Seminars in Arthritis and Rheumatism 72 (2025) 152684

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Scoping literature review to identify candidate domains for the OMERACT Systemic Lupus Erythematosus core outcome set

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https://doi.org/10.1016/j.semarthrit.2025.152684

Available online 27 February 2025

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ARTICLE INFO

Keywords:
Systemic Lupus Erythematosus
Core domain set
Domains
Literature Review

ABSTRACT

Objective: To identify candidate Systemic Lupus Erythematosus (SLE) domains from the literature for consideration towards the development of the SLE Core Outcome Set.
Methods: This was a comprehensive scoping literature review of SLE clinical trials and systematic reviews published since 2010. Studies were identified from 5 databases and were screened for eligibility. Candidate domains were extracted from the included studies. Candidate domains were winnowed and binned by the Outcome Measures in Rheumatology (OMERACT) SLE Advisory Group.
Results: Of the 4063 studies identified, 507 met inclusion criteria and proceeded to data extraction. Multiple domains and items were extracted, which winnowing and binning reduced to 25 candidate domains.
Conclusion: The 25 candidate domains cover the important aspects of SLE and the 4 core areas of disease impact according to OMERACT framework. The 25 candidate domains constitute a feasible and manageable number of domains to proceed with to the core domain consensus stage that covers the wide range of impact of SLE. The candidate domains will be supplemented by ongoing qualitative research with patients living with SLE to identify additional domains before proceeding to the consensus stage.

Background

Systemic Lupus Erythematosus (SLE) is a heterogeneous autoimmune disease with unique and complex clinical presentations [1–3]. The multisystemic nature of SLE can involve multiple organ systems [3,4] resulting in a wide range of symptoms which can significantly influence the patient's quality of life [5]. The impact of a disease, especially a multisystemic heterogeneous disease such as SLE, can occur through many different facets beyond symptomology of disease activity.

Outcome Measures in Rheumatology (OMERACT) has defined 4 core areas that assess the impact of an intervention on health or a health condition, which are manifestations and abnormalities, life impact,

death and lifespan, and lastly societal and resource use [6]. The individual concepts or constructs that define single areas of disease impact are referred to as domains [7]. To capture the true impact of a disease, the most important domains should be measured in all clinical trials and research studies. Standardizing the capturing and measuring of domains can be achieved with a core outcome set (COS) [7].

In 2018, the OMERACT SLE Working Group was re-established to update the OMERACT SLE COS [8]. The COS consists of a Core Domain Set (CDS) and the measurement instruments to capture the domains. The first phase of the COS update is developing a new CDS, which begins with candidate domain generation where multiple projects are undertaken to identify domains from various sources. To identify candidate SLE domains from the literature, we conducted this scoping literature review.

The decision to conduct a scoping literature review in place of another type of review was due to the nature of our topic. Identifying all the different domains of SLE is a very broad concept, and having a strict concept and selection criteria as required with a systematic review could risk missing important domains or require many reviewers and a long time to complete [9]. To ensure strong methodological quality, the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist [10] was followed and the scoping literature review was registered with Open Science Framework [11].

Methods

Literature search

Keywords targeting the 4 core areas to capture the broad range of domains were prepared in conjunction with an experienced librarian and search terms were individualized for the five databases searched: Medline, Embase, Cochrane, CINALH, and PsycINFO **(Appendix A)**. The inclusion criteria were SLE clinical trials and systematic reviews, written in English, and published since 2010. The rationale for this decision was that the clinical trials would capture all domains that have been highly developed and researched, while the systematic reviews would capture more novel and important domains still being developed and researched without yielding an unmanageable number of articles.

Study selection

Study requirements included being in English language and meeting the PICOC; population: Adults (18+) living with SLE, intervention: all interventions pharmacological and non-pharmacological, control: standard of care therapy and placebo as per trial design, outcome: SLE preliminary domains, context: controlled and non-controlled trials, systematic reviews, and meta-analyses. Study selection was not restricted to specific types of clinical trials as to prevent omitting domains not typically captured in current controlled trials.

Study screening

Study screening was performed using Covidence software [12]. Duplicate studies were removed before screening. The first round of screening of titles and abstracts was performed by 3 reviewers (WN, CMJ, AT) with 1 reviewer per article due to the large number of articles identified. An agreement test was performed on the first 100 articles with the 3 reviewers, which yielded a 98 % agreement, and the 2 disagreements were resolved with discussion. Full-text screening was performed by 2 reviewers (WN, FK) with 2 reviewers per article. Any disagreement was resolved through discussion.

