Utilizing qualitative and quantitative methods to understand a new model of Type 1 and 2 SLE

NCT05426902

Document Date: May 9, 2019

Research Summary
Version Date: 09May2019

Protocol Title: Utilizing qualitative and quantitative methods to understand a new model of Type 1 and 2 SLE

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Purpose of the Study:
The aims of this study are to:

1. Identify lupus patients' experiences with physician-reported and patient-reported signs and symptoms of SLE, and modify the Type 1 and 2 SLE conceptual model to reflect patients' experiences.
2. Develop a preliminary parsimonious measure to rapidly assess Type 1 and 2 SLE activity; and
3. Conduct a pilot implementation study of the Type 1 and 2 SLE model into clinical care in Duke Rheumatology.

Background & Significance:

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease whose heterogeneity has confounded scientists, clinicians, and patients for decades. Current therapeutic efforts are directed at the inflammation that causes organ damage, yet patients often remain disabled by fatigue, myalgia, mood disturbance, and cognitive dysfunction. These symptoms are persistent and often resistant to immunosuppression.

At Duke, we have developed a new conceptual model that characterizes SLE activity into two dimensions:

- Type 1: Classically considered SLE activity and recorded in physician-reported measures of SLE activity. Includes synovitis, rashes, serositis, nephritis, CNS lupus, and other objective signs.
- Type 2: Symptoms of fatigue, myalgia, mood disturbance, and cognitive dysfunction; typically not included in physician-reported measures of SLE, but are frequently reported by patients. Physicians

may ascribe these symptoms to depression or fibromyalgia, while patients identify them as SLE-related.

We hypothesize that Type 1 and 2 SLE activity varies in intensity over time, including some periods of minimal activity (neither Type 1 or 2) and mixed activity (both Type 1 and 2).

Patient-reported measures have had limited acceptance in the study of SLE, possibly due to the incongruence between Type 1 physician-reported activity and Type 2 patient-reported symptoms. According to over 1000 patients with SLE, a patient-defined-flare includes extreme fatigue (87% of the flares), aching joints (80%), muscle weakness or pain (74%), and forgetfulness (61%). Of these symptoms, only aching joints would be counted as active lupus by a rheumatologist; the remaining symptoms are likely Type 2 activity of SLE. While the authors of this study suggested that we need to re-educate our patients about lupus flares, we suggest we change how we think about SLE.

We are currently piloting two patient-reported outcomes (PRO) measures for Type 1 and 2 SLE: The Fibromyalgia Severity Score (FSS) allows patients to indicate areas of pain, extent of fatigue, waking unrefreshed, and cognitive symptoms. The FSS was designed to diagnose fibromyalgia, but we have found this scale clinically useful to efficiently measure the current extent of Type 2 SLE symptoms. The Systemic Lupus Activity Questionnaire (SLAQ) is a 24-symptom patient-reported measure of SLE activity. It partially correlates with the physician-reported Systemic Lupus Activity Measure. We have found the SLAQ clinically useful in highlighting important symptoms for patients, but the current scoring system combines Type 1 and 2 SLE activity, resulting in an assessment that is not clinically actionable.

The proposed research will build a brief preliminary PRO measure that combines features of the FSS and the SLAQ to indicate the current degree of Type 1 and Type 2 SLE activity, allowing for rapid assessment and appropriate treatment in practice.

The overall objective of this study is to develop a composite measure based on our conceptual model of Type 1 and 2 SLE to distinguish between these two symptom complexes, and then conduct a pilot implementation study of the measure within Duke Rheumatology. The central hypothesis is that Type 1 and 2 SLE are clinically distinct components of SLE that, once distinguished, will lead to improvements in the clinical management of SLE.

Methods:

Aim 1: Ensure the Type 1 and 2 SLE model matches the patient experience with lupus.

We will conduct a qualitative, descriptive study. For objective #1, we will conduct in-depth interviews. For objective #2, we will conduct cognitive interviews. In-depth interviews will be completed prior to cognitive interviews. Information learned in the in-depth interviews to develop patient-reported measures will be reviewed in the cognitive interviews.

In-depth interviews: During the in-depth interviews, participants will be asked to share their perspective on the experience with Type 1 and 2 SLE symptoms, treatments, and how their experience with lupus fits with the Type 1 and 2 SLE model. (See attachment for the question guide).

Cognitive interviews: Cognitive interviews determine how individuals process and respond to survey questions that were modified based on information learned during the in-depth interviews (Tourangeau 1984; Willis 2013). For our research, we seek to will learn how participants interpret each question and fit each symptom of the SLAQ and FSS into the Type 1 and 2 SLE model.

