria (> 5 wc/hpf), hematuria (> 5 rbc/hpf) or red cell casts in the absence of infection.
- 78. Histological evidence of active nephritis: according to WHO criteria. Sclerosis alone (without inflammation) will not be regarded as evidence of active nephritis.

Musculoskeletal Myositis: at least three of proximal muscle weakness, elevated muscle enzymes, positive muscle biopsy, and abnormal EMG.

- 40. Polyarthrititis with loss of function: active joint inflammation with clinically significant loss of the functional range of movement of the involved joints.
- 41. Arthritis: active joint inflammation.

Cardiovascular and respiratory

- 48. Pleuropericardial pain: localized sharp or dull pain in the chest aggravated by respiration.
- 49. Dyspnea: on exercise (not orthopnea alone).
- 53. Mild intermittent chest pain: nonspecific (not clearly pleuritic, pericardial, musculoskeletal, or angina).
- 58. Pulmonary function fall by > 20%: < 20% of expected (predicted for height, weight, sex, and age) or > 20% fall in total lung capacity (forced vital capacity) and/or DLCO.

Vasculitis

- 60. Major cutaneous vasculitis including ulcers: extensive gangrene and/or ulceration.
- 66. Minor cutaneous vasculitis: e.g. digital vasculitis with nailfold infarcts.

Renal

- 70. Accelerated hypertension: BP rising to > 170/110 (5th phase) within one month, if accompanied by Grade IV retinal changes (i.e. hemorrhages, exudates).

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App. 5: SELENA FLARE TOOL

Refer to Table 3

App. 6: RESPONSE INDEX FOR LUPUS ERYTHEMATOSIS (RIFLE)

ORGAN SYSTEMS	DEFINITION OF RESPONSES
<p>RENAL</p> <p><u>Proteinuria</u></p> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening	<p>Proteinuria <500 mg/24 h, or < 3+ by dipstick a) if baseline <500 mg/24 h, then increase of 500 mg/24 h then 100% increase</p> <p>Improvement by 50% but not to normal value <500 mg/24 h; proteinuria is considered due to reduction in GFR or the a <500 mg/24 h; do not count if reduction in proteinuria is due to addition of ACE inhibitors</p>
<p><u>RBC</u></p> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p><5 red blood cells/high power field a) if baseline 5-10 RBC/hpf, increase to >20 RCB/hpf OR increase by 200%</p> <p>50% reduction from baseline Decrease to <5 RBC/hpf</p>
<p><u>RBC casts</u></p> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening	<p>Any new cast OR a) if baseline 1-20 RBC casts, increase casts, 100% increase If baseline 1-10 RBC casts, no change means remains at a) if baseline >10 RBC casts, must be 50% reduction No RBC casts</p>
<p><u>Abnormal creatinine</u></p> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>a) Increase >0.3 mg/dL if baseline ≤ 1.5 mg/dL OR b) increase >0.3 mg/dL</p> <p>a) Decrease of 0.5 mg/dL if baseline ≤2.5 mg/dL OR b) decrease >2.5 mg/dL ≤1.0 mg/dL</p>
<p><u>Abnormal creatinine clearance</u></p> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>30% worsening</p> <p>30% improvement</p> <p>Normal for body mass</p>
<p>IMMUNE SYSTEM</p> <p><u>Autoantibodies</u></p> <p>--<u>Anti-dsDNA</u></p> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>Newly positive by any assay, or doubling of abnormal titer</p> <p>50% reduction in titer</p> <p>Absence of detectable anti-dsDNA antibodies by any assay</p>

ORGAN SYSTEMS	DEFINITION OF RESPONSES
<u>--aPL</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>Newly positive by ELISA or new dRWT (LAC) or doubling of previously abnormal ELISA value</p> <p>50% reduction in titer of any isotype without increase in any other dRWT normal (no LAC); aCL, IgG, and IgM in normal range; anti-β2-glycoprotein I in normal range</p>
<u>--abnormal complement</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>a) reduction of 25% in C4 to an abnormal range AND/OR b) reduction of 25% in C3 to an abnormal range</p> <p>50% improvement in either C3 or C4 a) normal C4 (unless C4 deficient), b) normal C3</p>
NEUROLOGICAL CNS <u>Psychosis</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New or progressive as per SLEDAI glossary</p> <p>Signs of improvement with no increase in anti-psychotic medication</p> <p>No psychosis but can be on stable medication</p>
<u>Seizures (any type)</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New or increase in frequency</p> <p>A 50% decrease in frequency (over 1 month) without an increase in seizure medications</p> <p>No seizures for 3 months (but can be on stable medications)</p>
<u>Impairment cognitive function</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New or progressive as per SLEDAI glossary; worsening Mini-Mental Exam</p> <p>Improvement in Mini-Mental Exam but not return to normalcy</p> <p>Normal mini-mental exam</p>
<u>TIA/stroke</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change	<p>New TIA or CVA due to lupus including secondary aPL syndrome</p> <p>Decreased frequency of TIA's over 3 months</p>