Data extraction

Data extraction was performed by 2 reviewers (WN, FK) with 2 reviewers per article. Data was collected in custom-made collection forms. Data collected included standard study information (first author, year of publication, type of study), SLE domains and outcomes and their definitions, and method of assessment or measurement tools.

Data synthesis

The items generated by the scoping review were preliminarily sorted by the 2 reviewers performing data extraction into domains. The resulting domains and the items forming them were reviewed by the OMERACT SLE Advisory Group, which includes 2 patient research partners (MD, YE) and clinician researchers, at 10 bi-weekly meetings [13]. A winnowing and binning of domains and items was conducted to eliminate any domains that were too broad, specific, or contextual and to combine any like-terms.

Domain definition

Definitions collected in the scoping literature review were supplemented with definitions identified from an additional literature search. The OMERACT SLE Advisory Group met monthly for 5 months to discuss, remove, and modify identified definitions until agreed upon definitions were established.

Results

Study selection

The results of the study selection are demonstrated in Fig. 1. After duplicates were removed, 4063 articles were identified. Title and abstract screening removed 1429 articles, 47 full-text articles could not be retrieved, and full-text screening removed 817 articles leaving 507 for inclusion.

Data synthesis

An extensive list of items was identified, and then winnowed and binned into 25 domains as shown in Table 1. Items that were not deemed to form domains on their own and were not winnowed out for being too specific, contextual, or broad were binned into the 25 domains either as sub-domains or examples to assist in the understanding of the domain as shown in Table 1. The 25 domains identified are: Adverse Events; Anxiety; Cognition Impact; Cognitive Function; Depression; Economic Cost Impact; Emotional Health (living with and managing SLE); Fatigue; Flares; Frailty, Health-Related Quality of Life, Pain Intensity: Pain Interference; Participation in all aspects of life (family, social, educational, work, and leisure activities); Patient Global Assessment of Disease Activity; Physical Function; Physician Global Assessment of Disease Activity; Reproductive Health; Sexuality; SLE Disease Activity; Sleep; Stress; Tissue/Organ Damage; Treatment Satisfaction; Use of Glucocorticoids Including Tapering. The items forming each domain in Table 1 are not the entire list of all items but rather examples to better explain the domain.

The 25 domains were then sorted into the core areas of OMERACT (Economic Cost, Adverse Events, Life Impact, and Pathophysiological Manifestations) to which they belonged (Fig. 2). Of the 25 domains, 9 domains were deemed to belong solely to a single core area, 11 domains were deemed to belong to 2 core areas, and 5 domains were deemed to belong to 3 core areas. The relative placement of the domains that belonged to >1 core area was intentional to demonstrate a corresponding proportion of how related the domain is to its respective core areas as illustrated in Fig. 2. The placement of domains in the core areas is not definite nor their limiting sole impact, but rather an interpretation of the main areas of impact of each domain and the complexities the domains can have with regards to their definition and classification.

Candidate domain definition

Definitions for the 25 candidate domains generated were captured in the scoping literature review and from an additional literature search. Definitions were reviewed by the OMERACT SLE Advisory Group,

