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Meeting report: the ALPHA project: a stakeholder meeting on lupus clinical trial outcome measures and the patient perspective

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ABSTRACT

Drug development in lupus has improved over the past 10 years but still lags behind that of other rheumatic disease areas. Assessment of prospective lupus therapies in clinical trials has proved challenging for reasons that are multifactorial including the heterogeneity of the disease, study design limitations and a lack of validated biomarkers which greatly impacts regulatory decision-making. Moreover, most composite outcome measures currently used in trials do not include patient-reported outcomes. Given these factors, the Addressing Lupus Pillars for Health Advancement Global Advisory Committee members who serve on the drug development team identified an opportunity to convene a meeting to facilitate information sharing on completed and existing outcome measure development efforts. This meeting report highlights information presented during the meeting as well as a discussion on how the lupus community may work together with regulatory agencies to simplify and standardise outcome measures to accelerate development of lupus therapeutics.

INTRODUCTION

This report summarises presentations and discussions of a meeting entitled, 'A Stakeholder Meeting on Lupus Clinical Trial Outcome Measures and the Patient Perspective', held virtually and hosted by the Lupus Foundation of America (LFA) on 18 August 2022. This meeting brought together researchers from around the globe who are leading efforts to improve outcome measures for lupus with the ultimate goal of developing more robust therapies for people living with lupus. The audience included lupus physicians, people with lupus, lupus clinical trialists and drug development policy consultants. This forum was a part of the global Addressing Lupus Pillars for Health Advancement (ALPHA) Project that the LFA began in 2018. The purpose of the meeting was to discuss drug development tools that aim to address challenges such as significant patient heterogeneity in lupus that often make successful evaluation of novel therapies in clinical trials difficult. Participants described the process of developing and refining outcome measures for lupus and discussed opportunities for collaboration. The meeting featured presentations by clinical investigators, an overview of the process for validating and qualifying a measure to meet the FDA's standards in the patient-focused drug development context, and a discussion of how the group might work together to move the entire field forward.

BACKGROUND

The ALPHA Project began in 2018 with the goal of bringing together international lupus experts to develop and implement strategies to address the critical barriers to improving health outcomes in lupus. In phase I, project leaders conducted a series of interviews and an online survey of lupus clinicians and scientists. This led to the identification of barriers for three different 'pillars': drug development, clinical care and access to care.[1] In phase II, which began in late 2019, the Global Advisory Committee (GAC) identified and prioritised actionable solutions for each pillar. The ALPHA Project is currently in phase III, as GAC members are working to drive progress in the implementation of top-ranked solutions for each pillar. The stakeholder meeting, described herein, was the first meeting in a series of convenings designed by the members of the GAC working on the Drug Development pillar to learn more about

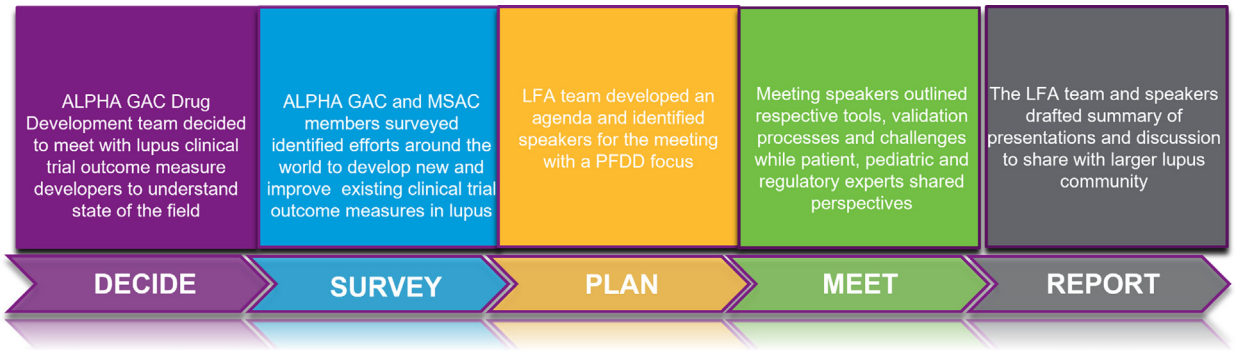

Figure 1 Diagram of lupus clinical trial outcome measure meeting development process. ALPHA, Addressing Lupus Pillars for Health Advancement; GAC, Global Advisory Council; LFA, Lupus Foundation of America; MSAC, Medical Scientific Advisory Council; PFDD, patient-focused drug development.

efforts to improve existing outcome measures or develop new ones (figure 1).

