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Original Article

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Validating treat-to-target endpoints in childhood lupus: data-driven sensitivity analyses from the UK JSLE cohort study

Chandni Sarker[1,‡], Andrea L. Jorgensen[2,‡], Kukatharmini Tharmaratnam[2], Eslam Al-Abadi[3], Kate Armon[4], Kathryn Bailey[5], Marek Bohm[6], Mary Brennan[7], Coziana Ciurtin[8], Janet Gardner-Medwin[9], Daniel P. Hawley[10], Alison Kinder[11], Alice Leahy[12], Gulshan Malik[13], Zoe McLaren[14], Elena Moraitis[15], Ellen Mosley[16], Athimalaipet V. Ramanan[17], Satyapal Rangaraj[18], Annie Ratcliffe[19], Philip Riley[20], Heather Rostron[6], Ethan S. Sen[21], Christian M. Hedrich[1,22], Michael W. Beresford[1,22,#], Eve M.D. Smith[1,23,*,#]

[1]Department of Women's & Children's Health, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK
[2]Department of Health Data Science, Institute of Population Health, University of Liverpool, Liverpool, UK
[3]Department of Rheumatology, Birmingham Children's Hospital, Birmingham, UK
[4]Department of Paediatric Rheumatology, Cambridge University Hospitals, Cambridge, UK
[5]Department of Paediatric Rheumatology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[6]Department of Paediatric Rheumatology, Leeds Children Hospital, Leeds, UK
[7]Department of Paediatric Rheumatology, Royal Hospital for Sick Children, Edinburgh, UK
[8]Centre for Adolescent Rheumatology, University College London, London, UK
[9]Department of Child Health, University of Glasgow, Glasgow, UK
[10]Department of Paediatric Rheumatology, Sheffield Children's Hospital, Sheffield, UK
[11]Leicester Children's Hospital, University Hospitals of Leicester NHS Trust, Leicester, UK
[12]Department of Paediatric Rheumatology, Southampton General Hospital, Southampton, UK
[13]Paediatric Rheumatology, Royal Aberdeen Children's Hospital, Aberdeen, UK
[14]Rheumatology Department, Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, UK
[15]Department of Paediatric Rheumatology, Great Ormond Street Hospital, London, UK
[16]Department of Paediatrics, Bradford Royal Infirmary, Bradford, UK
[17]University Hospitals Bristol NHS Foundation Trust & Bristol Medical School, University of Bristol, Bristol, UK
[18]Department of Paediatric Rheumatology, Nottingham University Hospitals, Nottingham, UK
[19]Department of Paediatrics, Musgrove Park Hospital, Taunton, UK
[20]Department of Paediatric Rheumatology, Royal Manchester Children's Hospital, Manchester, UK
[21]Paediatric Rheumatology, Great North Children's Hospital & Faculty of Medical Sciences, Newcastle University, Newcastle upon Tyne, UK
[22]Department of Paediatric Rheumatology, Alder Hey Children's NHS Foundation Trust Hospital, Liverpool, UK
[23]School of Infection & Immunity, University of Glasgow, Glasgow, UK
*Correspondence to: Eve M.D. Smith, School of Infection & Immunity, University of Glasgow, 120 University Place, Glasgow G12 8TA, UK.
E-mail: eve.smith@glasgow.ac.uk
[‡]C.S. and A.L.J. are joint first authors and contributed equally.
[#]M.W.B. and E.M.D.S. are joint last authors and contributed equally.

Abstract

Objectives: **To conduct data-driven sensitivity analyses to evaluate whether refined definitions of childhood-onset systemic lupus erythematosus (cSLE) treat-to-target goals provide better protection against moderate-severe flares and new damage, compared with original consensus-derived targets.**

Methods: **The UK JSLE Cohort Study was utilized. Childhood-SLE target attainment was determined at each visit. Removal or transformation of cSLE target criteria ('variations') were investigated, for Childhood Lupus Low Disease Activity State (cLLDAS), cSLE Clinical Remission on Steroids (cCR) and cSLE Clinical Remission off Steroids (cCR-0). The impact of such variations on the hazards of subsequent moderate-severe flare and new damage was assessed, using Prentice–Williams–Peterson (PWP) models. Two-sided *t*-tests compared the hazard ratios (HRs) obtained from the PWP gap-time models for the original and varied cSLE target definitions.**

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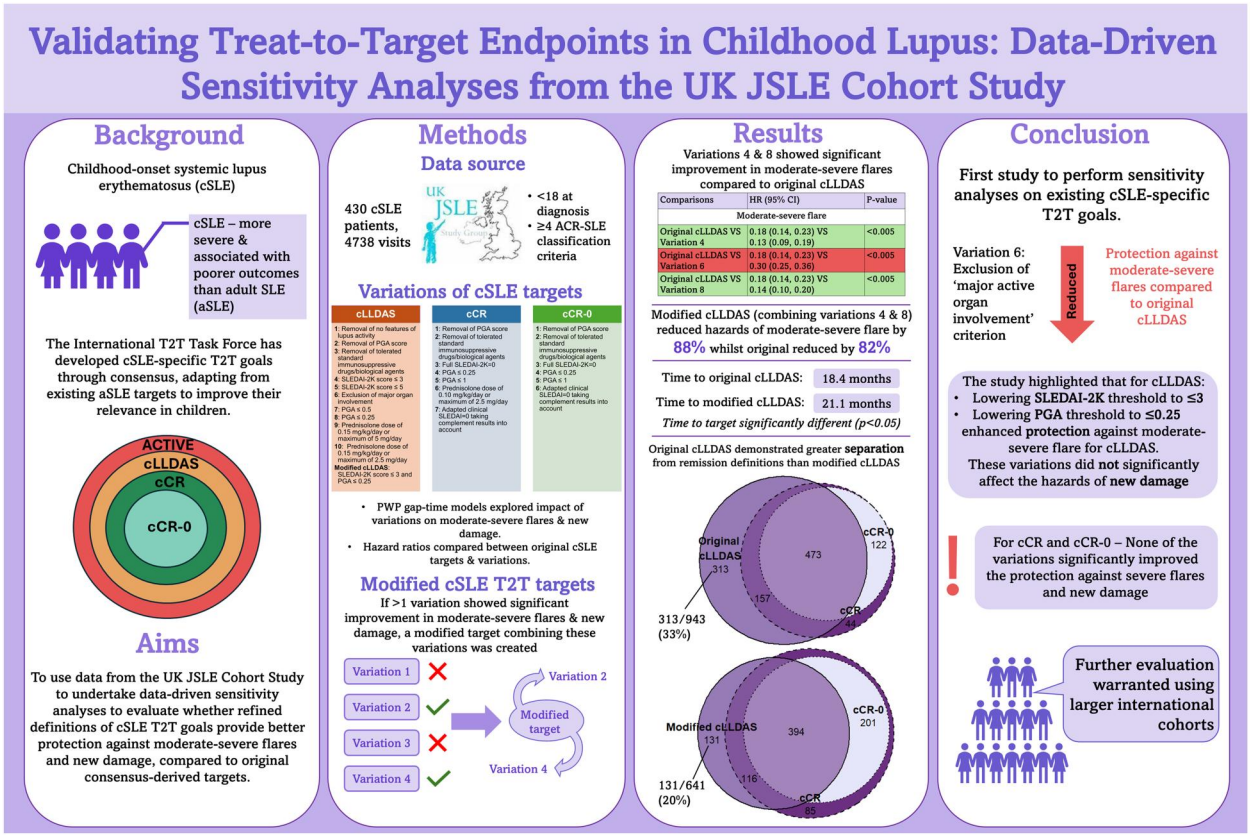
Results: **Two variations of cLLDAS demonstrated significantly better protection against moderate-severe flare, including transformation of SLEDAI-2K cut-off to ≤3 (HR 0.13 [0.09, 0.19], $P < 0.001$); and transformation of PGA cut-off to ≤0.25 (HR 0.14 [0.10, 0.20], $P < 0.001$). These variations in cLLDAS did not impact on the hazards of new damage. No variations of cCR and cCR-0 led to a significant improvement in hazards of moderate-severe flare/new damage (all $P > 0.05$). A modified version of cLLDAS, combining these two transformations was also assessed, demonstrating further improvement in protection against moderate-severe flare (HR 0.12 [0.08, 0.17], $P < 0.001$).**