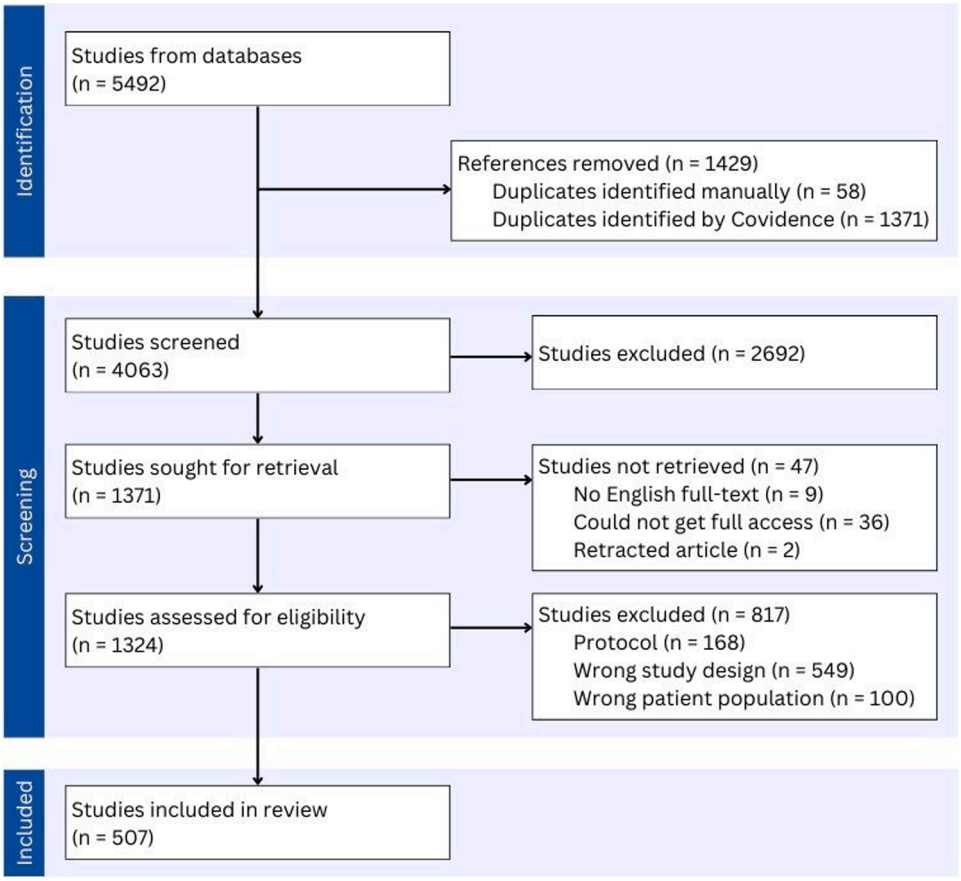

Fig. 1. PRISMA flow diagram of study selection.

modified in certain circumstances, and agreed upon. The agreed-upon definitions are shown in Table 2.

Conclusion

A comprehensive list of candidate domains has been identified through the scoping literature review. The 25 candidate domains capture the most impactful domains of SLE on patients. The candidate domains cover the 4 core areas that assess the impact of an intervention on health or a health condition, ensuring a broad coverage of the areas of impact is captured. Definitions for the candidate domains were identified in the literature, reviewed, and agreed upon. The definitions will establish common interpretations of each domain among collaborators (patients, clinicians, researchers, and more), which is necessary for the next stage of domain consensus to occur.

The 25 candidate domains identified include a number of life impact domains, of which several provide a subjective assessment (such as fatigue, cognition impact, pain interference, and stress) and capture the patient experience that is often under-represented in treatment outcomes [14]. These life-impact domains which capture the patient experience are essential for a holistic evaluation of patient's health. Our domain generation efforts identified discrepancies in domain prioritization between patients and other collaborators [15] that has been further reported in the literature [16]. The CDS will acknowledge the differing values of the many collaborators, especially that of patients, and ensure domains important to both patients and other collaborators are considered and included.

Potential limitations and controversies of the candidate domains are the levels at which the lines are drawn to classify and define the domains. Domains could be deconstructed and have their sub-items classified as domains; however, this would result in an extensive list of highly specific candidate domains. An extensive list would make the following consensus stage to decide the CDS arduous and laborious, and require the CDS to contain numerous domains and consequently measurement instruments to capture the important aspects of SLE. Conversely, the further binning of domains to combine related ones would result in domains that consist of multiple concepts only capturable by extensive composite nonfeasible measurement instruments that target multiple domains. The 25 candidate domains presented have been deemed to be adequately classified with only necessitated like-items binned together.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Vibeke Strand** is a founding member of the executive committee of Outcome Measures in Rheumatology (OMERACT) [1992 – present], an international consensus organization that develops and validates outcome measures in rheumatology randomized controlled trials and longitudinal observational studies and has received arms-length funding from as many as 36 sponsors.

Eric Morand reports grant/research support from AbbVie, Amgen, AstraZeneca, Biogen, Bristol Myers Squibb, Eli Lilly and Company, EMD Serono, Genentech, GlaxoSmithKline, Janssen, and UCB Pharma; consulting fees from AbbVie, AstraZeneca, Biogen, Bristol Myers Squibb, Eli Lilly and Company, EMD Serono, Genentech, GlaxoSmithKline, Janssen, Novartis, Servier, Wolf, and Zenas; honoraria for lectures/presentations from AstraZeneca, Biogen, Bristol Myers Squibb, EMD Serono and Gilead; travel support from AstraZeneca; and is a Board Director with Rare Voices Australia and Exosome Biosciences.

Ian Bruce reports financial support in the form of grants or contracts

Table 1
Candidate domains and example sub-items.

