Clinical trial outcomes for SLE: what we have and what we need

Laurent Arnaud [ID],[1] Ioannis Parodis [ID],[2] Hervé Devilliers,[3] Francois Chasset [ID] [4]

[1]Service de rhumatologie, Hôpitaux Universitaires de Strasbourg, Université de Strasbourg, Centre National de Référence Maladies Rares Est Sud-Ouest (RESO), Strasbourg, France
[2]Service de rhumatologie, Institut Karolinska, Stockholm, Sweden
[3]Servide de Médecine interne, CHU Dijon – Bourgogne, Hôpital F. MITTERRAND, Dijon, France
[4]Sorbonne Université, Faculté de médecine, AP-HP, Service de Dermatologie et Allergologie, Hôpital Tenon, and INSERM U1135, Paris, France

Correspondence to
Dr Laurent Arnaud; laurent.arnaud@chru-strasbourg.fr

ABSTRACT

The paradigm of drug approval in SLE currently relies on successful large phase III randomised controlled trials and a set of primary, secondary and additional end points. Taken together, these outcomes offer a nuanced understanding of the efficacy and safety of the investigational agent. In this review, we thoroughly examine the main outcomes used in SLE trials and highlight unmet requirements as well as potential venues for future trial design in SLE. Disease activity indices can be broadly categorised into global-specific and organ-specific indices, in particular for skin, joints and kidneys, but there is no universal consensus about their use in clinical trials. Because each of these instruments has its own intrinsic strengths and weaknesses, the assessment of treatment response has progressed from relying solely on one individual disease activity index to using composite responder definitions. Those are typically measured from the trial baseline to the end point assessment date and may be combined with the need to taper and maintain glucocorticoids (GCs) within prespecified ranges. Remission and low disease activity are two critical states in the perspective of 'Treat-to-Target' trials, but are not fully recognised by regulators. While significant progress has been made in clinical trial outcomes for SLE, there is a clear need for continued innovation. Addressing these challenges will require collaboration between researchers, clinicians, patients as well as with regulatory agencies to refine existing outcome measures, incorporate meaningful and ethnically diverse patient perspectives, foster relevant digital opportunities and explore new therapeutic avenues, including early use of investigational agents. By doing so, we can advance our ability to manage SLE effectively and safely and improve the lives of those living with this complex and impactful autoimmune disease.

INTRODUCTION

Despite significant advancements in our understanding of SLE and the emergence of targeted therapies, damage accrual, treatment-associated morbidity, suboptimal health-related quality of life (HRQoL) and refractory subsets of SLE remain critical unmet needs which underscore the urgency for the development of novel treatments.[1] Drug approval is heavily influenced by a paradigm that relies on successful phase III randomised controlled trials (RCTs). This paradigm has been established to ensure the

---

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The paradigm of drug approval in SLE typically relies on successful large phase III randomised controlled trials.

WHAT THIS STUDY ADDS

⇒ In this review, we thoroughly examine the main outcomes used in SLE trials and highlight unmet requirements as well as potential venues for future trial design in SLE.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Addressing these challenges will require collaboration between researchers, clinicians, patients and regulatory agencies to refine existing outcome measures, incorporate patient perspectives, identify reliable biomarkers and explore new therapeutic avenues.

---

rigorous evaluation of investigational drugs before they are introduced to the market. The foundation of this approach is based on conducting two pivotal phase III trials, each designed to assess the investigational drug's efficacy and safety in comparison to the current standard of care (SOC), by showing a statistically significant benefit compared with placebo regarding efficacy along with acceptable safety profiles.[2] The emphasis on demonstrating a 'significant difference' underscores the imperative of clinical relevance and meaningful impact that the new treatment must safely bring to patient outcomes.

Currently, SLE trials rely on a variety of outcomes to comprehensively evaluate treatments: primary end points hold central importance in assessing treatment efficacy, secondary end points provide additional insights, while other end points offer supplementary perspectives, including about safety. Additionally, post hoc criteria can be analysed after the trial's completion for exploratory purposes.

Taken together, these outcomes offer a nuanced understanding of the investigational treatment's impact on SLE. In this review, we will thoroughly examine the main outcome

Table 1 Comparison of SELENA-SLEDAI, SLEDAI-2K and BILAG-2004

Criterion	SELENA-SLEDAI	SLEDAI-2K	BILAG-2004
Number of items	24	24	97 (divided into 9 domains)
Scoring	Each item is scored as 0 (not present) or 1 (present)	Each item is scored as 0 (not present) or 1 (present)	Each item is scored on a scale of 0–4
Maximum score	105	105	Letter-based system
Organ involvement	Covers various organ systems and clinical manifestations (non-exhaustive)	Covers various organ systems and clinical manifestations (non-exhaustive)	Comprehensive assessment across nine domains
Capture of partial improvement/worsening	Cannot capture partial improvement	Cannot capture partial improvement	Has more granularity to capture partial improvement or worsening
Advantages	Simplicity in scoring and use	Simplicity in scoring and use	Comprehensive assessment across domains
	Used in clinical trials and research	Widespread adoption	Suitable for research and clinical trials
Limitations	Omission of certain SLE features	Omission of certain SLE features	Time consuming and complex
	Fixed weights for each item	Fixed weights for each item	Primarily suited for research

BILAG-2004, British Isles Lupus Assessment Group 2004; SELENA-SLEDAI, Safety of Estrogens in SLE National Assessment-SLE Disease Activity Index; SLEDAI-2K, SLE Disease Activity Index 2000.

measures used in SLE trials and highlight unmet requirements as well as potential venues for future trial design in the context of SLE.

ASSESSING DISEASE ACTIVITY IN SLE TRIALS

Assessing disease activity in SLE is a multifaceted process involving clinical evaluation, routine laboratory and immunological tests such as complement and anti-double-stranded DNA antibody levels as well as the use of disease activity indices.[3] The latter can be broadly categorised into two main types, that is, global-specific indices and organ-specific indices. They provide detailed information about the status of a specific organ or set of organs. Both types of indices are valuable tools in SLE trials, and are often used in combination to obtain a comprehensive understanding of a patient's disease status.

Global indices for disease activity

Global disease activity indices provide an overall assessment of the patient's disease activity, taking into account a wide range of clinical and laboratory parameters that may affect multiple organ systems. The most commonly used disease activity indices in trials are the Safety of Estrogens in SLE National Assessment-SLE Disease Activity Index (SELENA-SLEDAI), the SLE Disease Activity Index 2000 (SLEDAI-2K) and the British Isles Lupus Assessment Group 2004 (BILAG-2004) (table 1).

The SLEDAI and its evolutions, the SELENA-SLEDAI and SLEDAI-2K

The SELENA-SLEDAI[4] and SLEDAI-2K[5] represent enhanced iterations of the original SLEDAI. The primary advantage of the SLEDAI lies in its ease of use, making it a practical choice for clinicians. However, there are notable limitations (table 1).

The BILAG-2004

The revised BILAG-2004[6] is a comprehensive tool consisting of 97 items categorised across 9 domains, encompassing constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal and haematological aspects (table 1). Within each of these 97 items, disease activity is scored on a scale of 0 (absent), 1 (improving), 2 (unchanged), 3 (deteriorating) or 4 (new) based on observations from the preceding 4 weeks. Global scoring within the BILAG-2004 follows an intention-to-treat approach. In this framework, category A signifies severe disease activity necessitating systemic high-dose oral GCs (equivalent to prednisolone >20 mg/day) or systemic immunomodulators. Category B denotes moderate disease activity requiring systemic low-dose oral GCs (equivalent to prednisolone at a dose of ≤20 mg/day), intramuscular/intra-articular or soft tissue GC injections, or topical GCs, topical immunomodulators or antimalarials. Categories C, D and E represent mild disease, quiescent disease in a previously affected organ system and an organ system that has never been involved, respectively. It is worth noting that the calculation of algorithms is complex and time consuming, often necessitating the use of a computer, which may render it impractical for routine clinical use. Nevertheless, the BILAG-2004 excels in capturing improvements in individual organ systems, enabling a granular evaluation of disease activity. While it is possible to calculate a total numerical score by assigning points
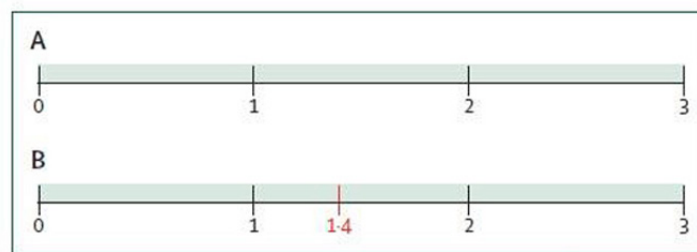
Figure 1 The Physician Global Assessment (PGA) as recommended by the PGA International Standardisation COnsensus in SLE consortium. (A) The PGA graph, consisting of a 0–3 visual analogue scale (VAS) with anchored values. (B) The correct way to score the PGA, by putting a vertical tick on the 0–3 VAS as a continuous measure with one decimal (eg, 1.4 on a 0–3 scale). The PGA scale ranges from 0='no disease activity' to 3='most severe disease activity'. Values ≥0.5 but ≤1 refer to mild disease activity; values >1 but ≤2 refer to moderate disease activity and values >2 up to 3 refer to severe disease activity. The PGA should be scored by experienced physicians, preferably by the same rater at each visit.

to each category,[7] this approach is generally discouraged due to its inherent complexity. For more streamlined assessment, the Easy BILAG[8] has been introduced. This simplified version incorporates all items that are present in ≥5% of the BILAG-biologics registry, along with the full constitutional and renal domains. It condenses the assessment into a concise, single-page format, facilitating quicker scoring of the BILAG-2004 index.