Conclusions: **Refining the cLLDAS definition by lowering the SLEDAI-2K cut-off to ≤3 and PGA to ≤0.25 may enhance protection against moderate-severe flare, but not new damage. No variations of cCR or cCR-0 showed significant improvement.**

Graphical abstract



Keywords childhood-SLE, treat-to-target, low disease activity

Rheumatology key message

- Two variations of cLLDAS were associated with enhanced protection against moderate-severe flares, but not damage.
- No modifications of the cCR and cCR-0 definitions improved protection against moderate-severe flare/new damage.
- Further studies are needed including larger, international longitudinal datasets to re-assess this.

Introduction

Childhood-onset systemic lupus erythematosus (cSLE) is a multisystem autoimmune disease, with onset under 18 years [1, 2]. The disease is characterized by significant morbidity and mortality, driven by severe flares and damage accrual [3]. It is well established that cSLE is more aggressive at presentation and during the disease course compared with those with adult-onset SLE (aSLE) [4, 5], with higher adjusted mean SLEDAI-2K scores during follow-up [6]. Notably, patients with cSLE also

display higher standardized mortality rates as compared with aSLE [4, 7], and reduced health-related quality of life (HRQOL) [8]. Comprehensive treatment strategies are crucial to reduce the occurrence of irreversible damage accrual, frequency of severe flares and improve health-related quality of life in cSLE patients [9].

Treat-to-target (T2T) strategies have been shown to improve outcomes for numerous chronic rheumatic diseases, including rheumatoid arthritis, psoriatic arthritis and juvenile idiopathic arthritis [10–13]. T2T involves the systematic optimization of a patient's treatment until a specific target is attained, with further adjustment of treatment if the target is no longer attained [14]. To date, there have been no clinical trials that explored a T2T approach in patients with cSLE. Thus, the TARGET LUPUS© research program, '**T**argeting disease, **A**greeing **R**ecommendations and reducing **G**lucocorticoids through **E**ffective **T**reatment, in **LUPUS**' has been established with the aim of developing T2T strategies for cSLE [15, 16].

An International cSLE T2T Task Force has produced evidence-based consensus derived cSLE-specific T2T targets, including Childhood Lupus Low Disease Activity State (cLLDAS) [17], cSLE clinical remission on steroids (cCR) and cSLE clinical remission off steroids (cCR-0) [18], endorsed by the Paediatric Rheumatology European Society (PReS). These cSLE-specific targets have been adapted from existing aSLE-specific targets, including modifications to improve their relevance to children and young people, e.g. introducing a weight-based corticosteroid dosing threshold to avoid unnecessarily high corticosteroid treatment for younger patients.

Conceptually, target attainment should protect against severe flares and new damage, as these are two of the main determinants of longer-term outcomes in cSLE [4, 6, 7]. Thus, the current study aimed to conduct data-driven sensitivity analyses to evaluate whether refined definitions of cSLE T2T goals could provide better protection against severe flares and new damage, as compared with the original consensus-derived targets (cLLDAS, cCR and cCR-0) in participants recruited to the UK JSLE Cohort Study.

Methods

Data source and data collection

Data from the UK JSLE Cohort Study and Repository were utilized, including longitudinal data from patients followed up between 2006 and 2020, from 22 paediatric rheumatology centres. Participants were included in the study if they were $<$18 years of age at diagnosis and had fulfilled $\geq$4 American College of Rheumatology (ACR) and/or Systemic Lupus International Collaborating Clinics 2012 classification criteria for SLE. Clinical and demographic data were obtained at baseline, as well as during each follow-up visit, including patient demographics (age at diagnosis, gender, ethnicity and disease duration at each visit), cSLE disease activity [including full Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K), clinical-SLEDAI-2K (cSLEDAI), the British Isles Lupus Assessment Grade-2004 (BILAG2004)], Systemic Lupus International Collaborating Clinics Standardized Damage Index (SLICC-SDI) scores and laboratory blood/urine measurements. Written, informed consent was obtained by participants and parents for recruitment to the UK JSLE Cohort Study. The UK JSLE Cohort Study received full ethical approval from the National Research Ethics Service Northwest (Liverpool, UK, reference 06/Q1502/77).

Existing target definitions

At each patient visit, attainment of the cSLE targets were assessed. The cLLDAS target definition consisted of the following criteria: (1) SLEDAI-2K score $\leq$4 with no major active organ involvement (cardiopulmonary, central nervous system, fever, renal and vasculitis), (2) no new features of lupus activity compared with previous assessment (no new SLEDAI-2K features), (3) physician global assessment (PGA) score of $\leq$1, (4) prednisolone dose of 0.15 mg/kg/day or a maximum of 7.5 mg/day and no intravenous methylprednisolone and (5) tolerated standard maintenance immunosuppressive drugs/biological agents.

In terms of the remission definitions, cCR had the following criteria: (1) cSLEDAI score equal to 0, (2) PGA score of $\leq$0.5, (3) prednisolone dose of 0.10 mg/kg/day or a maximum of 5.0 mg/day and no intravenous methylprednisolone and (4) tolerated standard maintenance immunosuppressive drugs/biological agents. The second remission definition, cCR-0, was similar to cCR, differing in relation to the corticosteroid criterion (criterion 3), which included for cCR-0 'no prednisolone or methylprednisolone'.

