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# Defining remission in childhood-onset lupus: PReS-endorsed consensus definitions by an international task force

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ABSTRACT

*Objective:* To derive childhood-onset SLE (cSLE) specific remission definitions for future treat-to-target (T2T) trials, observational studies, and clinical practice.
*Methods:* The cSLE International T2T Task Force conducted Delphi surveys exploring paediatric perspectives on adult-onset SLE remission targets. A modified nominal group technique was used to discuss, refine, and agree on the cSLE remission target criteria.
*Results:* The Task Force proposed two definitions of remission: 'cSLE clinical remission on steroids (cCR)' and 'cSLE clinical remission off steroids (cCR-0)'. The common criteria are: (1) Clinical-SLEDAI-2 K = 0; (2) PGA score < 0.5 (0–3 scale); (4) stable antimalarials, immunosuppressive, and biologic therapy (changes due to side-effects, adherence, weight, or when building up to target dose allowed). Criterion (3) in cCR is the prednisolone dose ≤0.1 mg/kg/day (maximum 5 mg/day), whereas in cCR-0 it is zero.
*Conclusions:* cSLE definitions of remission have been proposed, maintaining sufficient alignment with the adult-SLE definition to facilitate life-course research.

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## 1. Introduction

Childhood-onset Systemic Lupus Erythematosus (cSLE), also known as Juvenile-onset Systemic Lupus Erythematosus (JSLE), is a chronic, systemic autoimmune and inflammatory condition. In contrast to adult-onset SLE (aSLE), children and teenagers with cSLE often experience higher levels of disease activity, a higher medication burden, and more severe internal organ involvement. Specifically, they exhibit a higher prevalence of renal, cardiovascular, and neuropsychiatric involvement compared to their adult counterparts, with the majority developing significant damage by early adulthood [1–5]. Despite advancements that have led to improved 10-year survival rates, standardized mortality rates remain significantly higher in cSLE as compared to aSLE [6,7].

Treat-to-target (T2T) strategies have demonstrated their effectiveness in improving both short-term and long-term outcomes in chronic medical conditions, including rheumatoid arthritis, and diabetes [8–12]. T2T is focused on the goal of promptly managing disease activity, preventing organ damage, and enhancing health-related quality of life [13]. Interest in adopting T2T approaches is growing internationally for both cSLE [14–19] and aSLE [20]. To date, extensive validation of T2T endpoints has been undertaken in aSLE, demonstrating an association with improved outcomes [21–32]. However, no formal randomised trials to assess the value of intervening to achieve these targets have been conducted to date. The TARGET LUPUS© research program, '**T**argeting disease, **A**greeing **R**ecommendations and reducing **G**lucocorticoids through **E**ffective **T**reatment, in **LUPUS**' is dedicated to developing T2T strategies specifically tailored for cSLE [14,15].

SLE recommendations for T2T in both cSLE [33] and aSLE [20] point towards remission being the ideal target and Low Disease Activity (LDA) an alternative target when remission cannot be achieved. Achieving disease remission should offer a high degree of protection against adverse outcomes including end-organ damage [20,34,35]. Within TARGET LUPUS©, an International cSLE T2T Task Force has convened and developed a consensus based, age-appropriate definition of LDA; Childhood Lupus Low Disease Activity State (cLLDAS) [36]. Specific adaptations were made relating to prednisolone dosing, where a weight-based cut off has been introduced, and the definition of stable immunosuppression where additional qualifiers relate to weight, side-effects, and adherence have been added. Childhood-LLDAS maintains sufficient alignment with the aSLE LLDAS definition to promote life-course research that includes individuals with cSLE and aSLE together [36]. The International cSLE T2T Task Force also agreed upon principles and points to consider for cSLE T2T strategies that were endorsed by the Paediatric Rheumatology European Society (PReS) [37], to inform a T2T approach in clinical practice and future trials.

In this context, the International cSLE T2T Task Force aimed to formulate cSLE-specific definitions of remission. It sought to do this building on existing aSLE definitions but adapted to better suit children with cSLE whilst preserving sufficient alignment to enable future potential T2T studies that encompass both cSLE and aSLE patients.

