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TITLE: Sleep Disturbances in Lupus: Links to Stress, Trauma, and Health outcomes

PRINCIPAL INVESTIGATOR: Patricia Katz

CONTRACTING ORGANIZATION: University of California San Francisco

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14. ABSTRACT

The objective of this project is to identify the impact of stress and trauma on heterogeneity in lupus disease activity and symptoms, and the potential mediating role of sleep disturbances. The project addresses three aims: (1) Identify the association of current levels of stress and history of stressful and traumatic events with lupus symptoms and outcomes, both concurrently and longitudinally; (2) Identify current and longitudinal associations of sleep disturbances and changes in sleep disturbances with lupus health outcomes; and (3) Determine the relationship among stress/trauma, sleep disturbances and lupus symptoms and disease activity. To date, we have achieved the first two major tasks from the SOW projected to be completed in the first 6 months of the project: IRB approval from both the local IRB and HRPO, and development of the protocol, including interview protocol, manual of operations, and construction of database for entry of data. We had begun to recruit participants when the COVID-19 pandemic triggered a shut-down of research operations. We have now resumed with modified procedures, and have conducted 13 baseline assessments, with additional assessments scheduled.

15. SUBJECT TERMS
Lupus, sleep, stress, trauma, disease activity

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1. INTRODUCTION

The objective of this project is to identify the impact of stress and trauma on heterogeneity in lupus disease activity and symptoms, and the potential mediating role of sleep disturbances. The project addresses three aims: (1) Identify the association of current levels of stress and history of stressful and traumatic events with lupus symptoms and outcomes, both concurrently and longitudinally; (2) Identify current and longitudinal associations of sleep disturbances and changes in sleep disturbances with lupus health outcomes; and (3) Determine the relationship among stress/trauma, sleep disturbances and lupus symptoms and disease activity. 60 individuals with lupus will be enrolled for a 9-night data collection period during which sleep monitoring and a stress, sleep, and symptom diary will be completed. Prior to the monitoring period, comprehensive assessments of current stress and historical experiences of stressful and traumatic events will be conducted; patient-reported outcomes will be assessed; and physician assessments of disease activity and damage will be completed. Cognitive function will be assessed at the end of the monitoring period. A second 9-night study period will occur 12 months later. Monthly telephone calls will monitor use of glucocorticoids (GCs) and other medications and conduct brief assessments of stress and changes in health.

2. KEYWORDS:

Lupus, sleep, stress, trauma, disease activity

3. ACCOMPLISHMENTS

What were the major goals of the project?

Major task 1: IRB approval

	Target date	Completion
Local IRB approval	Month 3 (11/30/19)	06/12/19
HRPO approval	Month 6 (02/29/20)	12/19/19, 03/23/20

Major task 2: Protocol development

	Target date	Completion
Questionnaire, study visit protocol, manual of operations	Month 1 (09/30/19)	12/9/19
Database for data entry	Month 4 (12/31/19)	12/31/19
Study ready to recruit participants	Month 6 (02/29/20)	02/15/20

Major task 3: Baseline study visits

	Target date	Completion
Begin visits	Month 6 (02/29/20)	Began recruitment and scheduling 02/15/20. Paused due to COVID. Resumed study contacts July 1, 2020. As of 9/23/20, 13 baseline assessments have been conducted
Complete 60 baseline visits	Month 21 (05/31/21)	

Major task 4: Follow-up study visits

	Target date	Completion
Follow-up visits begin	Month 18 (02/28/21)	
Follow-up visits completed	Month 33 (05/31/22)	

Major task 5: Quality control and data cleaning

	Target date	Completion
Quality control checks during data entry	Months 6 – 33	Quality control is ongoing.
Data cleaning, baseline	Months 18-24	
Data cleaning, follow-up	Months 24-33	

Major task 6: Data analysis and manuscript preparation

	Target date	Completion
Analysis and manuscript preparation, baseline	Months 21-33	
Analysis and manuscript preparation, follow-up	M0nths 27-36	

What was accomplished under these goals?

Major task 1, IRB approval:
• We obtained both local IRB approval and HRPO approval.

Major task 2, Protocol development:
• We completed development of the interview protocol, including the cognitive functioning battery. The interview content was approved by both the local IRB and HRPO.
• Sleep diaries were developed.
• The database manager completed construction of the MS Access data entry program for the interview.
• Testing of the data entry program was conducted.
• The research assistant completed construction of the RedCAP program for entering data from the sleep diaries.
• The research assistant was trained on conducting both the interview and the cognitive assessments.
• Recruitment procedures were developed.
• Study recruitment began on February 15, 2020, with the first study visits scheduled for the week of March 9, 2020. However, due to COVID-19 restrictions, all non-essential research visits were cancelled beginning that week. At that point, 11 individuals had been contacted and screened eligible.