Studies suggest that 90% of clinical trials fail.[2 3] Lupus-related drug development has proved more challenging for reasons that are multifactorial including 'the heterogeneity of lupus, the wide age spectrum of affected individuals, including children, suboptimal clinical trial designs, and a lack of validated biomarkers mean many outcome measures may have limitations for regulatory decision-making'.[4] This and other factors led the GAC to agree that simplifying and standardising outcome measures was the highest priority solution for the Drug Development pillar and could contribute to better therapies—and health outcomes—for people with lupus. To facilitate information sharing on completed and existing outcome measure efforts, LFA and the GAC convened the virtual forum described in the next section.

OVERVIEW OF MEETING CONTENT

The meeting featured presentations on nine different outcome measure projects: six that investigators have completed or are well underway and three newer projects (list of presenters and summary of projects in table 1). Researchers from around the world serve as primary investigators for the projects described later, and their approaches to outcome measure development highlight the variety of different approaches to develop or refine outcome measures. This is a core priority of the LFA and one that has been a focus throughout the entire ALPHA Project.

In addition to the project overviews presented by researchers, the meeting included the following presentations:

- To frame the discussion, a lupus patient advocate who participated in the Patient Focused Drug Development Meeting hosted collaboratively by Lupus Research Alliance, Lupus and Allied Diseases and LFA shared his journey with lupus and clinical trials. He spoke candidly about the early challenges faced in his lupus journey along with the negative effects the disease has had on his quality of life. This patient account underscored the need to align trial endpoints with the well-characterised needs of people with lupus.
- Introductory remarks by Eric Morand, MBBS (Hons), FRACP, PhD highlighted challenges related to clinical trial endpoints in lupus and the need to collaborate to find solutions to avoid redundancy and obtain the best possible outcome.
- A presentation by Mary Beth Son, MD, an expert on paediatric lupus, on the importance of adapting clinical trial outcome measures for paediatric and adolescent populations.
- An overview of how the U.S. Food and Drug Administration (FDA) supports the development, validation and qualification of outcome measures in a patient-focused drug development context given by Tim Franson, MD, a Principal at Faegre Drinker Consulting and a regulatory expert.

Karen Costenbader MD, MPH, Lupus Foundation of America Medical Scientific Advisory Council Chair, moderated the meeting and Laura Schanberg, MD, gave concluding remarks. Following all of the presentations, meeting attendees participated in a facilitated discussion that is summarised below. The complete meeting agenda is included in online supplemental file 1.

CLINICAL TRIAL OUTCOME MEASURE DEVELOPMENT IN LUPUS: PAST, PRESENT AND FUTURE

During the first presentation, Dr Ronald Van Vollenhoven highlighted the *Definition of Remission in SLE (DORIS)* measure. In particular, he articulated that DORIS remission is associated with improved quality of life, fewer flares and better long-term outcomes including decreased damage; face, construct and content validity for DORIS has been demonstrated, and additional studies using DORIS are ongoing, but there have not been formal discussion with regulatory bodies about using it as a primary outcome in clinical studies.[5 6] His talk was followed by a presentation by Dr Morand, who discussed the *Lupus Low Disease Activity State (LLDAS)*. This talk highlighted that FDA has not approved LLDAS as a primary endpoint in trials due to concerns related