## 2. Methods

### 2.1. International task force

In July 2021, the cSLE T2T International Task Force was established with the aim of facilitating development of a T2T approach for cSLE [37]. The Task Force consists of 20 paediatric sub-specialists with significant expertise in cSLE, including paediatric rheumatologists ($n$ = 14), combined paediatric/adult rheumatologists ($n$ = 2), and nephrologists ($n$ = 4, including collaborators), as well as an adult rheumatologist with experience in developing aSLE T2T approaches [23–25]. The Task Force also includes three patient/parent representatives and two steering committee representatives (EMDS, MWB). The Task Force selection process was based on pre-defined criteria [36] relating to their clinical and research expertise, and involved inviting experts to self-nominate through various organisations, including the Paediatric Rheumatology European Society (PReS), the Childhood Arthritis and Rheumatology Research Alliance (CARRA), the UK JSLE Study Group, and the UK British Association for Paediatric Nephrology (BAPN). The resulting Task Force comprises members from the principle professional networks in paediatric rheumatology and nephrology across six continents (Europe, North America, South America, Asia, Africa, Australia).

### 2.2. Review of evidence

Literature related to the development of aSLE remission definitions was initially compiled, to ensure the Task Force was aware of how these definitions had been developed and any studies validating aSLE remission targets. Secondly, the literature was systematically reviewed to identify any previous initiatives deriving cSLE specific remission T2T targets, or evidence on existing aSLE T2T remission targets that was applicable to cSLE. Literature searches were conducted in the MEDLINE, EMBASE, and CINAHL databases. Searches were limited to studies: (1) published in English between January 1970 and August 2021; (2) focused on paediatric patients; (3) including at least three or more cSLE patients under 18 years of age. The search terms included three elements: a) paediatric, b) T2T, and c) cSLE-related terms (see Supplementary Table S1). Papers were excluded if they were: (1) reviews, (2) conference abstracts, (3) did not focus on cSLE or T2T, or (4) were non-human studies. A manual search of grey literature was conducted by reviewing the reference lists of all the included studies.

### 2.3. Delphi surveys

Four Delphi surveys (1a/1b, 2a/2b) were sent to Task Force members in advance of two meetings. The Delphi surveys explored use of aSLE DORIS 2017 remission definitions [35] in routine cSLE clinical practice. They sought to understand the experts' opinions on: (a) whether there should be combined overall remission targets, or if Lupus Nephritis should be targeted separately from all other manifestations of lupus; (b) ranking of different DORIS task force 2017 remission targets [35] for use in cSLE; (c) preferences for use of sequential remission target definitions in cSLE; (d) steroid dosing in remission; (e) potential alignment of cSLE remission(s) definitions with the DORIS task force 2017 framework [35] vs. the single DORIS task force 2021 definition of remission [34]; (f) operationalisation of components of the remission definitions in cSLE. Existing literature relating to each survey question was included within the surveys as relevant. Delphi 1a/2a results were communicated to the experts in Delphi 1b/2b respectively, alongside any interim proposals from the Steering Committee (EMDS, MWB) based upon the previous survey results. The outcomes of the Delphi surveys were used to guide discussions in the consensus meetings.

### 2.4. Consensus meetings

In November 2021 and January 2022, two virtual meetings took place with the aim of reaching consensus on the definition(s) of cSLE specific remission. These sessions included 17 voting members from the cSLE T2T Task Force, spanning West/East Europe, Africa, Australia, Asia, North and South America. MWB chaired the meeting, while EMDS facilitated the discussions (both non-voting participants). Three young adults with cSLE (NM, LB, LL), and one parent of a cSLE patient (JA), engaged actively in the discussions, representing the perspectives of patients and families (non-voting participants).

Modified nominal group technique (NGT) [38] was employed during both consensus meetings to ensure equitable involvement of all cSLE T2T Task Force members. Chair of the discussions (MWB) and facilitator (EMDS) contextualised each subject to be discussed, incorporating results from Delphi surveys, appropriate published literature and unpublished data detailing evidence associated with the topic in hand from the UK JSLE Cohort Study (where relevant and/or available). CSLE T2T

Task Force members were given the opportunity to express viewpoints without disruption, with a stipulated duration of one minute each. Following deliberation, participants cast anonymous votes on each item utilising an online polling system. A predefined threshold of ≥80% of participants was set for achieving 'consensus'. When <80% consensus was generated, further round(s) of NGT were undertaken leading to refinement of items, followed by subsequent voting rounds until consensus was attained (wherever feasible). The final definitions for remission in cSLE were endorsed by the PReS Executive Council and the Chair of the PReS cSLE Working Party, acting on behalf of all PReS members. A summary of the process used to reach a consensus on the definition(s) of remission for use in cSLE is shown in Fig. 1.