<input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	No TIA's over 3 months, can be on stable therapeutic anticoagulation
<u>Meningitis</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	(diagnosis requires lumbar puncture) New meningitis by LP (culture negative); for pre-existing meningitis, new physical findings; new obtundation; new papilledema Reduction in headache and meningeal signs, improvement in level of consciousness No meningeal signs, normal level of consciousness, no papilledema
ORGAN SYSTEMS	DEFINITION OF RESPONSES
<u>Pseudotumor cerebri</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	(diagnosis requires LP, CT, or MRI) New pseudotumor cerebri by LP, CT, or MRI; if present worsening headache and visual symptoms Improvement in signs (as in meningitis) without new treatment (i.e., remains on stable treatments) Asymptomatic and normal funduscopy exam
<u>Scleritis and episcleritis</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	New scleritis or episcleritis ≥50% improvement by ophthalmologic exam Normal ophthalmologic exam and on no medications
<u>Optic neuritis</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	New optic neuritis ≥50% improvement by ophthalmologic exam and/or visual acuity testing Normal ophthalmologic exam and/or visual acuity on no medications
<u>Uveitis</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	New uveitis ≥50% improvement by ophthalmologic exam Normal ophthalmologic exam
<u>Retinitis</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial	New retinitis ≥50% improvement by ophthalmologic exam Normal ophthalmologic exam

response <input type="checkbox"/> Resolution	
<u>Chorea</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	New or worsening chorea ≥50% improvement Not present
<u>Ataxia</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	New or worsening ataxia ≥50% improvement Not present
<u>Encephalopathy</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	New coma or deteriorating level of consciousness ≥50% improvement Not present

ORGAN SYSTEMS	DEFINITION OF RESPONSES
<u>Cord (transverse myelitis)</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New and or worsening sensory and/or motor symptoms or signs</p> <p>Any improvement in sensory and/or motor symptoms Complete resolution, normal neurologic exam</p>
PERIPHERAL NEUROLOGICAL <u>Cranial neuropathy</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New onset and/or worsening of pre-existing cranial neuropathy</p> <p>Decrease in total number of cranial nerves involved if originally more than one and/or improvement in a single cranial nerve if only one is involved (e.g., ptosis less marked if CN-III, improved sensation if CN-V, improved motor strength if CN-VII) Absence of any cranial neuropathy</p>
<u>Mononeuritis multiplex</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New mononeuropathy or progression of existing mononeuropathy</p> <p>Improvement in sensory, motor, or reflexes but not to normal in 3 months Normal sensory or motor exam</p>
<u>Neuropathy (sensory or motor)</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New sensory or motor neuropathy or progression of pre-existing</p> <p>Improvement in sensory or motor symptoms but not to normal Normal sensory or motor exam</p>
MUCOCUTANEOUS <u>Photosensitivity</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New lesions or worsening (number, frequency, or distribution)</p> <p>Decrease by $\geq 50\%$ (number, frequency, or distribution) No lesions in 3 months</p>
<u>Malar rash</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New lesions or worsening (number, frequency, or distribution)</p> <p>Decrease by $\geq 50\%$ (number, frequency, or distribution) No lesions in 3 months</p>
<u>Discoid/follicular</u>	

<u>plugging</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	New lesions or worsening (number, frequency, or distribution) Decrease by $\geq 50\%$ (number, frequency, or distribution) No lesions in 3 months
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ORGAN SYSTEMS	DEFINITION OF RESPONSES
<u>Bullous</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New lesions or worsening (number, frequency, or distribution)</p> <p>Decrease by $\geq 50\%$ (number, frequency, or distribution)</p> <p>No lesions in 3 months</p>
<u>Vasculitis</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New lesions or worsening (number, frequency, or distribution)</p> <p>Decrease by $\geq 50\%$ (number, frequency, or distribution)</p> <p>No lesions in 3 months</p>
<u>Mucocutaneous ulcers</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New lesions or worsening (number, frequency, or distribution)</p> <p>Decrease by $\geq 50\%$ (number, frequency, or distribution)</p> <p>No lesions in 3 months</p>
<u>Alopecia</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New onset of hair loss or worsening (number, frequency, or distribution)</p> <p>Decrease by $\geq 50\%$ (number frequency, or distribution)</p> <p>No hair loss in 3 months</p>
<u>Angioedema/urticaria</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New lesions or worsening (number, frequency, or distribution)</p> <p>Decrease by $\geq 50\%$ (number, frequency, or distribution)</p> <p>No lesions in 3 months</p>
<u>Panniculitis</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New lesions or worsening (number, frequency, or distribution)</p> <p>Decrease by $\geq 50\%$ (number, frequency, or distribution)</p> <p>No lesions in 3 months</p>
MUSCULOSKELETAL <u>Arthritis</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>Any new tender or swollen joints (even if synovitis in previous joints had improved)</p> <p>$\geq 50\%$ reduction in tender or swollen joints</p> <p>No tender or swollen joints</p>