Domain	Example Sub-Domains	Examples to Facilitate Understanding
Adverse Events	Adverse drug reactions	Infusion-related AEs
	Infection-related AEs	Bacterial
		Fungal
		Parasitic
		Viral
	Mortality	
	Severity of AEs	Mild, moderate, severe
Anxiety	Anxiety disorders	
	Anxious misery	Dread
		Worry
	Fear	Fearfulness
		Panic
	Hyperarousal	Nervousness
		Restlessness
		Tension
	Somatic arousal symptoms	Dizziness
		Racing heart
Cognition Impact	Cognitive ability	Application of cognitive abilities
	Cognitive impairment	Difficulties in cognitive abilities
	Patient's perceived cognitive ability	Inquiry, concentration, memory
	Support network perceived cognitive impairment	
Cognitive Function	Attention	Complex
		Simple
	Executive skills	
	Fluid cognition	
	Language/verbal fluency	
	Memory	Learning
		Recall
	Psychomotor speed	
	Reasoning/problem solving	
	Social processing	Basic social processing
		Complex social cognition
	Visual-spatial processing	
Depression	Decreased engagement	Loss of meaning, interest, purpose
	Decreased positive affect	
	Depression severity	
	Depressive symptoms	
	Depressive/negative mood	Sadness
	Negative views of self	Self-criticism
		Worthlessness
	Social cognition	Interpersonal alienation
		Loneliness
Economic Cost Impact	Direct costs	Drug costs
		Healthcare products
		Healthcare resource utilization (HCRU)
		Laboratory test costs
	Indirect costs	Self-care/non medical costs
		Work time missed
	Intangible costs	Suffering
Emotional Health (living with and managing SLE)	Body image	
	Coping	
	Guilt	
	Mental/emotional well-being	
	Mood disorders	
	Mood disturbances	
	Shame	
	Stigma	

Table 1 (*continued*)

Domain	Example Sub-Domains	Examples to Facilitate Understanding
Fatigue	Drained	
	Exhaustion	
	Severity of fatigue	
	Tiredness	
Flares	Flare rate/frequency	
	Mild, Moderate, Severe flare	
	Relapse	
	Time to flare	
Frailty	Capacity of body	
	Fitness	
Health-Related Quality of Life	Impact of health on daily functioning	
	Perceived health	
	Perception of well-being	Physical
		Mental
		Social
		Emotional
	Quality of life	
Pain Intensity	Pain reduction	
	Pain severity	
Pain Interference	Interference with daily life	
	Limitations in life tasks	Familial
		Leisure
		Social
		Education
		Work
Participation in all aspects of life (family, social, educational, work, and leisure activities)	Performing daily activities	
	Performing leisure activities	
	Role participation	
	Social function	
	Work productivity	Absenteeism
		Presenteeism
		Unemployment
		Work disability
		Work impairment
Patient Global Assessment of Disease Activity		
Physical Function	Functional ability	Aerobic capacity
	Physical activity	
	Physical capability	
	Physical fitness	
	Self-reported physical activity	
Physician Global Assessment of Disease Activity		
Reproductive Health	Fertility	Amenorrhea
		Aspermia
		Azoospermia
		Impaired sperm quality
		Infertility
		Ovarian failure
		Sterility
	Fetal outcomes	Still birth
		Congenital malformation
		Preterm birth
	Pregnancy outcomes	Bleeding during pregnancy
		Caesarean operation
		Eclampsia
		Ectopic pregnancy
		Intrauterine distress
		Maternal outcomes
		Miscarriage
		Postpartum hemorrhage
		Pre-eclampsia
Sexuality	Intimate relationships	
	Libido	
	Sexual esteem	

(*continued on next page*)

Table 1 (*continued*)