## 3. Results

### 3.1. Literature review

#### 3.1.1. Adult-onset SLE remission definitions and associated validation studies

In 2016, the Definitions of Remission in Systemic Lupus Erythematosus (DORIS) task force [35] proposed a framework describing eight potential definitions of remission. The DORIS task force initially recommended that 'remission' should be based on a validated instrument for ascertaining disease activity (e.g. SLEDAI, BILAG), supplemented with the Physicians Global Assessment (PGA) of disease activity. The DORIS task force was initially unable to reach consensus regarding whether serological activity should be absent for remission to be attained, leading to definitions of clinical (allowing serological activity) and complete remission (prohibiting serological activity). The DORIS Task Force also recommended that remission definitions should be further qualified as being either 'on' or 'off' treatment, with remission off therapy only allowing maintenance antimalarial treatment; and remission on therapy allowing adults with SLE to be on stable maintenance antimalarials, low-dose corticosteroids (prednisolone ≤5 mg/day), maintenance immunosuppressives / biologics. The DORIS Task Force recommended that remission should be a durable state but could not agree upon the length of time which remission had to be sustained to qualify as being in remission [35].

The DORIS Task Force reconvened in 2018 and 2020 to consider emerging data from cohorts, registries, and clinical trial datasets, to inform a final definition of remission for aSLE [34]. In summary, four aSLE cohorts including approximately 4000 patient from the following cohorts: Amsterdam ($n$ = 268) [29,39], GLADEL ($n$ = 1350) [30,31], ALMENARA ($n$ = 308) [40–42] and Hopkins ($n$ = 2000) [26,43] demonstrated that attainment of remission, based on the clinical SLEDAI with some treatments allowed, was associated with diminished damage accrual. The Amsterdam, ALMENARA and Hopkins cohorts also demonstrated that attainment of this remission definition was associated with better HRQOL [26,39,40,42,43], particularly regarding physical health [29,39]. The GLADEL and ALMENARA cohorts showed an association between attainment of this remission definition, and reductions in hospitalisation [41,44]. Simpler definitions of remission were assessed in the LUMINA cohort (Systemic Lupus Assessment Measure = 0, $n$ = 558) [30,45] and the Padua cohort (Clinical SLEDAI = 0, $n$ = 293) [46,47], also demonstrating protection against damage accrual with attainment of such definitions.

The Asia-Pacific Lupus Collaboration cohort ($n$ = 1707, 12,689 visits) undertook one of the most rigorous studies, comparing attainment of LLDAS with eight different DORIS task force remission definitions (varying in terms of serological activity, corticosteroid and immunosuppressive use) [24]. Definitions excluding serological activity provided most protection against disease flares. Unfortunately, high stringency definitions (e.g. complete remission without immunosuppression and corticosteroids) were rarely attainable, limiting their applicability. There was a high degree of overlap between the least stringent remission definitions and LLDAS in terms of protective value, highlighting the need for adequate separation between LLDAS and remission targets [24].

Collectively these studies underscore the benefits of achieving remission in SLE, including reduced damage, hospitalisation risk, and improved HRQOL [24,26,29–31,39–41,43–46]. The duration of remission varied among the cohorts, but it was evident that longer periods of sustained remission were associated with greater protection against damage accrual [1,15,26,29–31,38,42,43,45,47,48]. Based on the above data and expert opinion, the DORIS task force published the '2021 DORIS task force definition of remission in SLE' [34]. These included final recommendations advising a single definition of remission in SLE, based on a Clinical SLEDAI of 0, Evaluator's Global Assessment <0.5 (0–3 scale), prednisolone 5 mg/day or less, and stable antimalarials, immunosuppressives, and biologics. Regarding duration, the DORIS task force agreed that, sustained remission should be the goal, but for the purposes of clinical trials, a definition of remission should be able to be met at any point in time, concluding that duration does not need to be included within the remission definition [34].