ORGAN SYSTEMS	DEFINITION OF RESPONSES
<u>Myositis</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New myositis, or increasing weakness in 2 muscle groups, or increase of $\geq 50\%$ in CK and/or aldolase</p> <p>Decrease by $\geq 50\%$ (number, frequency, or distribution) N lesions in 3 months</p>
<u>Tendinitis</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New tendinitis (even if previous tendinitis improved) or worsening or existing tendinitis. Must be distinguished from the tender points of fibromyalgia.</p> <p>$\geq 50\%$ improvement No tendinitis</p>
CARDIAC <u>Pericarditis</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New pericarditis, worsening by echo of pre-existing pericarditis, or signs of cardiac tamponade (pulsus paradoxicus)</p> <p>Any improvement in symptoms No evidence of pericardial disease</p>
<u>Myocarditis</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New or worsening by echo and/or clinical symptoms or signs</p> <p>Improved symptoms and/or improved echo but not normal No symptoms, echo return to baseline, enzymes normal</p>
<u>Valvular abnormalities</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New murmur confirmed by echo or worsening valvular function by echo</p> <p>Reduction in valvular vegetations or valvular dysfunction by echo Normal valvular function and integrity by echo</p>
<u>Pulmonary hypertension</u>	

<input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New onset, or increase of ≥ 20 mm Hg in pulmonary artery (PA) pressure by either echo or arteriogram</p> <p>Decrease by ≥ 20 mm Hg in PA pressure by echo or arteriogram</p> <p>Normalization to < 25 mm Hg in PA pressure by echo or arteriogram</p>
<p>PULMONARY <u>Pleuritis</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution</p>	<p>New symptoms or any increase in frequency or severity of symptoms, or increase in pleural effusions</p> <p>Any improvement in symptoms and/or reduction in pleural effusions</p> <p>No signs or symptoms and normal chest x-ray (CXR)</p>

ORGAN SYSTEMS	DEFINITION OF RESPONSES
Pneumonitis <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	Any new pneumonitis or any worsening in any pulmonary function tests (PFTs) or CR or CT Any improvement in symptoms, PFTs, or CXR/CT No signs or symptoms and normal PFTs and CXR/CT
ORGAN SYSTEMS	DEFINITION OF RESPONSES
Hemorrhage <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	Any new hemorrhage or worsening of hemorrhage as assessed by signs or symptoms Improvements by signs or symptoms (e.g., CXR) Asymptomatic and CXR returns to baseline
GASTROINTESTINAL Vasculitis <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	New or worsening Any improvement by colonoscopy Asymptomatic, guaiac negative, normal colonoscopy
Colitis <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	Any new or worsening symptoms ≥50% improvement in bowel movements and/or decreased abdominal pain or blood loss Asymptomatic, guaiac negative, normal colonoscopy
Serositis (peritonitis) <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	Any new symptoms; worsening or symptoms or increase ascites by ultrasound Any improvement in symptoms, reduction of ascites by ultrasound Asymptomatic and no ascites by ultrasound
Pancreatitis <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	Any new symptoms; worsening of symptoms of increase of amylase or lipase Any improvement in symptoms or amylase or lipase Asymptomatic and normal amylase and lipase
Hepatitis <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	Any new or worsening of liver transaminases Any improvement in symptoms or liver transaminases Asymptomatic and normal liver transaminases

ORGAN SYSTEMS	DEFINITION OF RESPONSES
<u>Protein losing enteropathy</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>Any new or increasing symptoms or decreasing serum albumin (in 2 consecutive determinations)</p> <p>Any improvement in serum albumin and decrease in frequency of bowel movements</p> <p>Asymptomatic and normal serum albumin</p>
HEMATOLOGIC <u>Splenomegaly</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>Any new or increase in size of spleen by physical exam and ultrasound</p> <p>Any reduction in size by physical exam or ultrasound</p> <p>Asymptomatic and normal size by exam or ultrasound</p>
<u>Hemolytic anemia</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New hemolysis or decrease in hematocrit (HCT) by 20% and lab confirmation of hemolysis</p> <p>Any improvement in HCT and decrease in reticulocyte count</p> <p>Return to baseline HCT and normal reticulocyte count</p>
<u>TTP</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>Any new or worsening features of thrombotic thrombocytopenic purpura</p> <p>Improvement in smear, HCT, platelet count, fever, or neurologic status; improvement in renal status</p> <p>Asymptomatic and no ascites by ultrasound</p>
<u>Leukopenia</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New to <3,000/cu mm or decrease of $\geq 25\%$ from pre-existing leukopenia</p> <p>50% improvement >3,000/cu mm</p>
<u>Lymphopenia</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New to <1,000/cu mm or 25% decrease from pre-existing lymphopenia</p> <p>50% improvement >1,000/cu mm</p>