Domain	Example Sub-Domains	Examples to Facilitate Understanding
	Sexual experience	
	Sexual functioning	
SLE Disease Activity (Global as well as Organ Specific)	Cardiovascular	Coronary disease, acute coronary syndrome
		Arterial stiffness
		Cardiovascular disease
		Carotid disease
		Endocarditis
		Endothelial function
		Hypertension
		Myocardial infarction
		Myocarditis
		Pericardial effusion
		Pericarditis
		Peripheral edema
		Stroke and transient ischemic attack
		Thromboembolic event
		Valvopathies
	Constitutional	Fever
		Weight loss
	Gastrointestinal	Ascites
		Colitis
		Duodenitis
		Enteritis
		Gastritis
		Hepatitis
		Intestinal ischemia
		Intestinal lesions
		Pancreatitis
		Peritonitis
		Protein losing enteropathy
	Hematological	Chronic anemia
		Hemolytic anemia
		Leukopenia
		Thrombocytopenia
		Thromboembolic events
	Immunological / Laboratory Tests	Immune related tests
		Non-immune related test
	Mucocutaneous	Alopecia
		Livedo reticularis
		Lupus rash
		Mucosal ulcers
		Sicca syndrome
		Skin lesions
	Musculoskeletal	Arthralgia
		Arthritis
		Arthropathy
		Myalgia
		Myositis
		Swollen joints
		Tender joints
	Neuropsychiatric	Diffuse syndromes
		Focal syndromes (CNS and PNS)
	Ophthalmic	Optic neuritis
		Retinal disease
		Scleritis
	Remission	Complete
		Organ-Specific
		Overall
		Partial
		Time to remission
	Renal	Lupus nephritis
		Renal flare
		Renal function
		Sclerosis
	Respiratory	Pleural effusion
		Pneumonitis
		Pulmonary embolism
		Pulmonary hypertension
		Shrinking lung syndrome
		Sinusitis
	Urinary Tract	Neurogenic bladder
		Urinary tract dysfunction
	Vasculitis	Small, medium, large vessels
Sleep	Insomnia	
	Interference with daily life	
	Sleep disorders	
	Sleep disturbance	
	Sleep efficiency	
	Sleep latency	
	Sleep quality	
Stress	Daily stressful events	
	Degrees of stress from events	
	Perceived stress	
Tissue/Organ Damage	Chronic damage	
	Cumulative damage	Diabetes
	Endocrine organ damage	
	Neuropsychiatric damage	
	Non-renal damage	
	Renal damage	Chronic kidney disease
		End stage renal disease
	Time to initial damage	
Treatment Satisfaction	Satisfaction with information on treatment	
	Satisfaction with treatment outcomes	
Use of Glucocorticoids Including Tapering	Reduction of glucocorticoids dose	
	Use of glucocorticoids	

TIA: transient ischemic attack, PNS: peripheral nervous system, CNS,: central nervous system,.

from Janssen, Astra Zeneca and GSK; consulting fees from GSK, Astra Zeneca and Janssen; and has served on boards for AstraZeneca and Merck Serono.

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Ioannis Parodis reports research funding and/or honoraria from Amgen, GlaxoSmithKline, Astra-Zeneca, Janssen Pharmaceuticals, Aurinia Pharmaceuticals, Novartis Elly Lilly and Company, Otsuka Pharmaceutical, Gilead Sciences and F. Hoffmann-La Roche AG.

Alfred Kim reports grants or contracts with Rheumatology Research Foundation, National Multiple Sclerosis Society, GlaxoSmithKline, Novartis, and BMS; **c**onsulting fees from Alexion Pharmaceuticals, AstraZeneca, Aurinia Pharmaceuticals, Kypha Inc, and Pfizer Inc.; honoraria from GlaxoSmithKline and Exagen Diagnostics; patents with Kypha US Patent 1102931882; and reports leadership or fiduciary role with Lupus Foundation of America, St Louis Rheumatology Association,