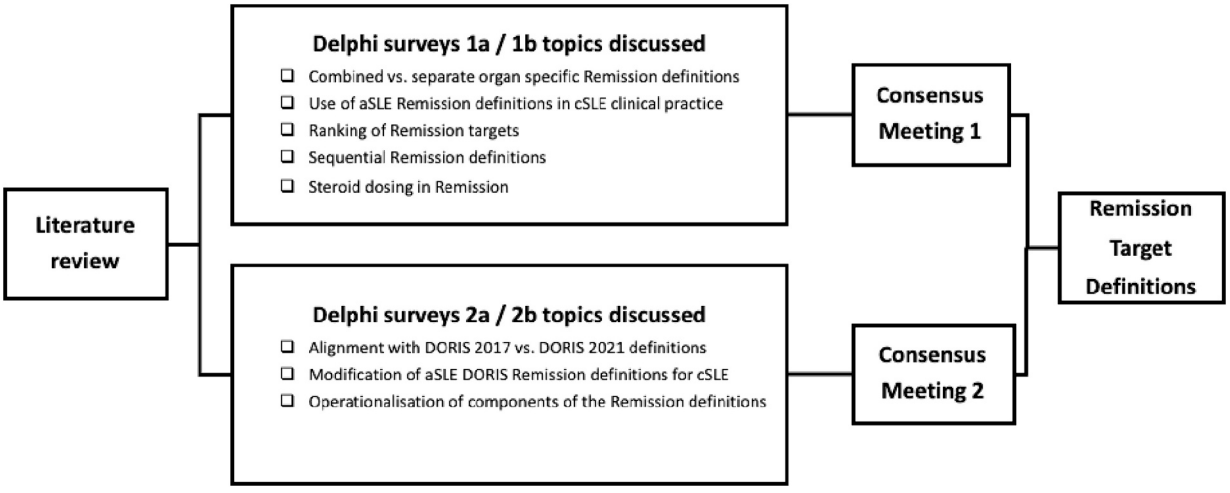


**Fig. 1.** Summary of the process used to reach consensus definition(s) of Remission.
aSLE = adult Systemic Lupus Erythematosus. cSLE = childhood onset Systemic Lupus Erythematosus. DORIS = Definition Of Remission In Systemic Lupus Erythematosus task force. NGT = Nominal Group Technique. Eighteen core Task Force members and four collaborators participated in the Delphi surveys. Seventeen voting Task Force members were included in the consensus meetings.

#### 3.1.2. Evidence informing cSLE specific remission definition(s)

Assessment of the literature demonstrated the absence of remission definitions specific to cSLE. Two studies [14,16] were identified that evaluated aSLE remission target definitions from the 2017 DORIS task force framework [35]. A study including 430 UK JSLE Cohort Study participants, between 2006 and 20, across 22 sites demonstrated that clinical remission on-treatment (SLEDAI-2 K defined), clinical remission on-treatment (BILAG-defined), clinical remission off-treatment (SLEDAI-2 K defined) and clinical remission off-treatment (BILAG-defined) were attainable in 61%, 42%, 31% and 21% of participants respectively, over a median of two years of follow-up (Table 1) [14]. Attainment of these remission target definitions drastically reduced the risk for both severe flare and new damage. BILAG-defined remission definitions were more difficult to attain than SLEDAI-2 K based definitions. The risk of severe flare in cSLE progressively reduced as cumulative time in each remission target increased [14], in line with results from aSLE studies [23,24].

A single centre study from the Netherlands ($n = 51$), demonstrated that 53% of children with cSLE attained complete remission on-treatment, and 22% complete remission off-treatment during follow-up[16]. Both remission target definitions were in keeping with the 2017 DORIS task force framework for remission in SLE [35] and based upon the Safety of Estrogens in Lupus National Assessment (SELENA) SLEDAI score (Table 1). The literature review did not demonstrate any other manuscripts evaluating aSLE derived remission targets in cSLE.

### 3.2. Agreed key principles underpinning development of cSLE remission definitions

#### 3.2.1. Combined vs organ specific targets

Given the inherent variability between children with cSLE, the International cSLE Task Force discussed the extent of remission targets and whether remission should encompass cSLE in its entirety or include organ specific remission targets. It was noted that the cLLDAS definition covers cSLE as a whole [36], and that both the DORIS task force 2017[35] and 2021[34] frameworks for remission in aSLE support the use of overall remission targets. The cSLE T2T Task Force recognised the importance of lupus nephritis (LN) as a particularly significant organ manifestation. However, for the majority of children with cSLE this was noted to coexist with other clinical and/or laboratory anomalies [49,50]. Furthermore, it was noted that individuals initially presenting principally with LN might subsequently develop additional manifestations during the disease course, which could go unnoticed if the target solely concentrates on renal outcomes. In view of these complexities, consensus was reached in favour of an all-inclusive cSLE target, that encompasses the entirety of the condition (Table 2).