The Physician Global Assessment
The Physician Global Assessment (PGA) is a visual analogue scale (VAS) score that serves as a reflection of a clinician's overall judgement regarding the disease activity in SLE. While the PGA is generally acknowledged as a valid and responsive instrument for assessing SLE, its reliability can exhibit significant variability.[9] This variation arises from the diverse interpretations and subjective nature of its scoring. Recent advancements in standardisation efforts, exemplified by the PGA International Standardisation COnsensus in SLE study, have led to an evidence-based and expert-driven consensus on standardising the PGA scoring in SLE.[10] This consensus has resulted in 14 carefully formulated recommendations that encompass the utilisation of PGA in SLE assessment, the design of the PGA scale (figure 1), practical considerations for PGA scoring and the establishment of a clear relationship between PGA values and various levels of disease activity. It is important to note that the PGA may be influenced by factors beyond disease activity, with a notable bias stemming from the impact of fatigue, which may not always be directly related to SLE disease activity.[11] This underscores the importance of considering multiple clinical indicators and patient-reported outcomes (PROs) when assessing SLE disease activity comprehensively.

The SLE-DAS
The SLE Disease Activity Score (SLE-DAS) is a relatively recent addition to the arsenal of disease activity indices used in the assessment of disease activity in SLE.[12] The SLE-DAS represents a continuous assessment of disease activity and can be computed online at https://SLE-DAS.eu. Despite its user-friendly nature and the superior predictive value of SLE-DAS for damage accrual compared

with SLEDAI-2K, one of the key shortcomings of the SLE-DAS, akin to the SLEDAI, lies in its inability to capture improvements or deteriorations within several individual organ systems. This limitation arises because the scoring of most individual organ systems in the SLE-DAS relies on a dichotomous approach (ie, are either considered present or absent). Consequently, the SLE-DAS creates the illusion of a continuous DAS, which in our view may be misleading. It is therefore essential to acknowledge that while SLE-DAS offers certain advantages, such as its predictive value for damage accrual, clinicians should exercise caution when interpreting its results due to its inherent limitations in assessing changes within specific organ systems. In clinical practice, a comprehensive evaluation that considers both global disease activity and organ-specific manifestations remains essential for a thorough understanding of the disease status of a patient with SLE.

Organ-specific disease activity indices for SLE trials
Organ-specific disease activity indices are designed to evaluate disease activity in particular organ systems, such as the skin, kidneys or joints.

Cutaneous Lupus Erythematosus Disease Area and Severity Index and revised version of the Cutaneous Lupus Erythematosus Disease Area and Severity Index for skin involvement
Global activity scores which do not capture partial response are not appropriate for assessment of cutaneous response. The Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) is the most common outcome measure used to assess skin involvement in both SLE and in cutaneous lupus erythematosus (CLE) trials.[13] CLASI comprises two subscores, which separately assess CLE activity (CLASI-A) and damage (CLASI-D). CLASI activity is scored to a maximum of 70 points and assesses erythema (from 0 to 3), scale/hypertrophy (from 0 to 2), which are rated separately in 13 different areas, in addition to sections focusing on mucous membrane involvement and hair loss in the past 30 days.[14] CLASI-A can be used to classify skin severity into mild (CLASI-A 0–9), moderate (10–20 points) and severe (21–70 points).[15] Damage is scored to a maximum of 80 points and includes

the presence of dyspigmentation and scarring including a specific focus on scarring alopecia.[14] The CLASI has been validated in both adult patients and children and can be scored by dermatologists and rheumatologists with good intra-rater and inter-rater reliability.[16 17] A revised version of the CLASI (R-CLASI) has been developed by adding items for oedema and infiltration, which are important for rare CLE subtypes,[18] but the R-CLASI has not been used in clinical trials yet. In trials, skin response can be assessed by an improvement in CLASI-A score ≥4 points (or ≥20%),[13] which corresponds to the minimal clinically significant improvement.[15] Also, a CLASI-A decrease ≥50% from baseline has been associated with improvement in HRQoL in adults[19] and children,[20] which further supports the use of CLASI-50 response as a key outcome measure in clinical trials.[21–23] Alternatively, other outcomes using CLASI-A changes have been used in recent CLE trials, including per cent change from baseline of CLASI-A[23 24] and a CLASI-70 response (≥70% decrease in the CLASI-A score from baseline).

Of note, regulatory agencies are encouraging the development of investigator global assessments (IGA) of skin involvement in clinical trials,[25] and the cutaneous lupus activity-IGA was recently derived through a comprehensive international consensus exercise and subsequently crafted by experts in the field of CLE. Studies regarding the validation and applicability of this new instrument are still ongoing.[25] The scoring is based on the severity of morphological features averaged across all affected areas of the body. These morphological features encompass erythema, scale, oedema/infiltration, the degree of follicular plugging/follicular hyperkeratosis on the scalp and secondary alterations observed in CLE plaques, such as the presence of vesicles, erosion and crusting. A CLA-IGA score of 0 or 1 (clear or almost clear) is used as the primary end point (along with CLASI-70 response) in the ongoing phase III CLE trial of litifilimab.[26]

Assessing musculoskeletal involvement in SLE trials

Musculoskeletal symptoms are among the most prevalent and impactful manifestations of SLE. Currently, the assessment of joint involvement in clinical trials primarily relies on clinical evaluation, often using tools like the SLEDAI or the BILAG. This assessment typically considers the number of swollen and tender joints, which are combined to create an active joint score. However, emerging evidence suggests that incorporating imaging techniques, particularly ultrasound (US), can substantially enhance the detection of subclinical joint inflammation and help identify patients who respond positively to treatment.[27] In contrast, the SLEDAI exhibits limited sensitivity, specificity and responsiveness in assessing musculoskeletal involvement. While both BILAG and SLE-DAS show improved performance, they still fall short of the accuracy achieved through imaging techniques.[28] Notably, recent efforts have been directed towards refining the musculoskeletal domain of the BILAG-2004 index to integrate US findings.[29] For instance, within this domain,

moderate inflammatory arthritis now includes synovitis, defined by either observed joint swelling or the presence of musculoskeletal US evidence indicating inflammation in joints and their surrounding structures. It is important to note that other imaging modalities, such as fluorescence optical imaging[30] or thermography,[31] remain relatively underused in the context of SLE. Nonetheless, these technologies hold potential for further enhancing our understanding of musculoskeletal involvement and may offer valuable insights in the future.

Assessing kidney involvement in SLE trials

Kidney involvement is seen in 30%–60% of people with SLE and is termed lupus nephritis (LN).[32] When not treated adequately and promptly, LN may result in severe kidney damage. Recent advancements in LN treatment with the introduction of add-on medications like belimumab or voclosporin in combination regimens together with conventional immunosuppression hold promise for improving outcomes in these patients.[33] However, it is essential to note that response rates in the clinical trials that led to the approval of belimumab and voclosporin did not exceed 45%, underscoring the remaining need for more effective management strategies. Several clinical trials of late phases (II or III) are currently ongoing, which promises heartening prospects. Importantly, the end points used across these trials are largely variable, highlighting the critical necessity for standardisation of definitions of treatment response.