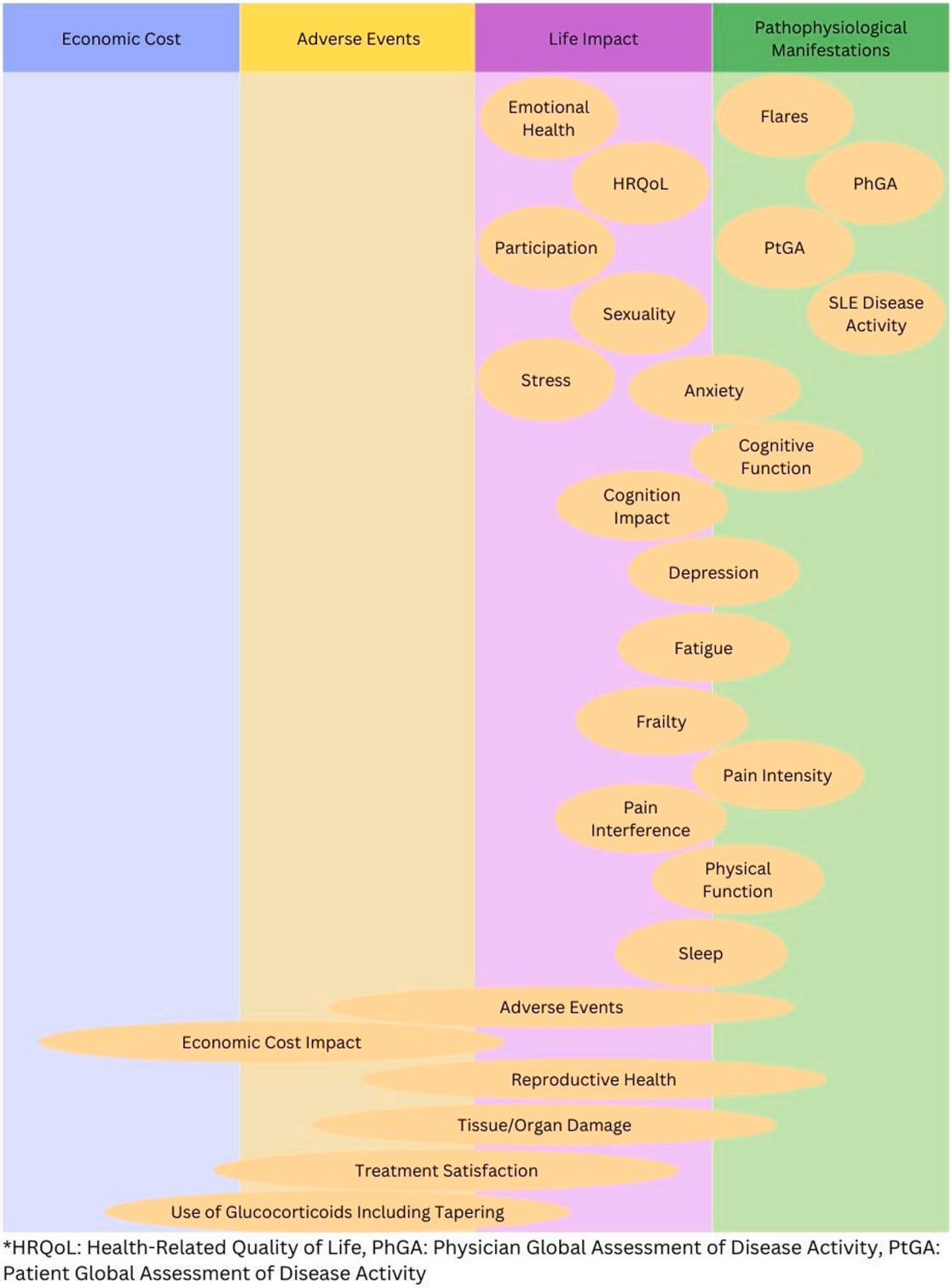

Fig. 2. Candidate domains and core area placement
*HRQoL: health-related quality of life, PhGA: physician global assessment of disease activity, PtGA: patient global assessment of disease activity.

Rheumatology Research Foundation and Lupus Research Alliance.

Yashaar Chaichian reports support in the form of grants or contracts from Lupus Therapeutics, LLC, Eli Lilly & Company, Amgen Inc, Stanford University, Discovery Innovation Fund in Basic Biomedical Sciences; personal support for attending meetings and/or travel: Lupus Therapeutics, LLC.

Sandra Navarra reports support in the form of consulting fees and honoraria from AstraZeneca and a relationship with SLE Special Interest Group, Philippine Rheumatology Association.

Kimberly Trotter is on the GSK Data Safety Monitoring Board.

Oshrat Tayer-Shifman reports a relationship in the form of grant/contract and consulting fees from AstraZeneca; honoraria from GSK, AstraZeneca and AbbVie and support for attending meetings from AstraZeneca, Neopharm and Megapharm.

Table 2
Candidate domains and definitions.