#### 3.2.2. Single vs multiple remission targets

The cSLE T2T Task Force expressed a keen interest in establishing a clear pathway for progression between targets of increasing stringency, building on the DORIS task force 2021 single definition of remission, through development of a second remission target promoting remission off corticosteroids. This was deemed crucial given the significant impact that corticosteroids have on a child's growth, development, and damage accrual in cSLE [48,51,52]. Task Force patient representatives underlined the strong dislike of any corticosteroid treatment even in low dose. In a qualitative study exploring the view of children with cSLE to inform a cSLE T2T approach, a 17-year-old cSLE patient is quoted: *'I just wanted to come off them. Even when I was only on half a tablet, I didn't feel happy with being on them'* [15]. The cSLE T2T Task Force was cognisant that in aSLE, even low dose corticosteroid use contributes to damage accrual, independently of the presence of clinical or serological disease activity

**Table 1**
Summary of literature relating to attainability, associations and predictors of remission target attainment in cSLE.

| Definition of remission | Remission attain-ment | Predictors of remission attainment (OR, 95% CI, *p*-value) | Impact of remission on 'severe flare' during follow-up (HR, 95% CI, p-value) | Impact of remission attainment on 'new damage' accrual (HR, 95% CI, p-value) | Cohort, number of participants |
|---|---|---|---|---|---|
| **Clinical Remission on-Tx (SLEDAI)**[a] | 61% | - Low C3: 0.44 (0.25, 0.76), $p = 0.004$<br>- ESR ≤50 mm/h: 7.08 (1.84, 27.30), $p = 0.004$ | 0.19 (0.15,0.24) $p < 0.001$ | 0.27(0.14,0.50) $p < 0.001$ | **UK JSLE Cohort[14] n = 430** |
| **Clinical Remission on-Tx (BILAG)**[a] | 42% | - Low C3: 0.40 (0.23, 0.70), $p = 0.001$<br>- Asian: 5.20 (1.70, 15.84), p = 0.004<br>- White British: 3.09 (1.04, 9.21), $p = 0.043$ | 0.13 (0.09,0.20) $p < 0.001$ | 0.10 (0.03,0.42) $p = 0.001$ | |
| **Clinical Remission off-Tx (SLEDAI)**[a] | 31% | -Low C3: 0.51 (0.26, 0.99), $p = 0.049$<br>-Renal disease: 0.32 (0.13, 0.80), $p = 0.014$ | NA | 0.33 (0.28,0.40) p < 0.001 | |
| **Clinical Remission off-Tx (BILAG)**[a] | 21% | - Lymphopenia: 0.46 (0.22, 0.97), $p = 0.041$ | NA | NA | |
| **Complete Remission on-Tx**[a] | 53% | NA | NA | NA | **Rotterdam cSLE Cohort[16] n = 51** |
| **Complete Remission off-Tx**[a] | 22% | NA | NA | NA | |

Within the UK JSLE Cohort Study, remission on treatment based upon clinical-SLEDAI (remission on-treatment SLEDAI-defined) or pBILAG scores (remission on-treatment BILAG-defined), as comprised by the following items: 1) cSLEDAI = 0 or pBILAG domains scoring D or E; 2) PGA ≤ 0.5; 3) prednisolone dose ≤5 mg/day, no intravenous methylprednisolone; 4) tolerated standard maintenance doses of immunosuppressive drugs/biological agents, excluding investigational drugs. Remission off treatment based upon clinical-SLEDAI (remission off-treatment SLEDAI-defined) or pBILAG scores (remission off-treatment BILAG-defined): excluded criterions (3) and (4) from the above definitions (antimalarials allowable) [14]. Within the Rotterdam cSLE Cohort, Complete Remission off treatment was defined as a PGA <0.5, SELENA-SLEDAI = 0, without prednisolone or usage of other immunosuppressives. Complete remission ON treatment was defined similarly, but allowed prednisolone ≤5 mg/day and maintenance treatment with other immunosuppressives [16]. OR = odds ratio. HR = hazards ratio. CI = confidence interval. Tx = treatment. SLEDAI = SLE disease activity index. BILAG = British Isles Lupus Assessment Grade. n = number. NA = not available.