• In response to COVID restrictions, we have moved to alternative procedures that will permit us to collect data remotely. New protocols were developed and IRB modifications were made to reflect new study procedures. Changes in the protocol are:

- Mail out of sleep actigraph with instructions for use and return materials.
- Video and/or phone instructions to supplement the mailed materials
- Telephone administration of study interview.
- Collection of disease activity information from electronic health records.

Because we are not conducting in-person visits at this time, we are not able to obtain blood specimens for banking. However, we are preferentially recruiting participants who receive their care at UCSF so that we can collect disease activity information from their electronic health records at the times closest to their study assessments.

As of 9/23/20, we have successfully completed 13 baseline assessments, 2 are scheduled, and 14 people are in the “pipeline” for scheduling.

Major task 5: Quality control and data cleaning:
Regular quality control checks are ongoing for our questionnaire data. We experienced a delay in the processing of actigraph sleep data because the servers used by Dr. Stone’s lab were involved in a ransomware attack that resulted in their complete shutdown until just recently. Once that group is back up and running, we will take a first look at the actigraph data.

What opportunities for training and professional development has the project provided?
Nothing to report.

How were the results disseminated to communities of interest?
Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?

During the next reporting period, we plan to continue recruitment and conducting baseline assessments, with the intention of completing the total number of baseline study visits on time, by the end of Month 21 (May 31, 2021). Follow-up assessments will begin in March/April 20201. These will be conducted using the same remote procedures or in person, if possible.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?
Nothing to report.

What was the impact on other disciplines?
Nothing to report.

What was the impact on technology transfer?
Nothing to report.

What was the impact on society beyond science and technology?
Nothing to report.

5. CHANGES/PROBLEMS

Changes in approach and reasons for change
Because of the COVID-19 pandemic, we have changed the study protocol so that study procedures are all done remotely, with actigraphs and other materials sent out and returned by mail, and questionnaires completed by phone. Per UCSF IRB approval, consent documents are signed via DocuSign after a phone consent discussion.

Actual or anticipated problems or delays and actions or plans to resolve them
• Due to the COVID-19 pandemic, all non-essential in-person research was put on hold at UCSF from March through June 2020, so we were delayed in beginning baseline assessments. We have now implemented remote procedures and are successfully conducting assessments. Technically, UCSF has approved resumption of in-person non-essential clinical research, under some restrictions. However, we are finding that our patients do not want to risk COVID exposure by attending a non-clinical research visit, so we will continue the remote procedures.

• Because assessments are conducted by phone now, we have reduced the components of our cognitive testing battery to 3 cognitive tests that can be conducted by phone. While it would be optimal to include the larger battery, we believe that we will still obtain valuable information from this abbreviated set of tests. These tests will be included in the larger battery if we are able to resume in-person visits.

• We had planned to collect blood specimens from participants during their study visits and conduct clinical assessments of disease activity. However, with the change to remote visits, we are preferentially recruiting individuals who receive their clinical care at UCSF so that we can collect information about their disease activity from their clinical visits closest to the study assessments.

Changes that had a significant impact on expenditures
Due to COVID-19 restrictions on in-person research visits, our expenditures for participant reimbursements are delayed. We have also incurred costs for USPS priority mailing, but these are likely to be offset by reductions in costs to pay for participant parking.

The subcontract expenditures from Dr. Stone's lab have also been delayed due to overall delays in the project as described above. Those expenditures will be charged to the project as the work progresses.

Significant changes in use or care of human subjects
We made modifications to our IRB protocol and consent to address the addition of remote study assessments. The revised documents and approval letters have been submitted to HRPO

Significant changes in use of vertebrate animals
Not applicable

Significant changes in use of biohazards and/or select agents
Not applicable

6. PRODUCTS

Publications, conference papers, and presentations
Nothing to report

Website(s) or other internet site(s)
Nothing to report

Technologies or techniques
Nothing to report

Inventions, patent applications, and/or licenses
Nothing to report

Other products
Nothing to report

7. PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Patricia Katz
Project Role:	PI
Research identifier (e.g., ORCID ID)	0000-0002-8146-2519, eRA Commons: PATKATZ
Nearest person month worked:	0.6
Contribution to the project	Overall project direction, supervision of all project activities, liaison with funder