Domain	Definition
Adverse Events	Any untoward medical occurrence in a participant, which does not necessarily have a causal relationship with the trial intervention.
Anxiety	Fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), and somatic symptoms related to arousal (racing heart, dizziness).
Cognition Impact	The extent to which cognitive function is perceived (by the patient and their support network and immediate circle, as well as the healthcare team) to interfere with daily functioning and a patient's life.
Cognitive Function	Mental acuity, concentration, verbal and nonverbal memory, verbal fluency, and other cognitive domains and their noted changes (this includes subjective and objective assessments).
Depression	Negative mood (sadness, guilt), views of self (self-criticism, worthlessness), and social cognition (loneliness, interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning, and purpose).
Economic Cost Impact	The resources that is expended or forgone as a result of a health problem. It includes health sector costs (direct costs), the value of decreased or lost productivity by the patient (indirect costs), and the cost of pain and suffering (intangible costs).
Emotional Health (living with and managing SLE)	A construct consisting of multiple domains that describes one's expression, perception, and conceptualization of emotions which includes knowledge, reactivity, and regulation of emotions. It is your ability to cope with both positive and negative emotions
Fatigue	Range of symptoms from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles.
Flares	An increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and/or lab measurements. The increase must be considered clinically significant and in most cases, should prompt the consideration of a change or an increase in treatment.
Frailty	A clinically recognizable state in which the ability of people to cope with everyday or acute stressors is compromised by an increased vulnerability brought by declines in physiological reserve and function across multiple organ systems.
Health-Related Quality of Life	A term referring to the health aspects of quality of life, generally considered to reflect the impact of disease and treatment on disability and daily functioning. It has also been considered to reflect the impact of perceived health on an individual's ability to live a fulfilling life.
Pain Intensity	The intensity of the sensation of pain, encompassing the entire spectrum from a complete absence of pain to the most extreme levels of discomfort.
Pain Interference	Consequences of pain on relevant aspects of one's life. This includes the extent to which pain hinders engagement with social, cognitive, emotional, physical and recreational activities.
Participation in all aspects of life (family, social, educational, work, and leisure activities)	The involvement of people in all areas of life, and the participation restrictions they experience (functioning of a person as a member of society).
Patient Global Assessment of Disease Activity	A patient's self-perception of the degree of SLE disease activity.
Physical Function	One's ability to carry out various activities that require physical capability, ranging from self-care (activities of daily living) to more vigorous activities that require increasing degrees of mobility, strength or endurance.
Physician Global Assessment of Disease Activity	The physician's judgement of the degree of SLE disease activity.
Reproductive Health	Refers to the state of complete physical, mental, and social well-being in all matters relating to the reproductive system and implies that people can have a satisfying and safe sex life and that they have the capability to reproduce and the freedom to decide if, when, and how often to do so.
Sexuality	A person's behaviors, desires, and attitudes related to sex and intimacy.
SLE Disease Activity	Reversible manifestations (global as well as organ specific) of the underlying inflammatory process and is a reflection of the type and severity of organ involvement at each point in time.
Sleep	Perceptions of sleep quality, sleep depth, and restoration associated with sleep.
Stress	A state of worry or mental tension caused by a difficult situation.
Tissue/Organ Damage	Damage is a health state related to tissue/organ structure and function. The degree of reduced tissue/organ function relates to physiologic impairment. Damage can occur before a diagnosis of SLE but should be attributable to SLE. Damage to a tissue/organ is irreversible, but the functional consequences on that tissue/organ may improve over time through physiological adaptation or treatment.
Treatment Satisfaction	The individual's rating of attributes of the process and outcomes of their therapeutic plan.
Use of Glucocorticoids Including Tapering	The use of any form of administration of glucocorticoids including tapering and stopping.

Ali Duarte-Garcia reports a relationship in the form of grants/contracts with Rheumatology Research Foundation, Lupus Research Alliance, Centers for Disease Control and Prevention National Institutes of Health.

Lai-Shan Tam reports a relationship with GSK in the form of grant/contract and support for attending meetings.

Manuel F. Ugarte-Gil reports grants or contracts from Janssen; consulting fees from Tecnofarma; and honoraria from Astra-Zeneca and GSK.

Guillermo Pons-Estel hold a reports support in the form of a grant from Janssen, Boehringer Ingelheim; speaker honoraria from GSK, Werfen, Novartis, Pfizer and Janssen; support for attending meeting from AbbVie and Pfizer; and participation on the advisory boards of Janssen, AstraZeneca, GSK, and Novartis.

Mandana Nikpour holds a National Health and Medical Research Council of Australia (NHMRC) Investigator Grant; reports research grants from Janssen and Boehringer Ingelheim; consulting fees and honoraria from Janssen, Boehringer Ingelheim and GSK; and support for attending meetings from AstraZeneca and Boehringer Ingelheim.

Alberta Hoi reports financial support in the form of a grant from AstraZeneca, BMS, Merck Serono, GSK, Eli Lilly, UCB and Janssen; consulting fees from UCB Advisory Board; speakers' fee/honoraria from Novartis and Janssen.

Juanita Romero-Diaz reports support for attending meetings from Boehringer.

Keishi Fujio repots grants/contracts from Chugai, Asahikasei Pharma, AstraZeneca, Tsumura, Abbvie, Bristol Myers, Eisai and Taisho; consulting fees from Asahikasei Pharma; honoraria from Chugai, Abbvie, Asahikasei Pharma, Bristol Myers, AstraZeneca, Tanabe Mitsubishi, Eisai Gilead, Eli Lilly, Pfizer, Taisho, Astellas, Daiichi-Sankyo, Novartis, GlaxoSmithKline, Alexion Pharma; participates on the Board of Asahikasei Pharma.