[a] All definition of remission utilised in these papers were in keeping with the 2017 DORIS task force framework for remission in SLE [35].

**Table 2**
Statements underpinning cSLE remission target definitions.

| Item | Agreement |
|---|---|
| **Combined vs organ specific targets:** | 100% |
| • cSLE remission definitions should encompass a combined overall target | |
| **Two remission target definitions are warranted for use in cSLE:** | 94% |
| • First is closely aligned to the aSLE DORIS task force 2021 remission definition [34] | |
| • Second is more stringent requiring discontinuation of corticosteroids | |
| **Names for the cSLE remission targets:** | 100% |
| • cSLE Clinical Remission (cCR) | |
| • cSLE Clinical Remission Off steroids (cCR-0) | |
| **Durability of remission targets:** While the goal of treatment is sustained remission, a definition of remission should be able to be met at any point in time; therefore, duration should not be included in cSLE definitions of remission. | 85% |

[21], that mortality is closely linked to the accumulation of damage [53–57], and that the most recent 2023 EULAR SLE treatment recommendations promote withdrawal of corticosteroids where possible [58]. Collectively, these considerations lead to agreement that two remission targets are required for cSLE: the first, 'cSLE Clinical Remission (cCR)' would be closely aligned with the aSLE DORIS task force 2021 definition of remission to enable life course research; the second, 'cSLE Clinical Remission off steroids (cCR-0)' going beyond this to promote discontinuation of corticosteroids (Table 2). It was noted that the more stringent definition would be particularly relevant when implementing T2T in clinical practice rather than in T2T trials, due to the length of time which is likely to be required to meet this definition.

#### 3.2.3. Durability of remission

Whilst the cSLE T2T Task Force agreed that achieving sustained remission is ideal, the lack of comprehensive data supporting this approach was challenging. Only a single study has explored the relationship between the duration of remission and risk of severe flares or new damage in cSLE [14]. In line with the aSLE DORIS task force remission criteria [34], the cSLE T2T Task Force determined that remission should be definable at any time rather than necessitating a prolonged period of remission for its achievement (Table 2).

### 3.3. Consensus cSLE remission definitions (Table 3)

Table 3 summarises the consensus agreed criteria for cCR and cCR-0 remission definitions, which each include four criteria.

*Criterion 1 - Disease activity:* A clinical SLEDAI (cSLEDAI) score of zero was chosen to signify control of disease activity for both the cCR and cCR-0 remission definitions, in line with the aSLE DORIS task force 2021 criteria [34]. Moreover, the cSLE T2T Task Force agreed that as these lab markers (C3, C4, anti-dsDNA) lack consistent predictive value for disease flares, they should not drive treatment escalation in isolation, justifying use of the cSLEDAI [33].

*Criterion 2 - Physician global assessment (PGA) scale:* Although the paediatric rheumatology community are generally more accustomed to the 0–10 PGA scale, for most paediatric rheumatic diseases, the cSLE T2T Task Force accepted that the cSLE remission definitions could use the 0–3 PGA scale, to encourage alignment with the aSLE remission definition. The cSLE T2T Task Force recognised that a PGA score of zero is infrequently met in cSLE, due to the presence of subtle persistent cSLE features. Consequently, the cSLE T2T Task Force decided to adopt a PGA score of <0.5 as the cut-off for PGA within both the cCR and cCR-0 definitions.

**Table 3**
Consensus cSLE remission definitions.

| Criteria | cSLE Clinical Remission (cCR) | Clinical Remission off steroids (cCR-0) |
|---|---|---|
| **1. Disease activity** | cSLEDAI = 0 *(100%)* | cSLEDAI = 0 *(100%)* |
| **2. Physician global assessment score** | <0.5 *(94%)* | <0.5 *(100%)* |
| **3. Prednisolone (or equivalent) dosage** | 0.1 mg/kg/day maximum of 5 mg/day *(94%)* | 0 *(100%)* |
| **4. Immunosuppression** | Stable antimalarials, immunosuppressives, and biologics[a]. *(94%)* | Stable antimalarials, immunosuppressives, and biologics[a]. *(100%)* |

Percentages in bracket and italics represent the level of agreement within the cSLE T2T Task Force.

[a] Maintenance treatment is considered stable if changes are not due to disease activity, but made due to side-effects, adherence, growth and/or when building up to target dose.