In the vast majority of clinical trials and observational studies investigating treatment efficacy in LN, the outcomes are composite measures, comprising elements such as (i) decrease in proteinuria to levels under certain thresholds, most often 0.2–0.5 g/day for complete response and 0.7–1 g/day for partial response, (ii) no worsening in renal function, (iii) inactive urinary sediment and (iv) no need for rescue therapy (protocol violation). Regarding proteinuria, evidence comes from studies showing that early decreases of proteinuria levels predict favourable long-term renal outcome, as does attainment of levels <0.7–0.8 g/day within 1 year from treatment commencement.[34] The utility of urinary sediment is however debated because addition of haematuria to proteinuria has not revealed any clear benefit for the models, or has even been shown to worsen their predictive properties. Moreover, haematuria is only weakly, if at all, correlated with histopathological disease activity in kidney biopsies.[34]

Kidney biopsies play a pivotal role in diagnosing LN and guiding treatment decisions. In recent years, there has been a growing consensus that per-protocol repeat kidney biopsies are vital for accurately assessing treatment response and determining the appropriate level of immunosuppression. This stems from accumulating evidence indicating a considerable discordance between treatment response based on routine clinical measures on one hand and the histopathological findings in post-treatment kidney biopsies on the other. It is worth noting

that nearly 30% of patients classified as complete clinical responders according to clinical parameters exhibit treatable inflammatory kidney lesions in repeat biopsies, which without the biopsy would have gone unnoticed.[35 36] However, it is essential to acknowledge that kidney biopsies are invasive procedures with potential complications. This underscores the importance of developing reliable biomarkers in peripheral blood or urine, often referred to as the 'liquid biopsy'. Until such biomarkers that accurately reflect kidney inflammation are established, repeat kidney biopsies remain crucial for evaluating treatment effectiveness and guiding appropriate adjustments. A key study towards development of peripheral biomarkers that reflect immune aberrancies at the tissue level, conducted under the auspices of the Lupus Nephritis Trials Network (LNTN), is per-protocol repeat kidney biopsy in incident cases of LN, or in short ReBioLup (NCT04449991). While the adoption of per-protocol repeat kidney biopsies gains traction, the strength of the evidence supporting these efforts is constrained by the absence of universally accepted tissue-based definitions of treatment outcomes. To address this, an international task force has been established under the auspices of the LNTN with the objective of proposing evidence-based histological definitions of treatment outcomes in LN, informed by data derived from repeat kidney biopsies.

Collectively, standardisation of outcome definitions used in trials is an urgent need, and this must be done in joint efforts and based on data from prior clinical trials and observational studies. Until reliable peripheral biomarkers exist, kidney biopsy remains the gold standard for the diagnosis of LN and evaluation of treatment outcomes.

RESPONSE INDICES IN SLE TRIALS

The assessment of treatment response in SLE trials has progressed from relying solely on individual disease activity indices to embracing composite responder definitions (figure 2). These comprehensive definitions draw on a combination of these indices to assess changes in disease activity, typically measured from the trial's baseline to the end point assessment date. Both the SLE Responder Index-4 (SRI-4) and BILAG-based Combined Lupus Assessment (BICLA) are valuable composite indices (table 2) used in SLE clinical trials to evaluate treatment response. The choice between these indices may depend on the specific trial design and research objectives, but an increasing number of trials are using both indices.

The SLE Responder Index

The SRI-4 was developed in response to the need for a robust primary outcome measure for clinical trials, stemming from a post hoc analysis of the unsuccessful belimumab phase II trial.[37] This innovative index combines
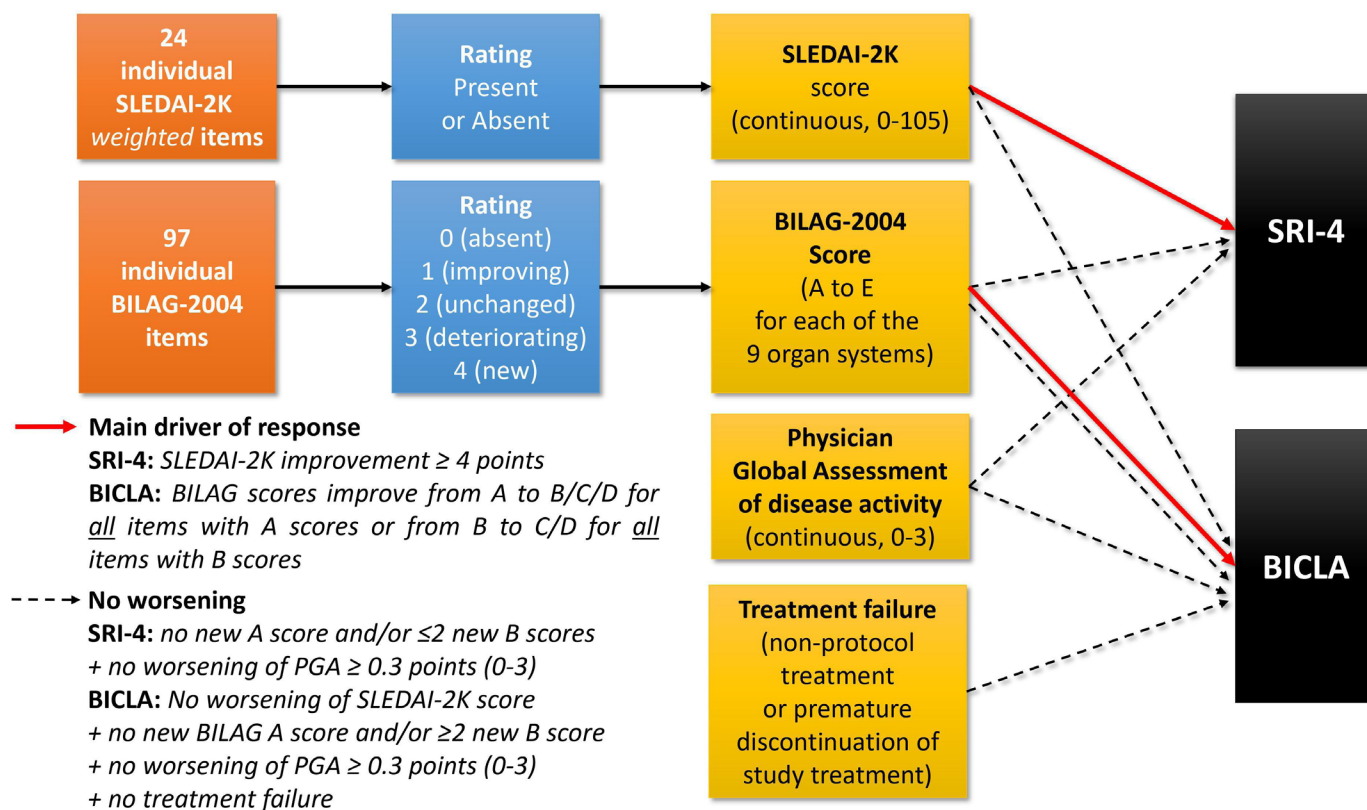

Figure 2 Combination of disease activity indices to obtain SRI-4 and BICLA response indices. BICLA, BILAG-based Combined Lupus Assessment; BILAG, British Isles Lupus Assessment Group; PGA, Physician Global Assessment; SLEDAI-2K, SLE Disease Activity Index 2000; SRI-4, SLE Responder Index-4.

Table 2 Comparison of the SRI-4 and BICLA composite response indices

Components	SRI-4	BICLA
SLEDAI	Main driver of improvement in SRI-4 ► Improvement of 4 points or more	► No worsening of the total SLEDAI-2K score from baseline
BILAG	► No worsening with no new A score and/or ≤2 new B scores	Main driver of improvement in BICLA ► BILAG scores improve from A to B/C/D for all items with A scores or from B to C/D for all items with B scores AND ► No worsening with no new A score and/or ≥2 new B scores
PGA	► PGA does not worsen by 0.3 points or more (10% or more)	► PGA does not worsen by 0.3 points or more (10% or more)
Treatment failure criteria	► N/A	► No treatment failure (defined as non-protocol treatment or premature discontinuation of study treatment)

BICLA, BILAG-based Combined Lupus Assessment; BILAG, British Isles Lupus Assessment Group; N/A, not available; PGA, Physician Global Assessment; SLEDAI-2K, SLE Disease Activity Index 2000; SRI-4, SLE Responder Index-4.

the components of the SELENA-SLEDAI (nowadays SLEDAI-2K), BILAG-2004 and PGA to effectively gauge changes in disease activity among patients with SLE (table 2). The primary objective behind creating the SRI was to capture improvements in SLE disease activity while ensuring that these improvements did not coincide with the worsening of other disease manifestations. Building on the foundation of SRI-4, several modified versions of the SRI such as the SRI-5, SRI-6 and SRI-7 have been developed to accommodate varying levels of treatment response and stringency, but are infrequently used in SLE trials.

The BILAG-based Combined Lupus Assessment
The composite end point index BICLA was first introduced in the context of the anti-CD22 epratuzumab trial.[38] The criteria for a BICLA response are shown in table 2. In summary, the BICLA response criteria consider improvements in specific disease manifestations and assess overall disease stability and the absence of treatment failure. This composite end point provides a rigorous and standardised approach for determining the effectiveness of therapies in managing SLE.