Variations of the existing cSLE target definitions

Twenty-three variations of the existing cSLE target definitions were explored (10 variations in cLLDAS, seven for cCR and six for cCR-0), including the removal or transformation of current criteria. A description of these variations is provided in Table 1.

Statistical analyses

All analyses were conducted in R (Version 4.3.2) [19]. A threshold of $P < 0.05$ was considered statistically significant for analyses included in the study.

Descriptive analyses

Descriptive statistics of clinical and demographic characteristics were computed. Continuous and categorical variables were reported as medians and interquartile range (IQR) or frequencies and percentages, respectively. Normality of data were assessed using histograms and Shapiro–Wilks tests. The imputation strategy for accounting for missing weight values to define cSLE T2T endpoints is described in Supplementary Table S1.

Assessment of moderate-severe flare and new damage outcomes

The study assessed the impact of target attainment on two outcomes: moderate-severe flare and new damage. Moderate-severe flare was defined by a BILAG score of A or B in any organ

Table 1 Variations of the paediatric-specific cSLE targets.

	Description of modified criterion associated with each variation
cLLDAS	
1	Removal of 'no new features of lupus activity' criterion.
2	Removal of 'PGA score' criterion.
3	Removal of 'tolerated standard immunosuppressive drugs/biological agents' criterion.
4	Transformation of 'SLEDAI-2K score of ≤4 with no major active organ involvement' to SLEDAI-2K score of ≤3, with no major active organ involvement.
5	Transformation of 'SLEDAI-2K score of ≤4 with no major active organ involvement' to SLEDAI-2K score of ≤5, with no major active organ involvement.
6	Transformation of 'SLEDAI-2K score of ≤4 with no major active organ involvement' criterion to exclude 'no major active organ involvement'.
7	Transformation of 'physician global assessment score of ≤1' criterion to a threshold of ≤0.5.
8	Transformation of 'physician global assessment score of ≤1' criterion to a threshold of ≤0.25.
9	Transformation of 'prednisolone dose of 0.15 mg/kg/day or a maximum of 7.5 mg/day' criterion to 'prednisolone dose of 0.15 mg/kg/day or a maximum of 5 mg/day'.
10	Transformation of 'prednisolone dose of 0.15 mg/kg/day or a maximum of 7.5 mg/day' criterion to 'prednisolone dose of 0.15 mg/kg/day or a maximum of 2.5 mg/day'.
cCR	
1	Removal of 'physician global assessment score' criterion.
2	Removal of 'tolerated standard immunosuppressive drugs/biological agents' criterion.
3	Transformation of 'clinical SLEDAI = 0' criterion to full SLEDAI-2K = 0.
4	Transformation of 'PGA ≤0.5' to ≤0.25.
5	Transformation of 'PGA ≤0.5' criterion to ≤1.
6	Transformation of 'prednisolone dose of 0.10 mg/kg/day or maximum of 5 mg/day' to prednisolone dose of 0.10 mg/kg/day or maximum of 2.5 mg/day.
7	Transformation of 'clinical SLEDAI = 0' criterion to 'adapted clinical SLEDAI = 0, taking complement results into account'.
cCR-0	
1	Removal of 'physician global assessment score' criterion.
2	Removal of 'tolerated standard immunosuppressive drugs/biological agents' criterion.
3	Transformation of 'clinical SLEDAI = 0' criterion to full SLEDAI-2K = 0.
4	Transformation of 'PGA ≤0.5' to ≤0.25.
5	Transformation of 'PGA ≤0.5' criterion to ≤1.
6	Transformation of 'clinical SLEDAI = 0' criterion to 'adapted clinical SLEDAI = 0, taking complement results into account'.

Variations 7 and 6 for cCR and cCR-0, respectively, refer to modifying the 'clinical SLEDAI = 0' criterion to use the 'adapted clinical SLEDAI = 0', which incorporates complement results but excludes anti-dsDNA. In these variations, only complement levels are considered when assessing disease activity.
Abbreviations: cCR, cSLE clinical remission on steroids; cCR-0, cSLE clinical remission off steroids; cLLDAS, childhood lupus low disease activity state; cSLE, childhood-onset systemic lupus erythematosus; cSLEDAI, clinical-SLEDAI-2K score; PGA, physician global assessment; SLEDAI-2K, systemic lupus erythematosus disease activity index 2000.

domain during patient follow-up. New damage was defined by an increase of SLICC-SDI score by ≥1 unit.

The effect of achieving both the original cSLE targets and each variation of these targets on both moderate-severe flare and new damage was analysed using Prentice–Williams–Peterson (PWP) gap-time models, which are well suited for exploring recurrent events, including new damage and moderate-severe flare [20]. Univariable PWP gap-time models [using 'coxph()' R function from 'Survival' R library] were first used to evaluate association between demographic factors as well as the various target definitions and the new damage/moderate-severe flare outcomes [21]. Subsequently, multivariable PWP gap-time models were implemented to test for association between attainments of each target definition in turn and moderate-severe flare, adjusting for significant factors identified in the univariable analyses with a P-value < 0.05. Multivariable models were not conducted for the new damage outcome, as no significant factors other than target state were established from univariable analyses. HRs and 95% confidence intervals (95% CIs) were reported.

The hazard ratios (HRs) for each target variation were compared with those from the original consensus-based targets using Student's t test for dependent samples ['survcomp' R library; 'h.comp()' R function] [22]. Bonferroni correction of P-values was utilized for multiple comparison testing.

Data-driven modified composite targets

When variations of multiple target criteria significantly reduced the hazards of moderate-severe flares and/or new damage, we explored the effect of combining these variations into a modified composite target to assess whether further reductions could be achieved. The same methods as previously described were applied, including descriptive analyses of attainability of

new target and univariable and multivariable PWP gap-time models comparing the impact on moderate-severe flares and new damage against the original consensus-derived cSLE targets. Venn diagrams were implemented, describing the overlap and separation in target attainability between the original and modified target definitions.

Results

Clinical and demographic characteristics of UK JSLE cohort patients

Data from the UK JSLE Cohort Study consisted of 430 individuals and 4738 follow-up visits, including 359 females (83.5%) and 71 males (16.5%). The median age at diagnosis was 12.8 years (IQR: 10.4, 14.6). The majority of the cohort were White British patients ($n = 218$, 52%), followed by 129 Asian (31%) and 72 African/Caribbean patients (17%). At study recruitment, damage and flares was reported in 66/430 (16.2%) and 328/430 (76.3%) of patients, respectively (Table 2).