*Criterion 3 - Prednisolone (or equivalent) dosage:* The cSLE T2T Task Force extensively debated this criterion, more so than others, and agreed that it could not fully conform directly to the corresponding aSLE DORIS task force criteria [34]. Regarding cCR, the cSLE T2T Task Force noted that adopting the aSLE remission definition's maximum corticosteroid dose (5 mg/day) could lead to relatively higher dosages for younger children with cSLE. Thus, the cSLE T2T Task Force considered either lowering the threshold to 2.5 mg/day or implementing a weight-based limit. A consensus was reached in that the ceiling dose of prednisolone for cCR should be 0.1 mg/kg/day, with a maximum of 5 mg, aiming for the lower of the two measures. The cSLE T2T Task Force also agreed that cCR-0 should include the complete discontinuation of corticosteroids.

*Criterion 4 - Immunosuppression:* The cSLE T2T Task Force recognised that, as with aSLE, discontinuing immunosuppressive therapy for children with cSLE is often not possible [59,60]. Echoing the corresponding cLLDAS target criterion, the cSLE T2T Task Force acknowledged that paediatric drug doses often need adjustments due to weight changes, drug form acceptability, or side effects [36]. Therefore, the cSLE T2T Task Force specified that treatment should be viewed as stable if modifications are made due to side effects, adherence issues, growth, or dose escalation towards a target level (Table 3).

## 4. Discussion

An International cSLE T2T Task Force of paediatric/adult rheumatologists, nephrologists, individuals with cSLE and parents, representing the major paediatric rheumatology networks from all continents [33], have reached consensus on cSLE-appropriate definitions of remission, known as 'cSLE Clinical Remission (cCR)' and 'cSLE Clinical Remission off steroids (cCR-0)', endorsed by PReS. These definitions build on the DORIS task force 2021 remission definition [34], with key adjustments for cSLE, including: a weight-based limit on corticosteroid doses within the cCR definition, and a second, more stringent remission target to promote discontinuation of steroid therapy. These cSLE remission definitions align well with those used in aSLE, supporting collaborative research over the patient's life span, and advocating for complete corticosteroid cessation whenever feasible.

The International cSLE T2T Task Force discussed the original DORIS task force 2017[35] framework and the updated 2021[34] single remission criteria extensively. They reflected that the initial approach considered various remission scenarios that could be encountered, whereas the streamlined single definition recognises the need for simplicity to improve uptake of T2T strategies into clinical practice. A single remission definition is also important for clinical trials, where multiple targets would otherwise be impractical, increasing the complexity and duration of such a trial. However, the cSLE T2T Task Force decided that in routine

care a second target would help to encourage corticosteroid discontinuation. Corticosteroid cessation is increasingly recognised as one of the most important outcomes in SLE trials [61,62], and is strongly supported by children with cSLE and families [15]. Despite introduction of the single DORIS task force 2021 definition of remission [34], recent studies have continued to investigate stricter remission criteria [63], underscoring their potential benefits, and challenging the DORIS task force's recommendation for a single definition of remission.

When defining the individual criteria for cCR and cCR-0, the cSLE T2T Task Force agreed that for Criterion 1, remission should be defined by the absence of clinical symptoms. They debated the options of using the full SLEDAI-2 K = 0, which would mandate the absence of anti-DNA antibodies and normal levels of complement for remission to be attained, or omitting these biomarkers from the remission definitions through use of the cSLEDAI = 0 definition (aligning with the DORIS task force 2021 definition [34]). The clinical SLEDAI was preferred for the following reasons; firstly, in children showing no signs/symptoms of cSLE activity, the requirement for C3, C4, and anti-dsDNA measurements could hinder applicability of the T2T approach, particularly in under-resourced healthcare settings. Secondly, during the generation of 'Principles and Points to Consider' for cSLE T2T, the cSLE T2T Task Force previously reached consensus that treatment should not be intensified based solely on C3, C4, and anti-dsDNA levels [33], underscoring the ambiguity regarding the reliability of these laboratory markers in predicting flares in inactive children with cSLE.

Criterion 2, relating to the PGA, remains the same as in aSLE [34,35]. Given that paediatric rheumatologists are generally more familiar with use of the 0–10 PGA scale, future initiatives to improve standardisation of PGA scoring on a 0–3 scale for cSLE are welcomed and could be aligned to similar aSLE efforts [64,65]. A recent aSLE study has assessed the ideal PGA threshold associated with physician defined remission, demonstrating that a PGA of <2 (0–10 scale), corresponding to <0.6 (0–3 scale) resulted in best prediction of physician remission [66]. Further work validating the proposed thresholds and comparing rating on both scales prospectively will be of value prior to embarking on a cSLE T2T trial.