During the cognitive interviews, participants will be asked to describe how they responded to each survey question, how the question distinguishes between Type 1 and 2 SLE symptoms, and if there are any symptoms that are not currently included on the survey. The questions asked during cognitive interviews will be dependent upon the results of the in-depth interviews. Therefore, a question guide will be submitted as an amendment to the IRB prior to starting interviews.

In-depth interviews and cognitive interviews: The in-depth and cognitive interviews will be conducted by a trained interviewer on the telephone or in-person. They will each last about 1 to 1.5 hours and will be audio-recorded with an encrypted recorder. If an individual wishes to not be audio-recorded, detailed

notes will be taken instead. Demographic information will also be collected (see attachment for demographic questionnaire).

As a standard practice used in qualitative research, changes may be made to the question guide and demographic questionnaire during study preparation, training, pre-testing, and data collection to improve phrasing, probes, or the flow of questions or to add related questions. If the changes are within the overall topic domains or related topics currently described within this protocol, the revised questionnaire(s) will not be submitted to the IRB. If the changes fall outside of the current domains or related topics, we will submit the revised questionnaire to the IRB for review before implementation.

Inclusion: Individuals are eligible to participate if they have an established diagnosis of SLE and are followed in the Duke Lupus Clinic. Participants will be selected based on the extent of their Type 1 and Type 2 symptoms. These classifications will be based patient- and physician-reported measures from the prior visit to the Duke Lupus Clinic. We will exclude patients with significant cognitive impairment as determined by the treating rheumatologist.

Sample size:
In-depth interviews: We will conduct 12 to 15 interviews with individuals who experience higher Type 2 symptoms and 12-15 interviews with individuals who experience lower Type 2 symptoms. We chose these samples sizes because thematic saturation is typically reached around 12 interviews (Guest 2006). The interviewers will assess based on informational redundancy whether 3 additional interviews are needed.

Cognitive interviews: We will conduct at least two rounds of 10 cognitive interviews. Each round will include five participants who experience higher Type 2 symptoms and five participants who experience lower Type 2 symptoms. If further changes are necessary to the measures reviewed during the initial two rounds cognitive interviews, an additional six interviews will be conducted.

Participant selection and recruitment: We will purposefully select participants (Patton 2005) to identify the range of experiences. We will enroll a diverse study population with respect to 1) race (i.e., white and African American individuals) and 2) age (i.e., a range of ages, with an emphasis on recruiting young women). We will also stratified based on individuals' experience with higher versus lower Type 2 symptoms. These classifications will be based patient- and physician-reported measures from the prior visit to the Duke Lupus Clinic. High Type 1 symptoms will be defined as a SLEDAI score ≥6 (Gladman 2002). High Type 2 symptoms will be defined as a fibromyalgia severity score (widespread pain index + symptom severity index) ≥12 (Wolfe 2011).

Lupus Clinic is held each Wednesday in Duke South Clinic 1J. Prior to each weekly clinic, the patient list will be reviewed to identify potentially eligible patients. Eligibility will be determined based on information obtained from the medical record, as well as through a discussion with the individual's treating rheumatologist in the Duke Lupus Clinic. Prospective participants will be approached about the study during routine clinic visits at the Duke Lupus Clinic. The study will be introduced by the individual's Duke Rheumatologist.

Reimbursement: Participants will receive $25 to reimburse them for their time participating in each interview.

Data Analysis: We will use descriptive statistics to summarize the demographic data and applied thematic analysis to analyze the qualitative data from the in-depth interviews and cognitive interviews.

In-depth interviews: Interviews will be audio-recorded and transcribed verbatim. Nvivo, a qualitative research software, will be used to facilitate analysis. First, we will each apply the same structural codes to group similar responses together. Thematic coding will follow, focusing on identifying the main themes and sub-themes for each conceptual group (Guest 2006). Intercoder reliability procedures will be conducted; discrepancies in coding will be discussed, resolved, and revised as necessary. Thematic code frequencies across transcripts will be examined to identify the most frequent and salient themes, and data

reduction techniques will be used to explore the nuances and to identify sub-themes. Descriptions of these themes and sub-themes, together with illustrative quotes, will be collected in data summary reports.

Cognitive interviews: After each interview, the interviewer will complete a debriefing form to identify 1) SLAQ modifications, and 2) Type 1 or 2 symptom assignment. The debriefing forms from each interview will be summarized after each set of 10 interviews to determine the main themes, problems with the patient-reported outcomes measures that arose during the interviews, and suggested modifications to the measures. Following the second round of interviews, it will be determined if an additional 6 interviews are needed to assess the revised measure.

Aim 2: Develop a preliminary parsimonious measure to rapidly assess Type 1 and 2 SLE activity.