Laurent Arnaud reports consulting fees and honoraria from Abbvie, AlfaSigma, Alpine, Astra-Zeneca, Biogen, BMS, Boehringer-Ingelheim, Chugaï, GSK, Grifols, Janssen, Kezar, LFB, Lilly, Medac, Merck, Novartis, Novo-Nordisk, Pfizer, Roche and UCB; and support for attending meetings from AstraZeneca, Novartis, Medac and Biogen.

Irene E.M. Bultink reports grants/contracts with Lupus Research Alliance, Amsterdam Reproduction and Development Research Institute, Amsterdam Rheumatology and Immunology Center and NVLE Foundation; consulting fees and honoraria from UCB, GSK and AstraZeneca; is Vice Chair of the medical advisory council of NVLE and a member of the Dutch Working Group on systemic lupus erythematosus.

Simone Appenzeller reports a relationship with National Council for Scientific and Technological Development.

José A. Gómez-Puerta reports a relationship in the form of consulting fees with GSK and Sanofi; honoraria from AstraZeneca, GSK, Janssen, Lilly and Otsuka; and support for meeting attendance from AbbView, AstraZeneca, Janssen and UCB.

Victoria P. Werth reports grants or contracts from Pfizer, Biogen, Gilead, Corbus Pharmaceuticals, AstraZeneca, Amgen, Regeneron, CSL Behring, BMS, Horizon, Rome Pharmaceuticals, Priovant, Ventus, Viela, NIH, DOD, VA; royalties or licenses from CLASI, CDASI, CDA-IGA, DMOMS; consulting fees from Janssen, Lilly, Pfizer, Biogen, BMS, Gilead, Amgen, Nektar, EMD Sorona, CSL Behring, Crisalis, Viela Bio, Argenx, Kwoya Kirin, Regeneron, AstraZeneca, Abbvie, GSK, Cugene, UCB, Rome Pharmaceuticals, Horizon, Merck, Sanofi, Calyx, Cabaletta Bio, Nuvig Pharmaceuticals, Takeda, Immunovant, Anaptysbio, Evommune, Innovaderm, Alpine Immune Sciences, Caribou, Xencor, Ventus; is on multiple advisory boards including the Data Safety Monitoring Board of AstraZeneca and the Medical Advisory Board of Lupus Foundation of America.

Anca Askanase reports grants/contracts from Idorsi, BMS, AstraZeneca, Cabaletta, UCB, Sanofi, Alumis, NKARTA; consulting fees from GSK, AstraZeneca and Novartis; and is on the Board of Amgen and Janssen.

Aaron Drucker reports royalties or licenses with National Eczema Association, Eczema Society of Canada, Canadian Dermatology Foundation, Canadian Institutes for Health Research, US National Institutes of Health and Physicians Services Incorporated Foundation; consulting fees from National Eczema Association, Canadian Agency for Drugs and Technologies in Health; honoraria from British Journal of Dermatology, American Academy of Dermatology, and Canadian Dermatology Today.

Zahi Touma reports a relationship in the form of consulting fees from AstraZeneca, Merck, GlaxoSmithKline, UCB, Janssen, LuCin, Ampel and AbbVie; and is on the Advisory Board of Novartis

Future Directions

Qualitative research of focus groups with patients living with SLE from around the world has been conducted and is in the data extraction stage further identifying candidate SLE domains important to patients. Domains identified from the focus groups will supplement this list if needed and further validate the identified candidate domains.

Once all domain generation research is complete, the consensus stage consisting of a 4-round Delphi consensus exercise will be held in 2025 to agree on the most important domains according to collaborators (patients, physicians, pharmaceutical representatives, and more). The Delphi will determine the most important domains that will form the core domain set. The first-round of the Delphi offers collaborators the opportunity to suggest additional domains to be considered for the CDS, and introduce any domains which may have been missed.

Acknowledgements

The Toronto Lupus Program is supported by Lupus Ontario, the Schroeder Arthritis Institute and the Murray B. Urowitz Chair in Lupus Research and donations via the UHN Foundation.

This work is funded by Outcome Measures in Rheumatology (OMERACT) the Arthritis Society Canada PhD Salary Award, the James F. CROTHERS Family Fellowships in Peripheral Nerve Damage, the Schroeder Arthritis Institute Student and Clinical Research Fellowship Award, the Ontario Graduate Scholarship, and the institute for Medical Science University of Toronto Fellowship Award.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2025.152684.

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