Table 1 Lupus clinical trial outcome measures

Project/measure name	Project lead(s)	Lupus phenotype	Focus of measure	Summary description
Completed initiatives				
Cutaneous LE Disease Area and Severity Index (CLASI)	Victoria Werth University of Pennsylvania USA	CLE	Disease activity	▶ Measures both cutaneous lupus activity and damage[8 9]; response correlates with changes in QoL and biomarkers, and meaningful response from patient perspective determined[10 11] ▶ Validation studies show excellent inter-rater and intra-rater reliability, responsiveness[8 12 13] ▶ Used in prospective international phase II and III trials, showing differences in response in treatment relative to placebo arms[14 15] ▶ Widely used as both primary outcome in phase I and II CLE trials and secondary outcome in SLE phase I–III trials[14 15]
Definition of Remission in SLE (DORIS)	Ronald van Vollenhoven Amsterdam University Medical Center Netherlands	SLE	Treat-to-target endpoint: remission	▶ Includes a SLE disease activity index without points for anti-DNA or low complement (cSLEDAI) and a PhGA (Physician Global Assessment) <0.5 (0–3), irrespective of serology[5 6]
LFA rapid evaluation of activity in lupus (LFA-REAL)	Anca Askanase Columbia University USA Stan Kamp and Joan Merrill Oklahoma Medical Research Foundation USA	SLE	Disease activity	▶ Two-part system with patient-reported outcome and clinician-reported outcome measures that allow for integration of both for targeted treatment decision-making ▶ Use does not require specialised training or fluency in English ▶ Has been used as an exploratory endpoint in several clinical trials and has proven effective[16 17]
Lupus Low Disease Activity State (LLDAS)	Eric Morand Monash University Australia	SLE	Treat-to-target endpoint: remission	▶ Concept definition is 'A state, which if sustained is associated with a low likelihood of adverse outcome, considering disease activity and medication safety'. Incorporates thresholds for disease activity and treatment burden especially glucocorticoid dose ▶ Formally validated in prospective multinational studies as protective against flare, damage, loss of quality of life and mortality.[18 19] Also validated in many retrospective cohort studies ▶ Extensive evaluation in post hoc analysis of clinical trials data, where it has good to excellent performance discriminating active treatment from placebo[20–22] ▶ Widely adopted prospectively as a key secondary outcome measure in SLE trials[23 24]
SLE Disease Activity Score (SLE-DAS)	Luís Inés Coimbra University Hospital Centre Portugal	SLE	Remission and level of disease activity Change measure Treatment response	▶ A SLE continuous measure with high sensitivity for changes in disease activity ▶ Includes 17 weighted clinical and laboratory parameters attributed to SLE disease activity including continuous measures, important manifestations absent from SLEDAI and an improved weighting system ▶ Validated in peer reviewed publications[25–28]
Ongoing initiatives				
Outcome Measures in Rheumatology (OMERACT)	Zahi Touma University of Toronto Canada	SLE	Pathophysiology and impact of health conditions	▶ Identifying key domains such as disease activity, health-related quality of life and functional ability ▶ Goal is to update original core domain set from 1998 ▶ Will continue to be updated following the results of additional studies aiming to generate a preliminary list of domains relevant for patients with SLE, physicians and other stakeholders and further analyses and vote on the final OMERACT SLE core domain set
Lupus Multivariable Outcome Score (LuMOS)	Michal Abrahamowicz McGill University Canada Peter Lipsky AMPEL BioSolutions USA	SLE	Treatment response	▶ Developed to capture change with the least number of features in trials; aggregates changes in SLEDAI score, selected BILAG items, prednisone dose and selected biomarkers[29] ▶ Validated using the Bliss-76 study[7] ▶ Study findings suggest that LuMOS 2.0 formula may be a potential primary endpoint in future SLE trials

Continued

Table 1 Continued

Project/measure name	Project lead(s)	Lupus phenotype	Focus of measure	Summary description
LRA/BMS Outcome Instrument	Ken Kalunian UC San Diego USA	SLE	Multiple—TBD	In development
Treatment Response Measure for SLE (TRM-SLE)	Eric Morand Monash University Australia	SLE	Treatment response	► Multi-domain ClinRO being developed for use in randomised clinical trials. Will measure domains that impact how the patient feels, functions and survives in accordance with FDA guidance[30]

to redundancy with *Systemic Lupus Erythematosus Responder Index* (SRI-4), steroid ceiling being a safety but not efficacy signal and the notion that the tool is not yet sufficiently validated. This presentation reiterated the notion that appropriate steps aligning with FDA guidance are required throughout the endpoint development process to gain regulatory approval. The third presentation by Dr Victoria Werth focused on her work on the *Cutaneous LE Disease Area and Severity Index (CLASI)* for skin lupus. Her talk outlined key challenges to obtaining clinical outcome assessment approval from the FDA even for a tool that clearly captures meaningful improvements in patient quality of life and clinical triallists globally consider it a valuable tool in clinical trials focused on CLE, which is used frequently as a secondary endpoint.

Dr Werth's talk was followed by an overview of the *SLE Disease Activity Score (SLE-DAS)* outcome tool by Dr Luís Inês. Dr Ines and colleagues developed the tool to determine clinically meaningful change using 17 weighted clinical and laboratory parameters for SLE which has been fully validated. Dr Anca Askanase, a meeting attendee and member of LFA's Medical Scientific Advisory Council, reiterated to the audience that the *Lupus Foundation of America Rapid Evaluation of Activity in Lupus (LFA-REAL)* was the first and only tool to-date with a patient-reported outcome component. The tool has also been included in phase III trials as an exploratory endpoint where it has proven to be an efficient measure.