It is interesting to note that assessment of responders using the SRI-4 and the BICLA may be discrepant. Briefly, the SRI-4 requires *complete* response in involved organ systems, as it is mainly driven by the SLEDAI-2K, while the BICLA necessitates improvement *in all* organ systems with BILAG grade A or B at baseline, as BICLA response is mostly driven by the BILAG-2004.

DISEASE ACTIVITY STATES
Remission and low disease activity are two critical concepts in the management of SLE (table 3), particularly in the perspective of 'Treat-to-Target' trials. Although related, both concepts represent different levels of *disease activity control* and provide clear and measurable treatment goals. By defining these states and using them as end points, it is possible to assess the effectiveness of different treatment regimens in achieving these outcomes.

Table 3 Definitions for DORIS-remission and LLDAS

Features	DORIS-remission	LLDAS
Main purpose	Defines a state of remission in SLE	Represents a state of low disease activity in SLE
Disease Activity Score	Clinical SLEDAI=0	SLEDAI-2K ≤4 with no activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever), and no haemolytic anaemia or gastrointestinal activity
		No new lupus disease activity compared with the previous assessment
Physician Global Assessment	<0.5 (0–3)	≤1 (0–3)
Glucocorticoids	Prednisolone ≤5 mg/day or equivalent	Prednisolone ≤7.5 mg/day or equivalent
Other treatments	Stable antimalarials, immunosuppressives and biologics	Well-tolerated standard maintenance doses of immunosuppressive drugs and approved biological agents

CNS, central nervous system; DORIS, Definitions Of Remission In SLE; LLDAS, Lupus Low Disease Activity State; SLEDAI-2K, SLE Disease Activity Index 2000.

Remission

The concept of 'remission' in SLE has historically lacked a consensus definition, leading to a need for a standardised framework. This prompted the establishment of the Definitions Of Remission In SLE (DORIS) initiative, aimed at providing a clear definition for remission in SLE. The initial findings of this initiative were published in 2016.[39] Ultimately, the DORIS Task Force arrived at a single recommended definition (table 3) for remission in SLE.[40] Of note, the DORIS-remission criteria primarily rely on clinical assessments, such as the clinical SLEDAI, PGA and prednisolone dose. While these are essential components, they may not fully capture the complexity of SLE, including subclinical disease activity that persists despite meeting clinical criteria. The DORIS criteria leave the question of whether to include the absence of serological activity in the definition of remission open-ended. Also, the criteria may not fully capture the patient's perspective and quality of life. Future research and refinements may address some of these limitations and provide more comprehensive criteria for evaluating remission in patients with SLE.

The Lupus Low Disease Activity State

The concept of a Lupus Low Disease Activity State (LLDAS) was introduced to address the challenge of achieving complete remission in SLE and to provide a more realistic and attainable treatment target compared with remission. Through a consensus methodology,[41] a comprehensive definition of LLDAS has been established and is shown in table 3. The establishment of LLDAS as a treatment target in SLE acknowledges the challenge of achieving complete remission and offers a more pragmatic goal for clinicians and patients. It takes into account various aspects of disease activity, medication usage and organ system involvement, providing a comprehensive framework for assessing and aiming for a state of lower disease activity in patients with SLE.

Flares

In 2011, an international working group established a definition of flare in SLE as follows: "A flare in SLE is defined as a measurable increase in disease activity in one or more organ systems, involving new or worsening clinical signs and symptoms and/or laboratory measurements. These changes must be considered clinically significant by the assessor and would usually prompt consideration of a change or an increase in treatment".[42] In other terms, a flare indicates a clinically significant rise in disease activity compared with the previous assessment. Various definitions of flare have been developed for SLE trials,[43] typically based on one or more of the following parameters: (a) increase in disease activity, as assessed using a validated disease activity index; (b) appearance of new or worsening disease manifestations, for instance, an increase in proteinuria may signal a renal flare; (c) change in the PGA scale towards more active disease and (d) need for treatment intensification, such as an increase in steroid dosage.

Flare definition using validated activity indices

Various instruments can be used for assessing flares in SLE trials, including the SELENA-SLEDAI Flare Index (SFI, *cf. below*[4]), the SLEDAI-2K (increase in score ≥4 points)[42] or the BILAG 2004 (severe flare is defined as a score of 'A' in any system, moderate flare as two 'B' scores and mild flare as a single new 'B' score). Using the SLE-DAS, flares are defined as a score increase of ≥1.72.[44]

The SELENA-SLEDAI Flare Index

The SFI was developed[4] as a composite tool that takes into account changes in the SLEDAI-SLEDAI (an increase in SELENA-SLEDAI score ≥3 points is considered mild/moderate flare while an increase ≥12 points is considered severe flare), additional organ manifestations not covered by the SLEDAI, changes in treatment, PGA and/or the need for hospitalisation due to lupus exacerbation. The SFI's main strengths lie in its ability to distinguish between mild/moderate and severe flares and its extensive validation across various clinical settings. It is worth noting that a revision of the SELENA Flare Index was conducted to define severe, moderate and mild flares separately based on clinical and/or treatment variables and by organ system.[45]

ASSESSING DAMAGE IN SLE TRIALS

In SLE, damage refers to the long-term, irreversible consequences or complications that can occur during the course of the disease. Unlike disease activity, which involves the presence of active symptoms and inflammation, damage in SLE represents the accumulated structural and functional changes that can affect various organs and systems in the body over time. Damage can lead to permanent impairment and disability but is complex to assess in SLE trials due to the generally short duration of follow-up.

The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index

Damage in SLE is often assessed using instruments like the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology Damage Index (SDI), which quantifies the cumulative damage in various organ systems. Each item or domain within 12 organ systems is assigned a score of 0 (no damage) or 1 (damage present) if it has persisted for at least 6 months and is considered irreversible. The total SDI score is the sum of all individual scores across the organ systems and can range from 0 (no damage) to a theoretical maximum of 47 (severe damage). The SDI has been criticised for potential interobserver variability in scoring, as different clinicians may interpret damage items differently as well because some items on the SDI may overlap with disease activity, leading to challenges in distinguishing between active disease and damage. The SLICC group is currently

working on a revised version of the SDI. The main changes of the revised SDI[46] include the fact that damage assessment will take a life-course approach, and will be attributable to SLE when occurring before a diagnosis of SLE. Also, while damage to an organ is irreversible, the functional consequences on that organ may improve over time through physiological adaptation or treatment.

The Glucocorticoid Toxicity Index

Toxicities associated with GC use are central to the experience of most patients being treated for immune-mediated conditions.[47] The Glucocorticoid Toxicity Index (GTI) is a novel clinical tool developed to assess and quantify the adverse effects associated with the use of GCs[48] in patients with various medical conditions, including autoimmune diseases. The GTI provides a systematic and standardised way for clinicians and researchers to evaluate and monitor the cumulative toxicity of GC therapy over time. The GTI assesses a broad spectrum of GC-related adverse effects across different organ systems. A higher GTI score indicates a greater cumulative burden of GC-related toxicity. The clinical utility of the GTI lies in its ability to help clinicians assess the overall impact of GC therapy on a patient's health. The GTI may help guide treatment decisions, such as adjusting GC dosages, considering alternative therapies or implementing preventive measures to reduce the risk of specific adverse effects. In both clinical research and practice, the GTI is a valuable tool for evaluating the balance between the benefits of GC therapy in controlling disease activity and the potential harm from adverse effects. Of note, other parameters related to GC use, such as the proportion of patients able to reach and maintain a daily GC dose ≤7.5 mg or ≤5 mg, or to discontinue GC is of great interest and should be incorporated in future SLE trials.

PATIENT-REPORTED OUTCOMES IN SLE TRIALS

The incorporation of PROs and patient perspectives into clinical trial end points is crucial. SLE profoundly affects patients' quality of life, and PROs provide valuable insights into their experiences and treatment priorities. Of note, the correspondence between PRO measurement and the achievement of remission is highly inconstant and depends on the domain investigated.[49] Consequently, in-depth knowledge of PRO instruments and the domains covered is an essential prerequisite for using these tools in clinical trials.

Generic PROs

Generic PROs and HRQoL questionnaires evaluate the impact of health on different aspects of a patient's daily life, regardless of whether or not the limitations reported are attributed to lupus. An alteration in scores may therefore be linked to a medical background non-related to SLE.