We will analyze data collected through the Duke Lupus Registry (DLR) (IRB Pro00008875) and Sub-studies of the DLR (IRB Pro00094645). Working closely with the Duke Center for Health Measurement, Dr. Eudy will use patient- and physician-reported data collected from 800 patient visits in DLR to develop an effective and efficient indicator of Type 1 and Type 2 SLE activity.

Data Collection: Age, gender, race/ethnicity, employment status, marital status, living arrangement, and medication adherence will be ascertained by self-report. In addition, the DLR collects information from medical records including: insurance, medication details, disease duration, and comorbidities. The DLR also collects the following information at each clinic visit:

- Patient-Reported Measures: Modified Systemic Lupus Activity Questionnaire (SLAQ), Fibromyalgia Severity Scale, Patient global assessment, current medications
- Physician-reported measures: Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Physician's Global Assessment, LFA-REAL
- Routine Lupus Labs: CBC with differential, creatinine, C3 and C4, anti-dsDNA antibody, C-reactive protein, sedimentation rate, complete urinalysis, and urine protein:creatinine

Data Analysis: Robust cluster analysis. Dr. Eudy will expand on our preliminary cluster analysis using latent profile analysis to include detailed patient-, physician- and laboratory measures. *Power Calculation*: In order to identify 4 clusters using 8 predictive variables, a minimum sample size of 320 patients is needed. If the cluster analysis identifies 7 distinct clusters, there will be sufficient power to include 5 predictive variables in the model with 350 patients. Differences in phenotypes across clusters, including patients' demographic, SLE history, patient- and physician-reported measures, and laboratory tests will be estimated by ANOVA and Chi-squared test.

Using our new knowledge about the quantitative differences in SLAQ responses by cluster, the qualitative information about symptoms from patient interviews, and clinical expertise, we will revise the SLAQ and create a new scoring system with individual Type 1 and 2 SLE scores. This new scoring system will be tested using 800 patient visits to determine if the new Type 1 and 2 SLE scores correspond to cluster assignment. Using logistic regression models, Dr. Eudy will compare three commonly used physician-reported SLE measures, the SELENA-SLEDAI, physician's global assessment, and LFA-REAL™ to determine if model fit improves with physician-reported measures. Goodness of fit will be assessed by the Hosmer-Lemeshow chi-square test, and model discrimination will be assessed using C statistics to estimate the area under the receiver operating characteristic curve. To account for patients potentially contributing more than one visit to this analysis, generalized estimating equations (GEE) will be used.

Inclusion: Patients who are enrolled in the Duke Lupus Registry and gave informed consent through the Duke Lupus Registry (DLR) (IRB Pro00008875) and Sub-studies of the DLR (IRB Pro00094645).

Compensation: Data collected from patients enrolled in the Duke Lupus Registry will be retrospectively analyzed. No compensation will be provided as part of this analysis.

Aim 3. Conduct a pilot implementation study of the Type 1 and 2 SLE model into clinical care.

To impact patients, the Type 1 and 2 SLE model needs to be translated into an actionable tool. The overall goal of Aim 3 is to develop and test a set of electronic medical record (EMR)-based tools that enable rheumatologists to assess, discuss, and treat Type 1 and 2 SLE.

Tool Development. Over the past year, the physicians in the Duke Lupus Clinic have organically developed approaches to assessing and discussing Type 1 and 2 SLE with their patients. Dr. Eudy will work with the providers in the Lupus Clinic to iteratively create SLE@Duke, a set of EMR-based tools to implement the Type 1 and 2 SLE model into clinical practice. Components will include a templated lupus note, dotphrases to assess and explain Type 1 and 2 SLE, the PRO survey, patient handouts, and suggested treatment plans. Dr. Eudy will assess provider satisfaction quarterly at the Lupus Clinic Meeting as SLE@Duke tools are tested in clinic, making iterative changes based on their feedback.

Pilot Testing. This aim will pilot the SLE@Duke program with the Duke Rheumatologists outside of the Duke Lupus Clinic, where an estimated one-third of Duke Rheumatology's SLE patients are seen by 11 rheumatologists and 4 nurse practitioners. Non-Lupus Clinic providers and patients will complete surveys to assess satisfaction with visits and the treatment of SLE.

Interventions. *SLE@Duke*. The components of SLE@Duke will be made available in Epic for providers to assess and discuss patients' Type 1 and 2 SLE activity at each clinic visit. *Physician & Clinic Training* will include Rheumatology Division Grand Rounds and in-person Academic Detailing sessions in each of the clinics. Accompanied by a Duke Lupus Clinic provider, Dr. Eudy will make frequent visits to the rheumatology clinics at 1J, Brier Creek, and South Durham to introduce the surveys, educate the nursing staff and providers on Type 1 and 2 SLE, and troubleshoot any issues that arise. The goal of these visits will be to introduce SLE@Duke, as well as solicit feedback on how to improve the tool.