Name:	Maria Dall'Era
Project Role:	Co-investigator, UCSF
Research identifier (e.g., ORCID ID)	eRA Commons: MARIADALLERA
Nearest person month worked:	0.24
Contribution to the project	Clinical expertise in lupus

Name:	Jennifer Niemi
Project Role:	Research assistant
Research identifier (e.g., ORCID ID)	
Nearest person month worked:	6.0
Contribution to the project	Development and testing of study interview protocol, development of sleep diary, development of sleep diary RedCAP data entry program, recruitment and screening of study participants, conduct of study visits

Name:	Stephanie Rush
Project Role:	Database manager
Research identifier (e.g., ORCID ID)	
Nearest person month worked:	0.6
Contribution to the project	Development of MS Acess data interview and entry program, data cleaning, creation of project codebooks creation of data analytic files.

Name:	Katie L. Stone
Project Role:	Co-investigator, California Pacific Medical Center Research Institute (CPMCRI)
Research identifier (e.g., ORCID ID)	eRA Commons: KSTONE
Nearest person month worked:	0.33
Contribution to the project	Overall project direction, supervision of all project activities, liaison with funder

Name:	Katherine Peters
Project Role:	Biostatistician, CPMCRI
Research identifier (e.g., ORCID ID)	
Nearest person month worked:	0.27
Contribution to the project	Developing scoring protocols for WatchPAT and actigraph data, including data transfer

Name:	Vicki Li
Project Role:	Project assistant, CPMCRI
Research identifier (e.g., ORCID ID)	
Nearest person month worked:	0.41
Contribution to the project	Reviewing and cleaning actigraphy files

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to report

What other organizations were involved as partners?

Organization Name:	California Pacific Medical Center Research Institute (CPMCRI)
Location of Organization:	San Francisco, CA
Partner's contribution to the project	Collaboration. Dr. Katie Stone's lab at CPMCRI is providing expertise in the collection and scoring of actigraph measurement of sleep.

8. SPECIAL REPORTING REQUIREMENTS
Nothing to report

9. APPENDICES
Nothing to report

Sleep Disturbances in Lupus: Links to Stress, Trauma, and Health Outcomes

Log Number: LR180023

W81XWH-19-1-0611

PI: Patricia Katz, PhD **Org:** University of California San Francisco **Award Amount:** $525,000

Study/Product Aim(s)

Specific Aims:

1. Identify the association of current stress and history of stressful and traumatic events with lupus symptoms and outcomes, concurrently and longitudinally.
2. Identify current and longitudinal associations of sleep disturbances and changes in sleep disturbances with lupus health outcomes.
3. Determine the relationship among stress/trauma, sleep disturbances, and lupus symptoms and disease activity.

Approach

60 individuals with lupus will complete a 9-night data collection period during which sleep monitoring and a stress, sleep, and symptom diary will be completed. Prior to sleep monitoring, comprehensive assessments of current stress and historical experiences of stressful and traumatic events will be conducted, and patient-reported outcomes and cognitive function will be assessed. A second 9-night study period will occur 10 months later. Monthly telephone calls will monitor use of glucocorticoids (GCs) and other medications and conduct brief assessments of stress and changes in health.

Do stress and trauma cause more severe disease activity in lupus by disturbing sleep?

Accomplishments: Study protocols have been developed and approved by the IRB. Study recruitment and baseline study assessments have begun.

Timeline and Cost

Activities CY	20	21	22
Protocol development, IRB approval			
Recruitment, baseline study assessments			
Follow-up assessments			
Data analysis, manuscript preparation			
Estimated Budget ($K)	**$190**	**$186**	**$148**

Updated: (September 23, 2020)

Goals/Milestones

CY20 Goal – Set-up and implement study

☑ Study protocols, questionnaires developed

☑ IRB approval

CY21 Goals – Continue study implementation

☑ Begin recruitment and baseline study assessments

☐ Complete 60 baseline visits, begin follow-up assessments

CY22 Goal2 – Complete data collection and prepare manuscript(s)

☐ Complete follow-up assessments

☐ Conduct data analyses

☐ Prepare and submit manuscript(s)

Comments/Challenges/Issues/Concerns

- Study procedures and timeline affected by COVID-19 pandemic
- Study assessments now being conducted remotely

Budget Expenditure to Date (through July 2020)

Projected Expenditure: $190,871

Actual Expenditure: $110,162