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Expert consensus achieved on a working core outcome set for cutaneous lupus erythematosus research in survey following the 5th International Conference on Cutaneous Lupus Erythematosus (ICCLE)

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INTRODUCTION

Cutaneous lupus erythematosus (CLE) is a potentially disfiguring and debilitating manifestation of lupus erythematosus, a heterogeneous autoimmune disease with a broad spectrum of organ system involvement and clinical presentations. Despite CLE's demonstrated impact on patients' quality of life, no drugs for treatment of CLE have been approved by the Food and Drug Administration. One proposed driver of this gap is a focus on SLE rather than its cutaneous counterpart in therapeutic development programmes. Another challenge is the lack of regulatory acceptance of and clarity on existing endpoints, which has inhibited some expansion into this area of the field.

To address an urgent unmet need for guidance around a standardised outcome measurement set in CLE research, a steering committee comprised of dermatologists and rheumatologists proposed a working core outcome set (COS) for randomised controlled trials and longitudinal observational studies. A COS comprises outcomes that must be assessed and documented in every clinical trial related to a specific medical condition.[1] This ensures uniformity in assessing and reporting outcomes across different clinical studies.

Following the Outcome Measures In Rheumatology (OMERACT) Filter 2.1 Onion framework,[2] the steering committee first classified candidate outcomes as 'core domains' (ie, relevant domains and subdomains that should be measured in every study for a given disease), 'important but optional' domains and 'research agenda' domains. Subsequently, they recommended candidate outcome measures for each core domain based on review of the literature (table 1).[3] The proposed COS (ie, core domain set and corresponding outcome measurement set) represents a 'working' set to bridge an urgent need while allowing more rigorous methodological approaches to continue in parallel via COMET (Core Outcome Measures in Effectiveness Trials) Initiative and OMERACT standards, with ongoing work by groups such as the International Dermatology Outcome Measures (IDEOM) Initiative.[4] This study aimed to assess the endorsement of the working COS by an international sample of CLE leaders and experts

METHODS

The proposed COS was presented at the recent Fifth International Conference on Cutaneous Lupus Erythematosus (ICCLE) (JFM). Subsequently, the ICCLE meeting attendees were invited to complete a six-survey assessing consensus on the proposed working COS, including endorsement of the 'core domain', 'full domain' (ie, core domains, optional important domains and research agenda domains) and 'core outcome measurement' sets. Additionally, they were asked to vote on their preferred CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index) primary endpoint with regard to percentage change compared with baseline (CLASI50, CLASI70 or CLASI90) and

Table 1 Working core outcome measurement set

Core domain	Outcome measurements		
	CLE-specific	Dermatological	Generic
Skin-specific disease activity	CLASI-A	–	–
Investigator global assessment of disease activity	CLA-IGA-(R)*		
Skin-specific disease damage	CLASI-D	–	–
Symptoms (pruritus, pain and photosensitivity)	CLEQoL (includes Skindex-29+3)	DLQI Skindex-29+3 12-Item Pruritus Severity Scale	Itch VAS/NRS Pain VAS/NRS
Health-related quality of life	CLEQoL (includes Skindex-29+3), LEQoL	Skindex-29+3 DLQI	SF-36, EQ-5D
Patient global assessment of disease activity	–	–	–

Table reproduced from Guo *et al*.[3]
*May be considered as a secondary or exploratory endpoint, complementary to CLASI; pending ongoing validation.
CLA-IGA, Cutaneous Lupus Activity Investigator's Global Assessment; CLA-IGA-R, CLA-IGA (revised version); CLASI-A, Cutaneous Lupus Erythematosus Disease Area and Severity Index-Activity; CLASI-D, Cutaneous Lupus Erythematosus Disease Area and Severity Index-Damage; CLEQoL, Cutaneous Lupus Erythematosus Quality of Life; DLQI, Dermatology Life Quality Index; LEQoL, Lupus Erythematosus Quality of Life Questionnaire; NRS, Numerical Rating Scale; SF-36, Short Form Health Survey; VAS, Visual Analogue Scale.

the complementary Cutaneous Lupus Activity Investigator's Global Assessment (revised version) (CLA-IGA-R) instrument as key secondary (vs co-primary endpoint). Appropriate patient-reported outcome measures were also considered, as outlined in table 1. Demographic data were collected, and descriptive statistics were calculated.

RESULTS

Survey results were collected from 46 out of 114 emailed meeting attendees (40.3% response rate). Respondents primarily identified themselves as dermatologists (95.6%), but also included one rheumatologist (2.2%) and one researcher (2.2%). The majority of respondents reported residency in Asia (65.2%), with smaller subsets from North America (26.1%) and Europe (8.7%). All 46 respondents endorsed the proposed working 'core domain set', and all but one (97.8%) endorsed the 'full core domain set'. All respondents voted to endorse the 'core outcome measures set', including the CLASI and CLA-IGA/CLA-IGA-R. Preference for CLASI percentage change from baseline endpoint was mixed; 43.5% voted in favour of CLASI50, while 39.1% preferred CLASI70 and 17.4% preferred CLASI90.

DISCUSSION

This report demonstrates strong consensus among an international cohort of CLE experts endorsing the use of the working COS proposed by Guo *et al*[3] for the much-needed standardisation of outcome measures used in CLE research. This effort is part of a wider effort by the lupus research community to develop organ-specific endpoints to combat the regulatory and trial design challenges of demonstrating treatment efficacy and safety in a complex, heterogeneous disease with highly variable manifestations across organ systems.[5]

CLE is a lupus manifestation for which an organ-specific approach to measuring treatment success is particularly needed. CLE often occurs without features of SLE and extrapolating CLE treatment effects from SLE clinical trials that fail to include CLE-specific measurement can be problematic. For example, measures such as the SLE Disease Activity Index only capture presence or absence of inflammatory rash, thus missing the granular detail required to detect meaningful therapeutic effects on skin disease.[6]

The working COS proposed by Guo *et al* and endorsed by experts during the Fifth ICCLE specifically serves as a direct response to the pressing need for more precise evaluation of CLE outcomes. It accomplishes this by standardising the assessment of multiple relevant domains of disease, including skin-specific disease activity and damage, investigator global assessment of disease activity, CLE symptoms, health-related quality of life and patient global assessment of disease activity. Adopting the proposed working COS should minimise heterogeneity in CLE outcome reporting in clinical trials which has historically hindered regulatory approval in CLE.

While consensus about measuring outcomes in CLE has been achieved, there is still disagreement regarding preferred CLASI endpoint as a per cent change from baseline. Multiple large clinical trials have used CLASI50 as a cut-off representing clinically meaningful improvement in patients with at least moderate skin involvement at baseline, and there is evidence that a 6-point or a 50% reduction in CLASI score reflects meaningful improvement in patients' quality of life.[7 8] This may explain why CLASI50 was preferred by more experts than more stringent endpoints, CLASI70 and CLASI90. Future studies may seek to clarify why some experts prefer more stringent CLASI endpoints.

This report establishes evidence of expert support for the working COS, which serves as timely, practical guidance for CLE researchers and regulators. A noted limitation of these findings is the lack of representation from patients, industry and other CLE stakeholders. Next steps include the development of a formal CLE COS following COMET Initiative methodology, which involves a wider range of stakeholders. The working COS may serve as a much-needed stopgap while more rigorous COS research is underway, including in the context of an ongoing IDEOM Initiative.

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