Outcomes & Evaluation. We will use the RE-AIM framework to guide our collection of comprehensive information about the reach, effectiveness, adoption, implementation, and maintenance of SLE@Duke (Table 1)[25].

Table 1: RE-AIM Framework for Implementation Assessment

Provider-Level Outcomes	**Patient-Level Outcomes**
REACH: ***participant characteristics; differences between participants & non-participants***	
- Frequency of rheumatologists using SLE@Duke[1] - Preference for paper vs EMR-based PRO[2]	- Frequency of Paper vs EMR-based PRO completion[1] - Preference for paper vs EMR-based PRO[3]
EFFECTIVENESS: ***the impact of the intervention on outcomes of interest***	
- Appropriate Type 2 SLE Treatment[1] - Length of visits[1] - Physician satisfaction with visit[2]	- Perceived quality of visit[3] - Discussion of the Type 1 and 2 model[3] - Understanding of lupus activity & treatment plan[3]
ADOPTION: ***proportion of the targeted population who initiate the intervention program***	
- % of lupus patients with assessment of Type 1 and 2 SLE in note[1] - % of lupus patients with treatment based on extent of Type 1 and 2 SLE[1]	- % of patients who report discussion of the Type 1 and 2 model during visit[3]
IMPLEMENTATION: ***consistency of the delivery of the intervention***	
- Perceived benefits and barriers of SLE@Duke[2] - How SLE@Duke fit into or conflicted with work flow[2] - Impact of SLE@Duke on burden on CMAs[2]	
MAINTENANCE: ***the long-term effects of the intervention program***	
- % of lupus patients with PRO in note at Month 1 vs. Month 6[1]	
[1]Collected from EMR; [2]Collected from provider survey; [3]Collected from patient survey	

This assessment method measures the extent to which each of these components has been met and provides a framework for identifying facilitators and barriers. During a 6-month period, we expect to see approximately 260 SLE patients outside of the Lupus Clinic. Data will be collected from three sources: (1) *Electronic Medical Record (EMR)* will be utilized to determine if SLE@Duke is incorporated into visit documentation; (2) *Provider surveys* will assess whether and how the Type 1 and 2 SLE model is used,

satisfaction with visits, and perceived barriers and benefits of SLE@Duke; (3) *Patient surveys* will assess the quality of the visit, discussion of Type 1 and 2 SLE model, and understanding of lupus activity and treatment plan.

Inclusion: All clinic staff and providers in Duke Rheumatology are eligible. Patients are eligible to participate if they have an established diagnosis of SLE and are followed in Duke Rheumatology. We will exclude patients with significant cognitive impairment as determined by treating rheumatologist.

Consent Process

Aim 1 (qualitative): All participants will provide oral informed consent before participating in interviews. We are requesting a waiver of *written* informed consent (i.e., a signed consent form) under 45 CFR 46.117(c)(1), which states the following: *An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds…that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.*

Additionally, we anticipate that some of the interviews will be telephone interviews, making written informed consent logistically difficult. We will email the oral consent form prior to the interview, allowing potential participants to read and decline participation prior to their scheduled interview. We may also distribute the oral consent form to potential participants during recruitment. Before the interview is conducted, study staff will first obtain consent to participate in the interview. Each participant's ID number will be written on the oral consent form, and we will document in a study log that informed consent has been obtained from each participant.

Aim 2 (patient-reported outcomes measure): The consent will be obtained through the Duke Lupus Registry (DLR) (IRB Pro00008875) and Sub-studies of the DLR (IRB Pro00094645) and includes use of medical information.

Aim 3 (implementation): Details of the implementation will be dependent on our findings from Aims 1 & 2. An addendum to the IRB with details of the implementation will be submitted prior to start of this phase of the study. If consent is applicable, it will also be submitted through process of an amendment.

Subject's Capacity to Give Legally Effective Consent: Patients who are not competent to provide informed consent in English will not be included.

Study Interventions: To be determined based on findings from Aims 1 and 2.

Risk/Benefit Assessment: Being included in this study does not pose any increased risk to participants involved. There is minimal potential risk for loss of confidentiality. The data obtained, may improve the care for patients with SLE in the future. The risk to each participant in this study is no greater than minimal, making it reasonable given the potential benefit to future patients.

Costs to the Subject: None

Data & Safety Monitoring: A data monitoring committee will not be used.

Privacy, Data Storage & Confidentiality: All data including the audiotapes and transcriptions will be maintained on a secure server. Participants will be assigned a unique identification number that will not be related to their name, date of birth, social security number, or medical record number. For data analysis, the unique ID number will be the only patient identifier used.