Table 2 Clinical and demographic characteristics of the patient cohort.

Clinical and demographic characteristics	Value
Sex, *n* (%)	
Males	71/430 (16.5)
Females	359/430 (83.5)
Ethnicity, *n* (%)[a]	
White British	218/419 (52.0)
Asian	129/419 (30.8)
African/Caribbean	72/419 (17.2)
Age at diagnosis (years), median (IQR)	12.8 (10.4, 14.6)
Length of disease from diagnosis (years), median (IQR)	2.0 (0.7, 4.0)
Length of time to diagnosis (years), median (IQR)	0.3 (0.1, 0.9)
Number of visits per patient, median (IQR)	10.0 (5.0, 15.0)
ACR criteria at diagnosis, median (IQR)	5.0 (5.0, 7.0)
SLEDAI-2K at diagnosis, median (IQR)	10.0 (6.0, 15.0)
BILAG score at diagnosis, median (IQR)	10.0 (4.0, 16.0)
ANA positive at study recruitment, *n* (%)	417/430 (97.0)
Anti-dsDNA positive during follow-up, *n* (%)	299/430 (69.5)
Anti-Sm positive at study recruitment, *n* (%)	67/430 (15.6)
Complement three (C3) levels during follow-up, median (IQR)	1.0 (0.8, 1.2)
Complement four (C4) levels during follow-up, median (IQR)	0.15 (0.10, 0.22)
SLICC-SDI score at study recruitment, *n* (%)[b]	
No damage (SLICC-SDI = 0)	344/410 (83.9)
Mild damage (SLICC-SDI = 1)	49/410 (12.0)
Moderate damage (SLICC-SDI = 2)	9/410 (2.2)
Severe damage (SLICC-SDI ≥3)	8/410 (2.0)
SLICC-SDI score at last visit, *n* (%)[b]	
No damage (SLICC-SDI = 0)	3150/4445 (70.9)
Mild damage (SLICC-SDI = 1)	865/4445 (19.5)
Moderate damage (SLICC-SDI = 2)	202/4445 (4.5)
Severe damage (SLICC-SDI ≥ 3)	228/4445 (5.1)
Number of flares present at study recruitment, *n* (%)	328/430 (76.3)
Number of flares during all follow-up visits, *n* (%)	2013/4738 (42.5)

Continuous variables are reported as medians and IQR, as data were skewed. Categorical variables are represented as frequencies and percentages. Self-reported ethnicity information was collected in accordance with the UK National Census categorizations. Data of patients who were of mixed race were grouped with those of the associated ethnic minority group.

[a] Ethnicity data was not available for 11 patients.

[b] SLICC-SDI score at study recruitment was not available for 20 patients.

Abbreviations: ACR, American College of Rheumatology; ANA, antinuclear antibodies; anti-dsDNA positive, anti-double stranded DNA antibody positivity; IQR, interquartile range; SLICC-SDI, SLICC standardized damage index.

Impact of attainment of original consensus-derived cSLE targets and corresponding variations of these target definitions on hazards of moderate-severe flare

A description of the attainability of the original cSLE target criteria and all exploratory variations, is provided in Supplementary Table S2, including the number of patients reaching each target during follow-up, the time to target attainment and the percentage of follow-up and duration of target attainment. Univariable PWP gap-time models demonstrated that attainment of the original consensus-derived cLLDAS, cCR and cCR-0 targets and all variations of the definitions (as detailed in Table 1) significantly reduced the hazards of moderate-severe flare (all $P < 0.001$). Clinical and demographic factors were also evaluated for their impact on the hazards of moderate-severe flare in univariable analyses. Disease duration over one year (HR 0.80, 95% CI: 0.74, 0.86) and being of White British (HR 0.79, 95% CI: 0.64, 0.97) or Asian (HR 0.78, 95% CI: 0.62, 0.98) ethnicity compared with African/Caribbean ethnicity significantly reduced the hazards of moderate-severe flare (all $P < 0.05$; Supplementary Table S3).

Within multivariable PWP gap-time models, attainment of the original consensus-derived cLLDAS, cCR and cCR-0 targets and all variations of the definitions significantly reduced the hazards of moderate-severe flares. We explored how variations of the target definitions compared with their original counterparts statistically, using Student's *t* test to compare the original cSLE target criteria to corresponding variations (Supplementary Tables S4–S6), to identify variations that performed significantly better or worse. These multivariable PWP gap-time models (Table 3) identified that two variations of cLLDAS were associated with better protection against moderate-severe flare, including transformation of SLEDAI-2K cut-off to ≤3 (variation 4, HR 0.13, 95% CI: 0.09, 0.19, $P < 0.001$); and transformation of PGA cut-off to ≤0.25 (variation 8, HR 0.14, 95% CI: 0.10, 0.20, $P < 0.001$). Conversely, modifying the cLLDAS criteria by removing the 'no major active organ involvement' component from the 'SLEDAI-2K score of ≤4 with no major active organ involvement' criterion (variation 6) significantly reduced protection against moderate-severe flares (HR 0.30 95% CI: 0.25, 0.36, $P < 0.001$;

Table 3 Multivariable PWP gap-time models assessing impact of target attainment on moderate-severe flare.