Medical Outcome Study Short Form 36

The Medical Outcome Study Short Form 36 (MOS SF-36) is a 36-item questionnaire whose latest version includes 8 domains with a score from 0 to 100 (100 for the best HRQoL), including physical function (PF), bodily pain (BP), physical role, general health, vitality, social functioning, emotional role and mental health. Two summary scores, the mental component summary and the physical component summary, derived from linear combinations of the domain scores, are normalised to a mean of 50 and an SD of 10 in the general population. In patients with SLE, it is commonly accepted that an improvement of at least 4 points in domain scores and at least 2.5 points in component summary scores is clinically important.[50] However, these values must be tempered by the fact that there is a considerable heterogeneity in score variation between groups defined by activity or remission. For example, a comparison of patients who did or did not achieve the SRI criterion shows a much greater difference for BP than for PF.

EuroQol EQ-5D

The EQ-5D questionnaire was developed to assess utility in medico-economic studies. It is a generic preference-based measure of health used in SLE for obtaining health state values to calculate quality-adjusted life years (QALYs). It consists of five questions/dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and a VAS. The impairment in each dimension is rated on a three-level or a five-level scale, depending on the version of the tool, with a summary score ranging from 0 (experience equal to death) or below 0 (experience worse than death) to 1 (optimal health, also termed full health state (FHS)). The VAS score ranges from 0 to 100 and is used to calculate QALYs for economic analyses. In the context of SLE, EQ-5D has been shown to have good psychometric properties, with FHS when used as an outcome measure in post hoc analyses of trial data showing robust ability to separate drug from placebo and clinical responders from non-responders,[51] while FHS attainment being linked to prevention of organ damage progression.[52] This underscores the robustness and meaningfulness of PROs if used wisely and suggests that they may hold promise as components in composite trial outcomes.

Functional Assessment of Chronic Illness Therapy-Fatigue Scale

Functional Assessment of Chronic Illness Therapy-Fatigue Scale is a 13-item unidimensional measure ranging from 0 to 52 (higher is less fatigue) that assesses self-reported fatigue and its impact on daily activities and function within the past 7 days. Its sensitivity to change has been demonstrated, and an improvement of 3–7 points is considered clinically important in SLE.[53] A recent study has demonstrated the mediating effect of fatigue in the relationship between disease activity and quality of life in physical domains, indicating the importance of collecting these data.[54]

Patient-Reported Outcome Measurement Information System

The Patient-Reported Outcome Measurement Information System (PROMIS) initiative by the National

Table 4 SLE-specific Quality of Life Questionnaire

Questionnaire	Lupus Quality of Life	SLE Quality of Life	Lupus Patient-Reported Outcome (LupusPRO)	Lupus Impact Tracker
Country of development	UK	Singapore	USA	USA
Number of items	34	40	43	10 from LupusPRO
Domains	Eight domains: physical health, emotional health, body image, pain, planning, fatigue, intimate relationships, burden to others	six domains: physical function, activities, symptoms, treatment, mood, self-image	Eight domains: symptoms, cognition, treatments, reproduction, physical health, pain/vitality, emotional health, body image, goals/aspirations, social support, coping, satisfaction with care	A unique dimension representing the impact of lupus
Time to complete	<10 min	<10 min	7–10 min	<5 min
Questions	5-point Likert scale (0–4)	7-point Likert scale[1–8]	5-point Likert scale (0–4)	5-point Likert scale (0–4)
Recall period	4 weeks	1 week	4 weeks	4 weeks
Scoring	Sum of items score by domain divided by 4 and multiplied by 10	A summary score: sum of all items. Domain scores: sum of item responses by domain	Sum of items score by domain divided by 4 and multiplied by 10	Sum of items score by domain divided by 4 and multiplied by 10
Interpretation	0: worst possible QoL to 100: best possible QoL	Overall score from 40 to 280 (the higher the score, the lower the QoL), score range varies by domain	0: worst possible QoL to 100: best possible QoL	0: no impact of lupus to 100: highest possible impact of lupus
Minimal clinically important difference	3–7 (depends on domain)	An average increase of 25 points has been described in patients reporting an improvement in their clinical condition	An increase in score of between 3 and 8 points, depending on the domain, was noted in patients presenting an improvement in their activity criteria	A mean improvement of 8 points was described in SRI-4 responders. A mean improvement of −4.2 points was noted in patients reporting an improvement in their clinical condition

QoL, quality of life.

Institutes of Health has developed self-report tools to measure health status in various domains, including fatigue, pain and physical functioning. PROMIS provides short-form questionnaires covering various domains (4–10 items per domain), a 29-item profile (PROMIS-29) which includes 4-item forms for 7 PROMIS domains, and a system of computerised adaptive testing to efficiently estimate individual trait levels. The latter has shown precision in studies of rheumatoid arthritis, osteoarthritis and SLE.[55] PROMIS's relevance to SLE has been confirmed through qualitative research indicating that its domains cover key areas of concern for patients with SLE. Advantages of PROMIS include brevity, precision, flexibility in administration and standardised scoring, although further research is needed to precisely define the potential contribution of these tools in clinical trials.

Disease-specific PROs

Disease-specific questionnaires (table 4) provide the advantage of capturing the specific concerns attributed to SLE by patients. Specifically, changes in body image, sexual problems, unpredictability of the disease or adverse effects of the treatments are all concerns of patients that are not captured by generic questionnaires.

Lupus Quality of Life

The Lupus Quality of Life (LupusQoL) has been widely studied and validated in various languages, it assesses eight domains like physical health and emotional well-being based on patients' experiences over the past 4 weeks. Higher scores indicate better quality of life. LupusQoL has demonstrated good psychometric properties, including reliability and validity, and has shown to be responsive to changes in patients' health status.[56]

Lupus Patient-Reported Outcome (LupusPRO) and Lupus Impact Tracker

The Lupus Patient-Reported Outcome (LupusPRO) was developed in the USA and validated in several languages. This tool includes both HRQoL and non-HRQoL domains like goals and care satisfaction.[57] The LupusPRO has good internal consistency and test-retest reliability for HRQoL domains, and it correlates well with disease activity measures, although minimum clinically important differences are currently being investigating. A psychometric analysis allowed to extract 10 items from the LupusPRO that best represent the impact of lupus on patients' daily lives. The resulting unidimensional instrument, Lupus Impact Tracker, showed good psychometric

qualities, and has the advantage of being short and easy to use.

SLE-specific Quality of Life Questionnaire

The SLE-specific Quality of Life Questionnaire was developed in Singapore. It has acceptable internal consistency and responsiveness but showed significant floor effects, indicating it may not measure the full range of QOL experienced by patients. It also showed acceptable concurrent validity with the SF-36.[58]

One of the major difficulties in using PROs in clinical trials is targeting the area in which a treatment should bring about improvement (eg, fatigue and general signs, body image and skin damage or cortisone sparing). The number of questionnaires proposed to patients cannot be multiplied unduly, for practical reasons and because patients risk exhaustion. The solution will probably partially come from the development of item banking and computer adaptive testing, which will make it possible to accurately estimate patients' level of perceived health in areas of interest, based on a limited number of targeted items. Second, the definition of thresholds for minimum clinically relevant or important improvement for each of the scales needs to be refined to enable the interpretation of results from clinical trials based on PRO. In this field, the interpretation of clinical trials will be considerably enriched by the results of descriptive epidemiological studies, enabling us to understand the complex links between disease activity and patients' feelings.

ADDITIONAL PERSPECTIVES FOR IMPROVING SLE TRIALS

Over the years, SLE trials have provided valuable insights into the efficacy and safety of various treatments, helping to shape new therapeutic guidelines and improve patient care. The suggested outcomes for SLE trials are shown in table 5. However, there remain several key areas where further research and development are needed to address the complex challenges posed by SLE (table 6). First, the development of more precise and sensitive outcome measures is essential. While traditional 'legacy' end points like the SLEDAI and BILAG have been valuable, they have limitations in capturing the full spectrum of SLE manifestations and assessing treatment responses accurately. The emergence of composite indices like the SRI-4 and the BICLA has been a major step forward, but there is still room for refinement, especially in measuring low disease activity and remission.