The cSLE T2T Task Force rigorously deliberated the appropriate prednisolone (or equivalent) ceiling dose for cCR, considering the risk of damage associated with glucocorticoids [21,48,67], evidence in aSLE relating to the risk of flare with steroid cessation [68–70], and the unique needs of younger children with cSLE [52,71]. A 'safe low-dose' of prednisolone does not exist in aSLE [21,53] and children with cSLE are at increased risk of corticosteroid-related damage due to longer duration of disease and higher disease activity [48]. Therefore, the cSLE T2T Task Force set a pragmatic prednisolone ceiling dose (0.1 mg/kg/day, with a maximum of 5 mg) for cCR, that aligns with the aSLE definition whilst minimising prednisolone dosage relative to patient size.

In developing Criterion 4 for cCR and cCR-0, the cSLE T2T Task Force aligned with the cLLDAS [36] definition, clarifying the term 'maintenance treatment' to minimise misinterpretation. Criterion 4 specifies that alterations in response to disease activity are not permissible. However, modifications due to side-effects, adherence difficulties, or growth are acceptable for attaining remission. In-keeping with the DORIS task force 2021 remission definition [34], the cSLE T2T Task Force acknowledged the challenge of discontinuing immunosuppressive therapy for children with cSLE, supporting long term treatment on stable immunosuppression to prevent flares.

This study is limited by the paucity of robust paediatric data currently available to directly inform development of cSLE remission definitions, namely two cohort studies [14,16]. In aSLE, the initial derivation of a framework for DORIS task force remission in 2017 was followed by considerable work testing different target definitions over an approximately 5 years period, a range of observational cohorts, registries and clinical trial data sets, informing development of the DORIS task force 2021 single remission definition [34]. Future directions must include the validation of cLLDAS, cCR and cCR-0 targets across international cSLE cohorts, investigating their attainability, impact on disease progression, and the optimal duration for maintaining these targets to improve patient outcomes. Understanding of the separation between different targets (cLLDAS, cCR, cCR-0) is also needed to refine T2T strategies and implementation. Sensitivity analyses of current target definitions should be undertaken, modifying the SLEDAI-2 K and PGA cut-offs as part of the validation process, with specific studies investigating the steroid dose cut-offs, balancing potential for damage and flare risk. Investigation of trajectories and time-to-target attainment against the backdrop of specific organ involvements and treatments, could help to guide therapeutic choices and provide a personalised approach to T2T implementation in clinical practice.

## 5. Conclusion

Remission criteria suitable for cSLE have been derived, drawing on insights from existing studies, aSLE criteria, and involving consensus of the specialised cSLE International T2T Task Force, and endorsed by PReS. Establishing and validating targets has been crucial for facilitating T2T trials in various diseases. This study marks a pivotal advancement in shaping T2T strategies for cSLE, with potential for significant impact on both clinical practice and research. The cSLE clinical and research community, steered by the International cSLE T2T Task Force, is now set to commence the validation of cLLDAS, cCR, and cCR-0 criteria in cSLE.

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## Contributor statement

EMDS and MWB convened the International cSLE T2T Task Force, undertook the Delphi surveys, organised and facilitated the consensus meeting and wrote the first version of the manuscript. All remaining authors participated in the Delphi surveys and consensus meeting, reviewed and contributed to revision of the manuscript. PReS Executive Council members participating in the cSLE T2T Task Force were AR, TA and MWB, and the Chair of the PReS SLE Working Party was SK.

## CRediT authorship contribution statement

**E.M.D. Smith:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Visualization, Writing – original draft, Writing – review & editing. **A. Aggarwal:** Conceptualization, Investigation, Methodology, Writing – review & editing. **J. Ainsworth:** Investigation, Methodology, Project administration, Writing – review & editing. **E. Al-Abadi:** Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. **T. Avcin:** Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. **L. Bortey:**

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## Declaration of competing interest

The authors declare that they have no competing interests in relation to this manuscript.

## Data availability

The data underlying this article are available on reasonable request to the Chief Investigator of the UK JSLE Cohort Study

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clim.2024.110214.

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