The next set of presentations were dedicated to the discussion of clinical trial outcome measures that are in the developmental phase. Dr Zahi Touma discussed ongoing work to update the core domain set in SLE, work planned by the SLE *Outcome Measures in Rheumatology (OMERACT)* Working Group. The generation of a preliminary list of domains has been initiated through several studies by the SLE OMERACT working group and at the final stage this will be followed by a vote to achieve consensus on the SLE core domain set. Dr Peter Lipsky's talk underscored the potential to use established data sets from previous clinical trials to validate *Lupus Multivariable Outcome Score (LuMOS)*, a tool that aggregates changes in Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, selected British Isles Lupus Assessment Group (BILAG) items, prednisone dose and selected biomarkers. Findings from initial studies suggest that the LuMOS 2.0 formula may be a potential primary endpoint in future SLE trials,[7] but free access to clinical trial data and data from cohort studies has been limited. Dr Eric Morand highlighted a new *Treatment Response Measure for SLE (TRM-SLE)* that his team at Monash University and other lupus stakeholder groups, including patients and paediatric rheumatologists, are pursuing. His presentation focused on the process applied to develop the SLE-specific measure and reiterated that the tool is being designed to capture how the patient feels, functions and survives in accordance with FDA guidance. Dr Ken Kalunian presented work on *Outcome Assessment in SLE Clinical Trials and Clinical Practice*. He described a unique clinical tool known as the Wolfe index score that showed correlations with SELENA-SLEDAI scores and how that data served as the premise for further developing a tool that better assesses musculoskeletal disease and outcomes in lupus by examining variations in assessment timing to inform clinical trial design. Specific details for each clinical trial outcome measure are outlined in table 1.

Dr Son rounded out the session with a presentation focused on considerations of the paediatric population when developing clinical trial outcome measures. She highlighted the unique concessions that must be made when considering children/adolescents for trials including ongoing growth and development, disease severity and severe organ involvement; and that outcome measures should consider the paediatric experience. Her talk reiterated that lack of paediatric involvement in trials leads to reduced access to medications for paediatric populations and increased risk for medication toxicities.

SUMMARY OF DISCUSSION

At the end of the meeting, participants joined in a facilitated discussion about current obstacles to developing effective outcome measures and ways the group might collaborate going forward. Several meeting participants noted the challenges of working with the U.S. FDA, which, although it is not the relevant regulatory agency for all participants in this global group, often sets precedents that other regulatory agencies follow. Given the heterogeneity of the disease, for example, therapies for lupus may target different symptoms and thus fall under the purview of different FDA review divisions. This has highlighted the variation in expectations for outcome measures across the agency and further complicates efforts to

develop these tools. Meeting participants suggested that it could be helpful to reach a consensus on what feedback is needed from the FDA to inform future efforts to develop or refine lupus outcome measures.

Following the presentation by Dr Franson on the FDA's drug development tool qualification programme and the patient-focused drug development paradigm, meeting participants also discussed the advantages and disadvantages of this programme. Although it may be advantageous for therapy developers to use outcome measures that have been formally qualified by the FDA, this process can be time consuming and is not required. One meeting participant noted, however, that the FDA does have to approve an endpoint for use in a study even if the endpoint does not go through the qualification programme. This person suggested that the use of newer outcome measures in trials, even as exploratory measures, may be another effective way to get the FDA to accept the use of these tools.

When discussing potential opportunities to collaborate, the meeting participants agreed it would be helpful to identify opportunities to share information in a way that would allow existing initiatives to continue. One example given was sharing non-proprietary formulas or data sets to facilitate additional analyses. In general, there was not a desire to consolidate the existing outcome measure efforts, with one participant noting that it may actually be beneficial to have multiple measures in development given the varying feedback researchers and sponsors have received from the FDA. Another participant suggested that the group work together to make the case, publicly, for the need for new outcome measures to advance lupus drug development efforts. Overall, participants were eager to share information and collaborate to continue to develop measures that will lead to better treatments for lupus patients.

Additional consideration should be given to how measures presented in the meeting can be used in the clinical setting as potential diagnostic, prognostic and evaluative tools for therapeutic utility. Although outcome measures are primarily developed for use in research, these measures also have an impact on how providers care for patients. Given this reality, participants agreed it is important to consider how the use of new or updated outcome measures could impact patients in a clinical care environment. Addressing current challenges related to lupus diagnosis and treatment due to limitations in how the disease is defined is a priority for the ALPHA Project's Clinical Care Implementation Team. A related publication by this working group is forthcoming.

NEXT STEPS

GAC members, patient representatives and outcome measure experts will reconvene regularly to share updates on progress as well as unanticipated challenges that arise throughout the outcome measure development and validation process. The LFA will continue to advocate for elevating the patient voice, both adult and paediatric, in activities associated with drug development. The LFA's prior support of measures like CLASI and LFA-REAL has been productive but not without regulatory challenges. Understanding specific regulatory guidelines for clinical trial outcome measures early in the development process can help avoid some of these challenges. Moreover, the LFA will continue to engage regulators on behalf of the entire lupus community to advocate for acceptance of standardised and simplified clinical trial outcome measures that reflect patient preference.

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