Face-to-face trials in SLE

With the approval of anifrolumab, there are now two biological therapies available for SLE. Phase III trials of belimumab and anifrolumab were conducted against placebo as an add-on to the SOC. Consequently, comparing the efficacy of belimumab and anifrolumab versus conventional immunosuppressive treatments (such as methotrexate for skin and joint involvement) remains to be undertaken formally. Moreover, direct comparisons between belimumab and anifrolumab are necessary, as indirect comparisons do not allow for definitive conclusions to be drawn.[59]

Table 5	Main instruments suggested for a general SLE trial, by end point
End points*	**Instruments**
Primary	**SRI-4 or BICLA**
Secondary	**SRI-4 or BICLA (based on the primary end point)**
Exploratory	**Change in active joint count (eg, JC-50)** **Change in CLASI-A (eg, CLASI-50)** **Change in glucocorticoid doses** **New flare (SELENA-SLEDAI Flare Index or BILAG-defined) and time to first flare** **Change in individual SRI-4 and BICLA components (eg, change in SLEDAI-2K)** Time to SRI-4 or BICLA response SRI-5 to SRI-8 (and time to SRI-5 to SRI-8 response) LLDAS (and time to LLDAS) DORIS-remission (and time to remission) Change in C3 and anti-double-stranded DNA levels Change in proteinuria Change in relevant transcriptomic signature (eg, type I interferons) PROs: SF-36, FACIT-F, EQ-5D, Lupus QoL and/or LupusPRO

*May vary with study design and statistical analysis plan (in particular the use of hierarchical secondary end points); exploratory outcomes in bold have been commonly used as secondary outcomes in previous SLE trials. In addition to efficacy end points, safety assessment is required throughout the trial.

BICLA, BILAG-based Combined Lupus Assessment; CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index activity; DORIS, Definitions Of Remission In SLE; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue Scale; LLDAS, Lupus Low Disease Activity State; LupusPRO, Lupus Patient-Reported Outcome; PRO, patient-reported outcome; QoL, quality of life; SELENA-SLEDAI, Safety of Estrogens in SLE National Assessment-SLE Disease Activity Index; SF-36, Short Form 36; SLEDAI-2K, SLE Disease Activity Index 2000; SRI-4, SLE Responder Index-4.

Table 6 Research agenda for SLE trials

Domains of improvement	Key elements for improvement
Education and training	Provide an overview of the landscape and current status of clinical trials in SLE. Develop training programmes for investigators to enhance their understanding of SLE and promote standardised assessment and data collection techniques.
Outcome measures and end points	Investigate novel and more clinically relevant outcome measures and end points. Systematic assessment of CLE by photographs at screening and at relevant end points to exclude cutaneous mimickers and objectively confirm CLE improvement.
Inclusion of real-world evidence	Explore the use of electronic health records for collecting real-world evidence. Investigate ways to integrate real-world evidence into traditional clinical trial methodologies to accurately reflect real-world cohorts of patients with SLE. Establish and promote collaborative patient registries for long-term data collection. Leverage registry data to identify long-term treatment outcomes and safety profiles.
Improved trial designs	Perform head-to-head trials; add active comparative arms in phase III trials. Implement adaptive trial designs to optimise resource allocation and increase efficiency. Explore Bayesian methods for adaptive randomisation and sample size adjustments. Investigate the feasibility of basket/umbrella trials to assess multiple interventions simultaneously.
Patient stratification and personalised medicine	Investigate potential molecular and genetic biomarkers (or combination of biomarkers with AI) for patient stratification and prediction of individual treatment response.
Novel imaging techniques	Investigate the use of imaging modalities (eg, MSK ultrasound, MRI) for more accurate assessment of disease activity.
Drug repurposing	Evaluate the potential for repurposing existing drugs for SLE treatment.
Enhanced patient engagement	Involve patients in the design of clinical trials (patient-centric trial design) to ensure relevance and feasibility. Implement initiatives to raise awareness among patients (particularly among ethnic minorities) and the public about the importance of clinical trial participation.
Digital health technologies	Evaluate the use of digital health technologies for remote monitoring and data collection. Develop digital strategies to enhance patient adherence and engagement throughout the trial. Use AI to assess CLE improvement based on digital photographs.
International collaboration and legal issues	Promote international collaboration of policymakers to harmonise regulatory requirements. Facilitate data and resource sharing to accelerate SLE research.

AI, artificial intelligence; CLE, cutaneous lupus erythematosus; MSK, musculoskeletal.

Early use of biological agents in SLE and cost-effective trials

The recent 2023 update of the EULAR recommendations for the management of SLE[60] highlights a critical area where research and clinical practice are evolving. This need revolves around the concept of using biological agents for early intervention in SLE, and raises questions about its relevance and cost-effectiveness beyond LN. Traditionally, first-line SLE treatment comprises non-biological medications like GCs, antimalarials and immunosuppressants. Biological agents have become more prominent in recent years, but determining the most appropriate timing and circumstances for using biological agents in SLE is a complex issue that requires further research, clinical trials and thoughtful consideration of clinical and socioeconomic factors. Despite potential clinical superiority in pivotal phase III trials, there remains high uncertainty around the cost-effectiveness

of new drugs in SLE.[61] Balancing the potential benefits of early intervention with the costs and resource implications remains a significant challenge in the field of SLE care and research and will need additional and dedicated trials to be confirmed as a valid strategy in SLE.

Ensuring that included patients have 'true SLE' and 'true active SLE'

There are no diagnosis criteria for SLE, and inclusion in trials relies on classification criteria. It is therefore crucial to ensure that included patients do have SLE. Common differential diagnoses (rosacea, seborrheic dermatitis, fibromyalgia, osteoarthritis) can be challenging and incorrectly attributing a manifestation to active SLE can impact the response rate, particularly in the placebo group. In a recent phase II trial evaluating the efficacy of low-dose interleukin (IL)-2 in SLE, the authors observed

a 100% response rate in the placebo group at two sites in Bulgaria. A post hoc analysis excluding these patients showed efficacy of low-dose IL-2, even though the overall study was otherwise negative.[62] The authors speculated that this high placebo response was driven by better adherence to concomitant background medications, including GC, during the trial period compared with their prior care, but it could be hypothesised that these patients did not truly have active SLE.

One way to improve the certainty of recruiting patients with active SLE is the use of Centralised Adjudication Committees (CACs), which are useful for assessing clinical end points that are not solely based on objective laboratory data and may thus be subjected to more variable interpretation.[63]

Elaborating clinical trials more similar to 'real-life' situations

Currently, the list of exclusion criteria in clinical trials often makes patient inclusion challenging and, more importantly, complicates the extrapolation of efficacy and tolerability data to real-world scenario. Indeed, it has been shown that nearly two-thirds of patients are ineligible to participate in non-renal SLE clinical trials.[64] In particular, the inclusion limitations in clinical trials are greatly influenced by authorised standard-of-care treatments, prior treatments and, especially, the washout periods for various treatments. Of note, some trials have suggested that background immunosuppressants could be safely withdrawn in patients with SLE with active but non-organ-threatening flare to support more interpretable trial results.

Need for international consensus: The Treatment Response Measure for SLE Taskforce

The Treatment Response Measure for SLE (TRM-SLE) Taskforce represents a groundbreaking global initiative that brings together a diverse group of stakeholders. Comprising SLE clinician-academics, patient advocates, industry collaborators and regulatory experts, this collaborative effort has a singular and ambitious objective: the development of a novel instrument for assessing treatment response in clinical trials for SLE.[65] At its core, the TRM-SLE Taskforce is dedicated to creating a new instrument for measuring treatment response in SLE clinical trials. This instrument is expected to address the limitations of existing outcome measures, such as the SLEDAI or BILAG, by offering improved sensitivity, specificity and relevance to patients' real-world experiences. Importantly, the taskforce includes patient advocates and representatives who ensure that the instrument being developed is patient-centric. Their involvement helps guarantee that the new measure considers clinical parameters and the quality of life and well-being of individuals living with SLE.

Improving the training of investigators in clinical trials

Specific training is mandatory to ensure data quality and integrity in clinical trials for SLE. Improving training and implementing more effective methodologies for adult learning can contribute to qualifying investigators and enhancing the clinical trial enterprise.[66]

Ensuring ethnic diversity

Incorporating ethnically diverse populations into clinical trials is an imperative step in advancing our understanding of SLE and improving patient care. This inclusivity enhances the generalisability of research outcomes. It ensures that medical advancements benefit all patients with SLE, irrespective of their racial or ethnic background. Of note, the EMBRACE study,[67] did not achieve its primary end point. While the importance of including diverse populations in SLE trials is clear, there are challenges to overcome. These may include language barriers, cultural differences and historical mistrust of clinical research within certain communities.[68] To address these challenges, researchers and trial organisers must engage with community leaders, collaborate with patient advocacy groups and develop culturally sensitive recruitment and informed consent processes.

The need for novel biomarkers

Furthermore, the pursuit of biomarkers for disease activity and treatment response prediction holds great promise. Identifying reliable biomarkers can aid in patient stratification, enabling more personalised treatment approaches. This is particularly relevant given the heterogeneity of SLE and the need for tailored therapies.[69] In addition to improving outcome measures, expanding the focus of clinical trials to address organ-specific manifestations of SLE is vital. Organ involvement significantly impacts patient outcomes, and organ-specific indices can provide more granular insights into treatment responses and disease progression. Lastly, long-term follow-up in clinical trials is essential to assess the durability of treatment responses, the risk of disease flares and the long-term impact on patient outcomes, including organ damage and quality of life.