<p>Neutropenia</p> <p><input type="checkbox"/> Not present</p> <p><input type="checkbox"/> Worsening</p> <p><input type="checkbox"/> Present/no change</p> <p><input type="checkbox"/> Partial response</p> <p><input type="checkbox"/> Resolution</p>	<p>New to <1,800/cu mm or 25% decrease from pre-existing neutropenia</p> <p>50% improvement >1,000/cu mm</p>

ORGAN SYSTEMS	DEFINITION OF RESPONSES
<u>Thrombocytopenia</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New to <100,000/cu mm or 25% decrease from pre-existing thrombocytopenia</p> <p>≥50% improvement ≥150,000/cu mm</p>
CONSTITUTIONAL <u>Fever</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New temperature to ≥38° C</p> <p>Improvement with or without antipyretics for 1 week <38° C on no antipyretics</p>
<u>Weight loss</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>New involuntary weight loss of 5% in 1 month</p> <p>Weight gain but not to baseline or desired weight No involuntary weight loss and either return to baseline or desired weight</p>
<u>Lymphadenopathy</u> <input type="checkbox"/> Not present <input type="checkbox"/> Worsening <input type="checkbox"/> Present/no change <input type="checkbox"/> Partial response <input type="checkbox"/> Resolution	<p>(palpable >1 cm diameter)</p> <p>Any new or increase in size and distribution of lymphadenopathy not due to infection</p> <p>Any decrease in size and distribution No lymphadenopathy</p>

App. 7: SLICC/ACR DISEASE DAMAGE INDEX

Items have to be present at least 6 months continuously

<i>Domain Items</i>	Unweighted Score
1. OCULAR Any cataract Retinal changes OR optic atrophy	0 1 0 1
2. NEUROPSYCHIATRIC Cognitive impairment or major psychosis Seizures requiring therapy for 6 months Cerebrovascular accident (CVA) (score 2 for > 1) Cranial/ peripheral neuropathy Transverse myelitis	0 1 0 1 0 1 2 0 1 0 1
3. RENAL Estimated glomerular filtration rate < 50% Proteinuria ≥ 3.5 grams/ day OR endstage renal failure (regardless of dialysis or transplantation)	0 1 0 1 3
4. PULMONARY Pulmonary hypertension Pulmonary fibrosis Shrinking lung Pleural fibrosis Pulmonary infarction OR resection not for malignancy	0 1 0 1 0 1 0 1 0 1
5. CARDIOVASCULAR Angina OR coronary artery bypass grafting Myocardial infarct (2 scores > 1) Cardiomyopathy (ventricular dysfunction) Valvular lesion (murmur) Pericarditis x 6 months or pericardectomy	0 1 0 1 2 0 1 0 1 0 1
6. PERIPHERAL VASCULAR Claudication x 6 months Venous embolism with swelling, ulceration OR venous stasis Minor tissue loss (pulp space) Significant tissue loss (score 2 if > 1)	0 1 0 1 0 1 0 1 2
7. GASTROINTESTINAL Infarction OR resection of bowel, spleen, liver OR Gallbladder (score 2 for > 1) Mesenteric insufficiency Chronic peritonitis Stricture OR upper GI surgery ever Pancreatic insufficiency (enzyme replacement or with pseudocyst)	0 1 2 0 1 0 1 0 1 0 1
8. MUSCULOSKELETAL Atrophy OR weakness Deforming OR erosive arthritis Osteoporosis with fracture OR vertebral collapse Avascular necrosis (score 2 for > 1) Osteomyelitis Ruptured tendon	0 1 0 1 0 1 0 1 2 0 1 0 1
9. SKIN Alopecia Extensive scarring OR panniculi other than pulp space and scalp Skin ulceration (excluding thrombosis) for more than 6 months	0 1 0 1 0 1
10. PREMATURE GONADAL FAILURE	0 1
11. DIABETES (irrespective treatment)	0 1
12. MALIGNANCY Tumor (score 2 for > 1)	0 1 2
<i>Total SLICC/ ACR Damage Score</i>	