		Factors adjusted for in all multivariable models				
		Target state attainment at any time point	Ethnicity		Disease duration	Increasing SLICC-SDI score during follow-up
			Asian	White British		
cLLDAS models, HR (95% CI); *P-value*:						
Original cLLDAS		0.18 (0.14, 0.23); **$P < 0.001$**	0.83 (0.68, 1.00); **$P = 0.045$**	0.83 (0.70, 0.99); **$P = 0.041$**	0.83 (0.77, 0.88); **$P < 0.001$**	1.09 (1.05, 1.14); **$P < 0.001$**
Variation 1	Removal of 'no new features of lupus activity' criterion.	0.21 (0.16, 0.26); **$P < 0.001$**	0.86 (0.71, 1.03); $P = 0.109$	0.86 (0.73, 1.03); $P = 0.010$	0.83 (0.78, 0.88); **$P < 0.001$**	1.09 (1.05, 1.13); **$P < 0.001$**
Variation 2	Removal of 'PGA score' criterion.	0.19 (0.15, 0.25); **$P < 0.001$**	0.82 (0.68, 0.99); $P = 0.040$	0.83 (0.69, 0.99); $P = 0.034$	0.83 (0.77, 0.88); **$P < 0.001$**	1.09 (1.05, 1.14); **$P < 0.001$**
Variation 3	Removal of 'tolerated standard immunosuppressive drugs/biological agents' criterion.	0.17 (0.14, 0.21); **$P < 0.001$**	0.85 (0.72, 1.02); $P = 0.080$	0.83 (0.71, 0.98); $P = 0.031$	0.84 (0.80, 0.90); **$P < 0.001$**	1.07 (1.03, 1.11); **$P = 0.001$**
Variation 4[a]	Transformation of 'SLEDAI-2K score of ≤4 with no major active organ involvement' to SLEDAI-2K score of ≤3, with no major active organ involvement.	0.13 (0.09, 0.19); **$P < 0.001$**	0.82 (0.67, 0.99); **$P = 0.036$**	0.82 (0.69, 0.98); **$P = 0.030$**	0.82 (0.77, 0.88); **$P < 0.001$**	1.10 (1.06, 1.14); **$P < 0.001$**
Variation 5	Transformation of 'SLEDAI-2K score of ≤4 with no major active organ involvement' to SLEDAI-2K score of ≤5, with no major active organ involvement.	0.18 (0.14, 0.23); **$P < 0.001$**	0.83 (0.69, 1.00); **$P = 0.048$**	0.84 (0.70, 1.00); $P = 0.050$	0.83 (0.77, 0.88); **$P < 0.001$**	1.09 (1.05, 1.14); **$P < 0.001$**
Variation 6[b]	Transformation of 'SLEDAI-2K score of ≤4 with no major active organ involvement' criterion to exclude 'no major active organ involvement'.	0.30 (0.25, 0.36); **$P < 0.001$**	0.82 (0.67, 0.99); **$P = 0.037$**	0.82 (0.69, 0.98); **$P = 0.033$**	0.82 (0.77, 0.88); **$P < 0.001$**	1.09 (1.05, 1.14); **$P < 0.001$**
Variation 7	Transformation of 'physician global assessment score of ≤1' criterion to a threshold of ≤0.5.	0.15 (0.12, 0.21); **$P < 0.001$**	0.82 (0.68, 0.99); **$P = 0.041$**	0.83 (0.70, 0.99); **$P = 0.039$**	0.83 (0.77, 0.88); **$P < 0.001$**	1.09 (1.05, 1.14); **$P < 0.001$**
Variation 8[a]	Transformation of 'physician global assessment score of ≤1' criterion to a threshold of ≤0.25.	0.14 (0.10, 0.20); **$P < 0.001$**	0.81 (0.68, 0.98); **$P = 0.032$**	0.82 (0.69, 0.98); **$P = 0.027$**	0.82 (0.77, 0.88); **$P < 0.001$**	1.10 (1.05, 1.14); **$P < 0.001$**
Variation 9	Transformation of 'prednisolone dose of 0.15 mg/kg/day or a maximum of 7.5 mg/day' criterion to 'prednisolone dose of 0.15 mg/kg/day or a maximum of 5 mg/day'.	0.17 (0.13, 0.23); **$P < 0.001$**	0.84 (0.69, 1.01); $P = 0.064$	0.84 (0.70, 1.00); **$P = 0.048$**	0.83 (0.77, 0.88); **$P < 0.001$**	1.09 (1.05, 1.14); **$P < 0.001$**
Variation 10	Transformation of 'prednisolone dose of 0.15 mg/kg/day or a maximum of 7.5 mg/day' criterion to 'prednisolone dose of 0.15 mg/kg/day or a maximum of 2.5 mg/day'.	0.16 (0.12, 0.22); **$P < 0.001$**	0.82 (0.68, 1.00); **$P = 0.045$**	0.83 (0.70, 1.00); **$P = 0.049$**	0.82 (0.77, 0.88); **$P < 0.001$**	1.08 (1.04, 1.14); **$P < 0.001$**
cCR models, HR (95% CI); *P-value*:						
Original cCR		0.18 (0.13, 0.23); **$P < 0.001$**	0.83 (0.69, 1.01); $P = 0.062$	0.83 (0.70, 1.00); **$P = 0.048$**	0.83 (0.77, 0.88); **$P < 0.001$**	1.10 (1.05, 1.14); **$P < 0.001$**
Variation 1	Removal of 'physician global assessment score' criterion.	0.18 (0.14, 0.24); **$P < 0.001$**	0.83 (0.69, 1.01); $P = 0.061$	0.83 (0.70, 1.00); **$P = 0.046$**	0.83 (0.77, 0.88); **$P < 0.001$**	1.10 (1.05, 1.14); **$P < 0.001$**
Variation 2	Removal of 'tolerated standard immunosuppressive drugs/biological agents' criterion.	0.15 (0.12, 0.19); **$P < 0.001$**	0.83 (0.69, 1.00); **$P = 0.049$**	0.81 (0.68, 0.97); **$P = 0.021$**	0.84 (0.79, 0.89); **$P < 0.001$**	1.07 (1.03, 1.12); **$P < 0.001$**

(continued)

Table 3 (continued)