Digital clinical trials

Finally, the integration of digital health technologies into clinical research, often referred to as digital clinical trials, has yet to be fully explored in the context of rare diseases like SLE. Digital clinical trials can potentially overcome geographical barriers that often limit the participation of patients with rare diseases like SLE. Researchers can use data analytics and artificial intelligence to identify potential participants, match them with suitable trials and streamline the recruitment process. This can reduce the time and resources required to initiate and conduct clinical trials, which is particularly advantageous in the context of rare diseases where patient recruitment can be challenging. One of the key advantages of digital clinical trials is the ability to collect real-time data from participants. This dynamic data collection can offer a more comprehensive and timely understanding of the disease's progression and treatment effects. Together, these technologies have the potential to transform the

landscape of clinical trials in SLE, making them more accessible, patient-centred and efficient. Additionally, e-health solutions can enhance patient education and self-management, which constitute essential elements of the non-pharmacological management of SLE.[70 71]

CONCLUSION

While significant progress has been made in clinical trial outcomes for SLE, there is a clear need for continued innovation. Addressing these challenges will require collaboration between researchers, clinicians, patients as well as with regulatory agencies to refine existing outcome measures, incorporate patient perspectives, identify reliable biomarkers and explore new therapeutic avenues. By doing so, we can advance our ability to manage SLE effectively and safely, and improve the lives of those living with this complex and impactful autoimmune disease.

ORCID iDs
Laurent Arnaud http://orcid.org/0000-0002-8077-8394
Ioannis Parodis http://orcid.org/0000-0002-4875-5395
Francois Chasset http://orcid.org/0000-0003-2580-8607

REFERENCES

1 Felten R, Sagez F, Gavand P-E, *et al*. 10 most important contemporary challenges in the management of SLE. *Lupus Sci Med* 2019;6:e000303.
2 Guidance for industry: systemic lupus erythematosus--developing medical products for treatment. 2010.
3 Arora S, Isenberg DA, Castrejon I. Measures of adult systemic lupus erythematosus: disease activity and damage. *Arthritis Care Res (Hoboken)* 2020;72 Suppl 10:27–46.
4 Petri M, Kim MY, Kalunian KC, *et al*. Combined oral contraceptives in women with systemic lupus erythematosus. *N Engl J Med* 2005;353:2550–8.
5 Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002;29:288–91.
6 Isenberg DA, Rahman A, Allen E, *et al*. BILAG 2004. development and initial validation of an updated version of the British isles lupus assessment group's disease activity index for patients with systemic lupus erythematosus. *Rheumatology (Oxford)* 2005;44:902–6.
7 Yee C-S, Cresswell L, Farewell V, *et al*. Numerical scoring for the BILAG-2004 index. *Rheumatology (Oxford)* 2010;49:1665–9.
8 Carter LM, Gordon C, Yee C-S, *et al*. Easy-BILAG: a new tool for simplified recording of SLE disease activity using BILAG-2004 index. *Rheumatology* 2022;61:4006–15.
9 Chessa E, Piga M, Floris A, *et al*. Use of physician global assessment in systemic lupus erythematosus: a systematic review of its Psychometric properties. *Rheumatology* 2020;59:3622–32.
10 Piga M, Chessa E, Morand EF, *et al*. Physician global assessment International Standardisation consensus in systemic lupus erythematosus: the PISCOS study. *Lancet Rheumatol* 2022;4:e441–9.
11 Mertz P, Piga M, Chessa E, *et al*. Fatigue is independently associated with disease activity assessed using the physician global assessment but not the SLEDAI in patients with systemic lupus erythematosus. *RMD Open* 2022;8:e002395.
12 Jesus D, Matos A, Henriques C, *et al*. Derivation and validation of the SLE disease activity score (SLE-DAS): a new SLE continuous measure with high sensitivity for changes in disease activity. *Ann Rheum Dis* 2019;78:365–71.
13 Chakka S, Krain RL, Concha JSS, *et al*. The CLASI, a validated tool for the evaluation of skin disease in lupus erythematosus: a narrative review. *Ann Transl Med* 2021;9:431.
14 Albrecht J, Taylor L, Berlin JA, *et al*. The CLASI (cutaneous lupus erythematosus disease area and severity index): an outcome instrument for cutaneous lupus erythematosus. *J Invest Dermatol* 2005;125:889–94.
15 Klein R, Moghadam-Kia S, LoMonico J, *et al*. Development of the CLASI as a tool to measure disease severity and responsiveness to therapy in cutaneous lupus erythematosus. *Arch Dermatol* 2011;147:203–8.
16 Krathen MS, Dunham J, Gaines E, *et al*. The cutaneous lupus erythematosus disease activity and severity index: expansion for rheumatology and Dermatology. *Arthritis Rheum* 2008;59:338–44.
17 Kushner CJ, Tarazi M, Gaffney RG, *et al*. Evaluation of the Reliability and validity of the cutaneous lupus erythematosus disease area and severity index (CLASI) in Paediatric cutaneous lupus among Paediatric Dermatologists and Rheumatologists. *Br J Dermatol* 2019;180:165–71.
18 Kuhn A, Meuth AM, Bein D, *et al*. Revised cutaneous lupus erythematosus disease area and severity index (RCLASI): a modified outcome instrument for cutaneous lupus erythematosus. *Br J Dermatol* 2010;163:83–92.
19 Chakka S, Krain RL, Ahmed S, *et al*. Evaluating change in disease activity needed to reflect meaningful improvement in quality of life for clinical trials in cutaneous lupus erythematosus. *J Am Acad Dermatol* 2021;84:1562–7.
20 AlE'ed A, Aydin POA, Al Mutairi N, *et al*. Validation of the cutaneous lupus erythematosus disease area and severity index and Pskindex27 for use in childhood-onset systemic lupus erythematosus. *Lupus Sci Med* 2018;5:e000275.
21 Morand E, Pike M, Merrill JT, *et al*. Deucravacitinib, a tyrosine kinase 2 inhibitor, in systemic lupus erythematosus: a phase II, randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol* 2023;75:242–52.
22 Morand EF, Furie R, Tanaka Y, *et al*. Trial of Anifrolumab in active systemic lupus erythematosus. *N Engl J Med* 2020;382:211–21.
23 Werth VP, Furie RA, Romero-Diaz J, *et al*. Trial of anti-Bdca2 antibody Litifilimab for cutaneous lupus erythematosus. *N Engl J Med* 2022;387:321–31.
24 Werth VP, Fleischmann R, Robern M, *et al*. Filgotinib or Lanraplenib in moderate to severe cutaneous lupus erythematosus: a phase 2, randomized, double-blind, placebo-controlled study. *Rheumatology (Oxford)* 2022;61:2413–23.
25 Guo LN, Perez-Chada LM, Borucki R, *et al*. Development of a working core outcome set for cutaneous lupus erythematosus: a practical approach to an urgent unmet need. *Lupus Sci Med* 2021;8:e000529.
26 Biogen. A 2-part seamless part A (phase 2)/Part B (phase 3) randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of Biib059 in participants with active subacute cutaneous lupus erythematosus and/or chronic cutaneous

lupus erythematosus with or without systemic manifestations and refractory and/or intolerant to Antimalarial therapy (AMETHYST). *ClinicaltrialsGov* 2023. Available: https://clinicaltrials.gov/study/NCT05531565

27 Mahmoud K, Zayat AS, Yusof MYM, *et al*. Ultrasound to identify systemic lupus erythematosus patients with musculoskeletal symptoms who respond best to therapy: the US evaluation for mUsculoskeletal lupus longitudinal Multicentre study. *Rheumatology (Oxford)* 2021;60:5194–204.

28 Shumilova A, Vital EM. Musculoskeletal manifestations of systemic lupus erythematosus. *Best Pract Res Clin Rheumatol* 2023;22:101859.

29 Sandler RD, Vital EM, Mahmoud K, *et al*. Revision to the musculoskeletal domain of the BILAG-2004 index to incorporate ultrasound findings. *Rheumatology (Oxford)* 2024;63:498–505.

30 Kisten Y, Arnaud L, Levitsky A, *et al*. Distinct fluorescence optical imaging patient clusters emerge for Seropositive and Seronegative rheumatoid arthritis. *ACR Open Rheumatol* 2023;5:474–80.

31 Sciascia S, Cecchi I, Massara C, *et al*. Thermography in systemic sclerosis patients and other rheumatic diseases: diagnosis, disease activity assessment, and therapeutic monitoring. *Autoimmun Rev* 2020;19:102449.