		Factors adjusted for in all multivariable models				
		Target state attainment at any time point	Ethnicity		Disease duration	Increasing SLICC-SDI score during follow-up
			Asian	White British		
Variation 3	Transformation of 'clinical SLEDAI = 0' criterion to full SLEDAI-2K = 0.	0.18 (0.13, 0.26); **$P < 0.001$**	0.80 (0.65, 0.97); **$P = 0.026$**	0.81 (0.68, 0.97); **$P = 0.025$**	0.81 (0.75, 0.87); **$P < 0.001$**	1.11 (1.06, 1.16); **$P < 0.001$**
Variation 4	Transformation of 'PGA ≤0.5' to ≤0.25.	0.18 (0.13, 0.24); **$P < 0.001$**	0.83 (0.68, 1.00); $P = 0.050$	0.82 (0.69, 0.99); **$P = 0.035$**	0.83 (0.77, 0.88); **$P < 0.001$**	1.10 (1.06, 1.14); **$P < 0.001$**
Variation 5	Transformation of 'PGA ≤0.5' criterion to ≤1.	0.17 (0.13, 0.23); **$P < 0.001$**	0.84 (0.69, 1.01); $P = 0.067$	0.84 (0.70, 1.00); $P = 0.052$	0.83 (0.77, 0.88); **$P < 0.001$**	1.10 (1.05, 1.14); **$P < 0.001$**
Variation 6	Transformation of 'prednisolone dose of 0.10 mg/kg/day or maximum of 5 mg/day' to prednisolone dose of 0.10 mg/kg/day or maximum of 2.5 mg/day.	0.17 (0.13, 0.22); **$P < 0.001$**	0.82 (0.68, 1.00); $P = 0.050$	0.82 (0.69, 0.99); **$P = 0.035$**	0.83 (0.77, 0.88); **$P < 0.001$**	1.09 (1.05, 1.14); **$P < 0.001$**
Variation 7	Transformation of 'clinical SLEDAI = 0' criterion to 'adapted clinical SLEDAI = 0, taking complement results into account'.	0.20 (0.14, 0.27); **$P < 0.001$**	0.80 (0.65, 0.97); **$P = 0.025$**	0.80 (0.67, 0.97); **$P = 0.019$**	0.81 (0.75, 0.87); **$P < 0.001$**	1.11 (1.06, 1.16); **$P < 0.001$**
cCR-0 models, HR (95% CI); *p-value*:						
Original cCR-0		0.17 (0.13, 0.23); **$P < 0.001$**	0.81 (0.67, 0.99); **$P = 0.037$**	0.82 (0.68, 0.98); **$P = 0.030$**	0.83 (0.77,0.89); **$P < 0.001$**	1.09 (1.04, 1.14); **$P < 0.001$**
Variation 1	Removal of 'physician global assessment score' criterion.	0.18 (0.14, 0.24); **$P < 0.001$**	0.81 (0.67, 0.99); **$P = 0.037$**	0.82 (0.68, 0.98); **$P = 0.029$**	0.83 (0.77, 0.89); **$P < 0.001$**	1.09 (1.04, 1.14); **$P < 0.001$**
Variation 2	Removal of 'tolerated standard immunosuppressive drugs/biological agents' criterion.	0.16 (0.13, 0.21); **$P < 0.001$**	0.82 (0.68, 0.99); **$P = 0.041$**	0.81 (0.67, 0.96); **$P = 0.019$**	0.84 (0.79, 0.89); **$P < 0.001$**	1.08 (1.03, 1.12); **$P = 0.001$**
Variation 3	Transformation of 'clinical SLEDAI = 0' criterion to full SLEDAI-2K = 0.	0.18 (0.13, 0.27); **$P < 0.001$**	0.79 (0.64, 0.96); **$P = 0.019$**	0.80 (0.67, 0.96); **$P = 0.019$**	0.81 (0.76, 0.87); **$P < 0.001$**	1.10 (1.06, 1.15); **$P < 0.001$**
Variation 4	Transformation of 'PGA ≤0.5' to ≤0.25.	0.17 (0.13, 0.24); **$P< 0.001$**	0.81 (0.67, 0.98); **$P= 0.032$**	0.81 (0.68, 0.97); **$P= 0.025$**	0.83 (0.77, 0.89); **$P< 0.001$**	1.09 (1.05, 1.14); **$P< 0.001$**
Variation 5	Transformation of 'PGA ≤0.5' criterion to ≤1.	0.17 (0.13, 0.23); **$P < 0.001$**	0.82 (0.67, 0.99); **$P = 0.041$**	0.82 (0.69, 0.98); **$P = 0.034$**	0.83 (0.77,0.89); **$P < 0.001$**	1.09 (1.04, 1.14); **$P < 0.001$**
Variation 6	Transformation of 'clinical SLEDAI = 0' criterion to 'adapted clinical SLEDAI = 0, taking complement results into account'.	0.20 (0.14, 0.27); **$P < 0.001$**	0.77 (0.64, 0.96); **$P = 0.017$**	0.80 (0.66, 0.96); **$P = 0.015$**	0.81 (0.76, 0.87); **$P < 0.001$**	1.10 (1.05, 1.15); **$P < 0.001$**

[a] Variations that showed significant improvement in risk of moderate-severe flares compared with original cLLDAS, see Supplementary Table S4.
[b] Variations that showed significant worsening in risk of moderate-severe flares compared with original cLLDAS, see Supplementary Table S4.
Hazard ratios (HRs) and 95% confidence intervals (95% CI) are reported. The *P* values highlighted in bold signify statistical significance on the impact of factors on moderate-severe flares.
Abbreviations: cCR, cSLE clinical remission on steroids; cCR-0, cSLE clinical remission off steroids; cLLDAS, childhood lupus low disease activity state; PWP, Prentice–Williams–Peterson; SLEDAI, systemic lupus erythematosus disease activity index; SLICC-SDI, SLICC standardized damage index.

Supplementary Table S4). No variations of cCR and cCR-0 led to a significant improvement in hazards of moderate-severe flare (all $P > 0.05$, Supplementary Tables S5 and S6).

Impact of attainment of original consensus-derived cSLE targets and corresponding variations of these target definitions on hazards of new damage

Univariable PWP gap-time models were conducted to assess the impact of target attainment on hazards of new damage. Attainment of all consensus-derived cSLE targets and corresponding variations significantly reduced the hazards of new damage (HRs ranging between 0.18 and 0.38, all $P < 0.001$, Supplementary Table S3). Comparisons between univariable PWP gap-time models for original cSLE targets and variations were conducted. In the univariable analyses, it was found that no variations of cLLDAS, cCR and cCR-0 were found to significantly influence the hazards of new damage as compared with the original definitions (Supplementary Tables S4–S6).

Modified version of cLLDAS

Significant improvements in protection against moderate-severe flare were identified with two variations of the original cLLDAS criteria: including lowering the 'SLEDAI-2K score of ≤4 with no major active organ involvement' to a score of ≤3 (variation 4) and reducing the 'physician global assessment score of ≤1' to a threshold of ≤0.25 (variation 8). Consequently, a modified definition of cLLDAS was evaluated, combining variations 4 and 8, resulting in a new, 'modified cLLDAS' with the following criteria:

- SLEDAI-2K score ≤3 with no major active organ involvement (cardiopulmonary, central nervous system, fever, renal and vasculitis).
- No new features of lupus activity compared with previous assessment.
- Physician global assessment score of ≤0.25.
- Prednisolone dose of 0.15 mg/kg/day or a maximum of 7.5 mg/day and no intravenous methylprednisolone.
- Tolerated standard maintenance immunosuppressive drugs/biological agents.

Comparisons of target attainability between original and modified cLLDAS showed that time to original cLLDAS (18.4 months [IQR 8.7, 31.7]) was significantly faster than modified cLLDAS (21.1 months [10.5, 36.3], $P < 0.05$), and percentage time spent in original cLLDAS (24.0% [IQR 13.0, 39.3]) was significantly longer than modified cLLDAS (18.9% [8.9, 36.6], $P < 0.05$, see Supplementary Table S7).

Univariable PWP gap-time models demonstrated that attainment of modified cLLDAS significantly lowered the hazards of moderate-severe flare (HR 0.11, 95% CI: 0.07, 0.16) compared with the original cLLDAS definition (HR 0.18, 95% CI: 0.14, 0.23, $P < 0.001$, see Table 4). Multivariable PWP gap-time models comparing original and modified cLLDAS targets (Table 4) also demonstrated that modified cLLDAS (HR 0.12, 95% CI: 0.08, 0.17, $P < 0.001$) significantly reduced the hazards of moderate-severe flare to a greater extent than original cLLDAS (HR 0.18, 95% CI: 0.14, 0.23, $P < 0.001$), with $P < 0.001$. Multivariable models could not be conducted for new damage as no other factor other than target state were found significant. The modified cLLDAS definition was associated with a numerically lower hazard of new damage (HR 0.14, 95% CI: 0.05, 0.39) compared with the original cLLDAS (HR 0.22, 95% CI: 0.11, 0.44). However, statistical comparisons between the univariable models demonstrated no significant reduction in the risk of new damage with modified cLLDAS compared with the original cLLDAS ($P = 0.096$, Table 4).

Attainability of modified cLLDAS vs original low disease activity and remission targets

It is important to demonstrate separation between low disease activity and remission targets if they are to be pursued in sequence. To evaluate this graphically, we analysed the degree of separation and overlap in the attainability of the original and modified cLLDAS and remission definitions using Venn diagrams (Fig. 1), showing that the original cLLDAS definition demonstrated greater separation from the remission definitions than the modified cLLDAS. Specifically, the original cLLDAS was attained independently (i.e. without overlapping with cCR or cCR-0) in 313 out of 943 visits (33.2%), compared with 131 out of 641 visits (20.4%) for the modified cLLDAS (Fig. 1).

Discussion

The T2T approach has been established as an effective strategy to optimize disease management and prevent complications in patients with chronic conditions. Previous studies using observational cohort datasets have demonstrated the utility of T2T strategies in mitigating adverse outcomes, such as disease flares and new damage [15, 23, 24]. The current target definitions for cSLE were developed through expert consensus, incorporating available evidence where possible [17, 18]. This current study aimed to consider whether refining cSLE-specific T2T definitions could further improve the impact of target attainment on protection against moderate-severe flares and new damage, through sensitivity analyses using data from the UK JSLE Cohort Study. These analyses showed that refinement of cLLDAS by lowering the SLEDAI-2K cut-off to ≤3 and PGA to ≤0.25 may enhance protection against moderate-severe flare, but not new damage, whereas no variations of cCR or cCR-0 led to significant improvement in the definitions.

An assessment of variations in the cLLDAS definitions revealed that excluding the 'no major active organ involvement' criterion resulted in a significant increase in the risk of moderate-severe flares compared with the original cLLDAS definition. This finding highlights the critical role of major organ involvement in determining outcomes, particularly when affecting the cardiopulmonary, central nervous and renal systems and vasculitis, as key determinants of flare risk [25]. This is consistent with previous studies showing that major organ

Table 4 Impact of modified cLLDAS attainment on moderate-severe flare and new damage.

	Univariable analyses			
	Moderate-severe flare		New damage	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Original cLLDAS	0.17 (0.13, 0.22)	**<0.001**	0.22 (0.11, 0.44)	**<0.001**
Modified cLLDAS (Combination of SLEDAI-2K score ≤3 with no major active organ involvement & PGA score of ≤0.25)	0.11 (0.07, 0.16)	**<0.001**	0.14 (0.05, 0.39)	**<0.001**
	Multivariable analyses			
Original cLLDAS	0.18 (0.14, 0.23)	**<0.001**	NA	NA
Modified cLLDAS (Combination of SLEDAI-2K score ≤3 with no major active organ involvement & PGA score of ≤0.25)	0.12 (0.08, 0.17)	**<0.001**	NA	NA
	Two-sided Student's *t* test comparing HRs extracted from PWP gap-time models			
Original cLLDAS VS modified cLLDAS (Combination of SLEDAI-2K score ≤3 with no major active organ involvement & PGA score of ≤0.25)	0.18 (0.14, 0.23) vs 0.12 (0.08, 0.17)	**<0.001**	0.22 (0.11, 0.44) vs 0.14 (0.05, 0.39)	0.096

Univariable and multivariable PWP gap-time models assessed the impact of achieving original or modified cLLDAS on moderate-severe flares and new damage, adjusting for ethnicity, disease duration and increasing SLICC-SDI. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were reported. The *P* values highlighted in bold signify statistical significance on the impact of original/modified cLLDAS on moderate-severe flares and new damage. Two-sided Student's *t* test compared original and modified cLLDAS on their impact on moderate-severe flares and new damage with *P* values highlighted in bold if there was a statistically significant difference between modified cLLDAS and original cLLDAS. cLLDAS, childhood lupus low disease activity state; Modified cLLDAS, a model combining variations 4 (SLEDAI-2K score ≤3 with no major active organ involvement) and 8 (PGA score of ≤0.25); NA, multivariable models were not conducted for new damage as no other factor other than target state were found significant.
Abbreviations: PGA, physician global assessment; PWP, Prentice–Williams–Peterson; SLEDAI, systemic lupus erythematosus disease activity index.

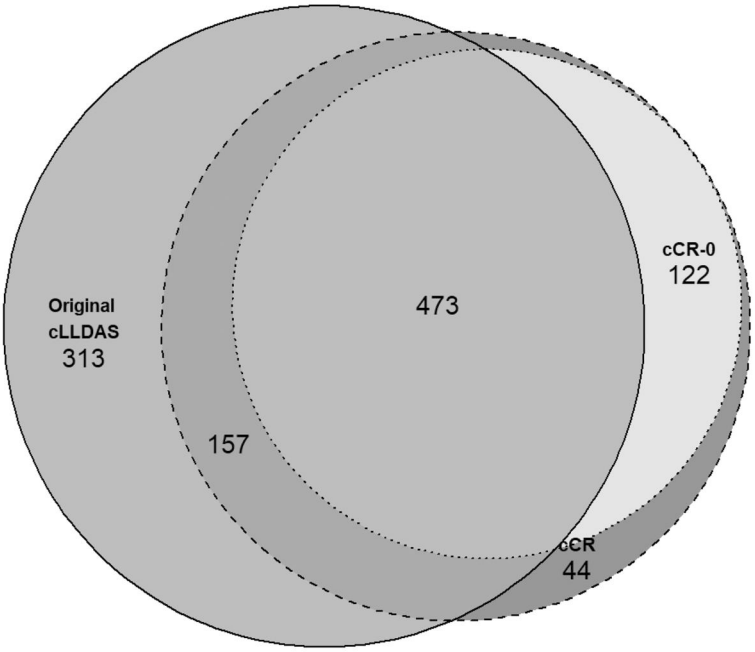
manifestations such as neuropsychiatric and renal involvement, as well as vasculitis, are strongly associated with flares in SLE [3, 26, 27].