32 Anders HJ, Ramesh S, Ming-hui Z, *et al*. Lupus nephritis (primer). *Nature Reviews* 2020. Available: https://search.proquest.com/openview/3f41e83de093cc10022e49923891af1a/1?pq-origsite=gscholar&cbl=2069613

33 Parodis I, Houssiau FA. From sequential to combination and Personalised therapy in lupus nephritis: moving towards a paradigm shift *Ann Rheum Dis* 2022;81:15–9.

34 Parodis I, Tamirou F, Houssiau FA. Prediction of prognosis and renal outcome in lupus nephritis. *Lupus Sci Med* 2020;7:e000389.

35 Malvar A, Pirruccio P, Alberton V, *et al*. Histologic versus clinical remission in proliferative lupus nephritis. *Nephrol Dial Transplant* 2017;32:1338–44.

36 Parodis I, Adamichou C, Aydin S, *et al*. Per-protocol repeat kidney biopsy portends relapse and long-term outcome in incident cases of proliferative lupus nephritis. *Rheumatology (Oxford)* 2020;59:3424–34.

37 Furie RA, Petri MA, Wallace DJ, *et al*. Novel evidence-based systemic lupus erythematosus Responder index. *Arthritis Rheum* 2009;61:1143–51.

38 Wallace DJ, Kalunian K, Petri MA, *et al*. Efficacy and safety of Epratuzumab in patients with moderate/severe active systemic lupus erythematosus: results from EMBLEM, a phase IIb, randomised, double-blind, placebo-controlled, Multicentre study. *Ann Rheum Dis* 2014;73:183–90.

39 vanA, Bertsias G, *et al*. A framework for remission in SLE: consensus findings from a large International. *Ann Rheum Dis Mars* 2017;76:544–61.

40 Correction: DORIS definition of remission in SLE: final recommendations from an international task force. *Lupus Sci Med* 2022;9:e000538corr1.

41 Franklyn K, Lau CS, Navarra SV, *et al*. Definition and initial validation of a lupus low disease activity state (LLDAS). *Ann Rheum Dis* 2016;75:1615–21.

42 Nikpour M, Urowitz MB, Ibañez D, *et al*. Frequency and determinants of flare and persistently active disease in systemic lupus erythematosus. *Arthritis Rheum* 2009;61:1152–8.

43 Adamichou C, Bertsias G. Flares in systemic lupus erythematosus: diagnosis, risk factors and preventive strategies. *Mediterr J Rheumatol* 2017;28:4–12.

44 Saraiva L, Cunha RN, Jesus D, *et al*. n.d. The SLE-DAS provides an accurate and feasible flare tool in the clinical setting: a validation study. *Rheumatology*

45 Petri MA, Merrill JT, Maciuca R, *et al*. Annals of the rheumatic diseases. Fri0293 validation of the revised Selena flare index in systemic lupus erythematosus. n.d. Available: https://ard.bmj.com/content/72/Suppl_3/A473.3

46 Johnson SR, Gladman DD, Brunner HI, *et al*. Evaluating the construct of damage in systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2023;75:998–1006.

47 Stone JH, McDowell PJ, Jayne DRW, *et al*. The glucocorticoid toxicity index: measuring change in glucocorticoid toxicity over time. *Semin Arthritis Rheum* 2022;55:152010.

48 Miloslavsky EM, Naden RP, Bijlsma JWJ, *et al*. Development of a glucocorticoid toxicity index (GTI) using Multicriteria decision analysis. *Ann Rheum Dis* 2017;76:543–6.

49 Thibault T, Rajillah A, Bourredjem A, *et al*. n.d. Health related quality of life, remission and low lupus disease activity state in patients with systemic lupus erythematosus. *Rheumatology*

50 Nantes SG, Strand V, Su J, *et al*. Comparison of the sensitivity to change of the 36-item short form health survey and the lupus quality of life measure using various definitions of minimum clinically important differences in patients with active systemic lupus erythematosus. *Arthritis Care Res (Hoboken)* 2018;70:125–33.

51 Lindblom J, Gomez A, Borg A, *et al*. EQ-5D-3L full health state discriminates between drug and placebo in clinical trials of systemic lupus erythematosus. *Rheumatology (Oxford)* 2021;60:4703–16.

52 Lindblom J, Zetterberg S, Emamikia S, *et al*. n.d. EQ-5D full health state after therapy heralds reduced hazard to accrue subsequent organ damage in systemic lupus erythematosus. *Front Med*;9.

53 Lai JS, Beaumont JL, Ogale S, *et al*. Validation of the functional assessment of chronic illness therapy-fatigue scale in patients with moderately to severely active systemic lupus erythematosus, participating in a clinical trial. *J Rheumatol* 2011;38:672–9.

54 Thibault T, Bourredjem A, Maurier F, *et al*. The mediating effect of fatigue in impaired quality of life in systemic lupus erythematosus: mediation analysis of the French EQUAL cohort. *Rheumatology* 2023;62:3051–8.

55 Katz P, Yazdany J, Trupin L, *et al*. Psychometric evaluation of the National Institutes of health patient-reported outcomes measurement information system in a Multiracial, Multiethnic systemic lupus erythematosus cohort. *Arthritis Care Res (Hoboken)* 2019;71:1630–9.

56 McElhone K, Abbott J, Shelmerdine J, *et al*. Development and validation of a disease-specific health-related quality of life measure, the Lupusqol, for adults with systemic lupus erythematosus. *Arthritis Rheum* 2007;57:972–9.

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

58 Leong KP, Kong KO, Thong BYH, *et al*. Development and preliminary validation of a systemic lupus erythematosus-specific quality-of-life instrument (SLEQOL). *Rheumatology (Oxford)* 2005;44:1267–76.

59 Neupane B, Shukla P, Slim M, *et al*. Belimumab versus Anifrolumab in adults with systemic lupus erythematosus: an indirect comparison of clinical response at 52 weeks. *Lupus Sci Med* 2023;10:e000907.

60 Rodríguez-Carrio J, Burska A, Conaghan PG, *et al*. EULAR points to consider for the measurement, reporting and application of IFN-I pathway activation assays in clinical research and practice. *Ann Rheum Dis* 2023;82:754–62.

61 Mandrik O, Fotheringham J, Ren S, *et al*. The cost-effectiveness of Belimumab and Voclosporin for patients with lupus nephritis in the United States. *Clin J Am Soc Nephrol* 2022;17:385–94.

62 Humrich JY, Cacoub P, Rosenzwajg M, *et al*. Low-dose Interleukin-2 therapy in active systemic lupus erythematosus (LUPIL-2): a Multicentre, double-blind, randomised and placebo-controlled phase II trial. *Ann Rheum Dis* 2022;81:1685–94.

63 Pike MC, Kelley L. Data quality challenges in systemic lupus erythematosus trials: how can this be Optimized *Curr Rheumatol Rep* 2012;14:324–33.

64 Dyball S, Collinson S, Sutton E, *et al*. Lupus clinical trial eligibility in a real-world setting: results from the British isles lupus assessment group-Biologics register (BILAG-BR). *Lupus Sci Med* 2021;8:e000513.

65 Connelly K, Eades LE, Koelmeyer R, *et al*. Towards a novel clinical outcome assessment for systemic lupus erythematosus: first outcomes of an international Taskforce. *Nat Rev Rheumatol* 2023;19:592–602.

66 Bechtel J, Chuck T, Forrest A, *et al*. Improving the quality conduct and efficiency of clinical trials with training: recommendations for preparedness and qualification of investigators and delegates. *Contemp Clin Trials* 2020;89:105918.

67 Ginzler E, Guedes Barbosa LS, D'Cruz D, *et al*. Fifty-two-week study of the efficacy and safety of Belimumab in patients of black African ancestry with systemic lupus erythematosus. *Arthritis Rheumatol* 2022;74:112–23.

68 Sheikh SZ, Englund TR, Burriss SW, *et al*. EMBRACE: one small story in lupus-one giant challenge in clinical trials. *ACR Open Rheumatol* 2022;4:747–52.

69 Felten R, Scherlinger M, Mertz P, *et al*. New Biologics and targeted therapies in systemic lupus: from new molecular targets to new indications. A systematic review. *Joint Bone Spine* 2023;90:105523.

70 Parodis I, Girard-Guyonvarc'h C, Arnaud L, *et al*. EULAR recommendations for the non-pharmacological management of systemic lupus erythematosus and systemic sclerosis. *Ann Rheum Dis* 2023;10.

71 Parodis I, Gomez A, Tsoi A, *et al*. Systematic literature review informing the EULAR recommendations for the non-pharmacological management of systemic lupus erythematosus and systemic sclerosis. *RMD Open* 2023;9:e003297.