Significant improvements in the risk of moderate-severe flares were observed when adjustments were made to the SLEDAI-2K and PGA cut-off thresholds. Lowering the SLEDAI-2K cut-off to ≤3 and the PGA score to ≤0.25 resulted in a substantial reduction in flare risk compared with the existing consensus-based cLLDAS definition. Furthermore, combining these two criteria into a modified cLLDAS definition led to an even greater reduction in the hazard of moderate-severe flares, decreasing from a hazard ratio of 0.18–0.12. Despite the statistical advantages of the modified cLLDAS definition in reducing flare risk, it was achieved by fewer patients overall, required a longer time to attain and resulted in patients spending a lower proportion of their follow-up period in this state. These findings raise concerns about the practical utility of the modified definition and its potential overlap with remission criteria. No variations of cCR and cCR-0 led to reduction in the hazards of severe flare or new damage compared with their original counterparts, suggesting that changes to the existing criterion may not be required.

The absence of an observed improvement in new damage may reflect the complex and multifactorial nature of damage development in cSLE. Previous studies have shown that disease duration, number and severity of flares and cumulative corticosteroid exposure are among the strongest predictors of long-term organ damage, often outweighing the effects of transient disease activity control [28–30]. In the present cohort, although refined targets reduced flare risk, the overall number of new damage events during follow-up was low, and follow-up duration may not have been sufficient to capture the long-term benefits of tighter disease control. Further studies utilizing larger, international longitudinal datasets are required to validate these findings and reassess their broader applicability.

There were limitations of the study that must be addressed. An overlap was highlighted between targets; for instance, a patient may attain both cLLDAS and cCR targets, which may suggest that the models do not solely represent the impact of a single T2T target on moderate-severe flares and new damage. The modified cLLDAS increased the overlap between targets. During follow-up, the number of new damage accrual events was relatively low, therefore, these findings must be validated

A – Venn diagram demonstrating attainability of original cLLDAS, cCR and cCR-0



B – Venn diagram demonstrating attainability of modified cLLDAS, cCR and cCR-0

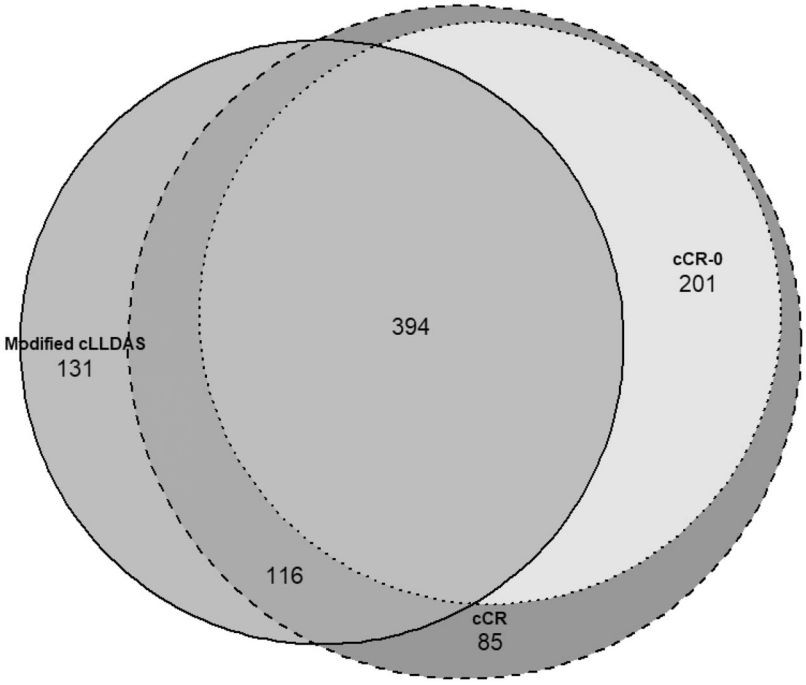


Figure 1 Venn diagrams showing the attainability of original/modified cLLDAS and remission definitions on a per visit basis. (**A**) Venn diagram showing attainment of original cLLDAS, cCR and cCR-0. (**B**) Venn diagram showing attainment of modified cLLDAS, cCR and cCR-0. cCR, cSLE clinical remission on steroids; cCR-0, cSLE clinical remission off steroids; cLLDAS, childhood lupus low disease activity state. **A**—Venn diagram demonstrating attainability of original cLLDAS, cCR and cCR-0. **B**—Venn diagram demonstrating attainability of modified cLLDAS, cCR and cCR-0

using larger national or international cohorts to further explore the impact of these variations on new damage. The study utilized real-world data reflecting routine practice across many centres but could lead to biases, while imputation may introduce inaccuracies affecting the findings of the study. Future research should incorporate larger international cohorts and establish clinical trial-based validation of cSLE T2T endpoints.

Although this study defined childhood-onset SLE as disease onset before age of 18 years, it is recognized that patients aged 16–18 may present with more 'adult-like' disease features, including lower rates of renal, neurological and haematological involvement and overall reduced disease severity. Including patients aged 17- and 18-year old could, therefore, potentially introduce some heterogeneity within the study population. Future studies could explore the robustness of these results when applying a stricter age cut-off (e.g. $<$16 years at onset). In addition, socioeconomic status is known to potentially influence disease activity, access to care and long-term outcomes in cSLE. Future studies incorporating socioeconomic indicators could provide valuable insights into how these factors may interact with T2T goal attainment and clinical outcomes.

Conclusion

This is the first study to perform sensitivity analyses on the consensus-derived, evidence-informed cSLE-specific T2T definitions, including cLLDAS, cCR and cCR-0. The findings demonstrate that modifying certain components of the cLLDAS criteria, specifically lowering the SLEDAI-2K threshold to $\leq$3 and the PGA threshold to $\leq$0.25 can potentially enhance protection against moderate-severe flares. However, no significant improvement was observed in reducing the risk of new damage with any of the variations explored. When considering potential adjustments to the target criteria, it is crucial to evaluate not only their impact on flare and damage risk but also their attainability and distinction from remission targets, ensuring that sequential attainment provides meaningful benefits for key outcomes. Although modified cLLDAS led to statistically greater protection from moderate-to-severe flare, there was greater overlap in the attainability of the original and modified cLLDAS and remission definitions. During the development of the original cSLE T2T targets, the international cSLE T2T Task Force aimed to align paediatric and adult SLE targets as closely as possible to facilitate life-course research and continuity in studies. Therefore, further evaluation of the cLLDAS T2T target using larger international cohorts is essential to refine the criteria, optimize protection against critical outcomes and determine whether adjustments are warranted.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

Deidentified participant data and a data dictionary defining each field will be made available to others upon reasonable request to the Chief Investigator for the UK JSLE Cohort Study, Professor Michael W Beresford (m.w.beresford@liverpool.ac.uk), following completion of the UK JSLE Cohort study Data Access Application Form. This can be obtained from the UK JSLE Cohort Study co-ordinator (Robertsc@liverpool.ac.uk). Additional related documents (e.g. study protocol, statistical analysis plan, informed consent forms) are not routinely available but requests may be considered on a case-by-case basis.

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