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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, CA

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Patricia Katz

E-Mail: patti.katz@ucsf.edu

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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.
Complete 60 baseline visits	Month 21 (05/31/21)	Baseline visits were completed as of September 22, 2021 (Month 25)

Major task 4: Follow-up study visits

	Target date	Completion
Follow-up visits begin	Month 18 (02/28/21)	Follow-up visits began in May 2021 (Month 21)
Follow-up visits completed	Month 33 (05/31/22)	Follow-ups were completed in July 2022 (Month 35)

Major task 5: Quality control and data cleaning

	Target date	Completion
Quality control checks during data entry	Months 6 – 36	Quality control is ongoing.
Data cleaning, baseline	Months 18-24	Cleaning for the baseline dataset has been completed.

Data cleaning, follow-up	Months 24-36	Cleaning of the follow-up dataset is close to completion. Estimated completion December 2022

Major task 6: Data analysis and manuscript preparation

	Target date	Completion
Analysis and manuscript preparation, baseline	Months 35-48	A baseline dataset has been created, linking the study-specific information to the larger cohort dataset. Initial analyses have begun.
Analysis and manuscript preparation, follow-up	Months 40-48	Once the clean follow-up dataset is ready, we will link to the larger cohort dataset, and will begin additional analyses.

What was accomplished under these goals?

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

Major task 2, Protocol development: COMPLETED
• 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 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 have only recruited 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.

Major task 3, Baseline study visits: COMPLETED
• While we had hoped to complete recruitment and baseline assessments by the end of Month 21 (May 2021), delays due to COVID pushed completion of baseline assessments to Month 25 (September 2021).

• We have completed the proposed number of baseline assessments (n = 61).

Major task 4, Follow-up study visits: COMPLETED
• The follow-up time was shortened to 10 months (instead of 12) to allow enough time for follow-ups for all participants within the study period. We are on track to complete follow-ups by July 2022.

• Follow-up study assessments began in May 2021 and were completed in July 2022.

• We achieved 100% retention for follow-ups.

Major task 5, Quality control and data cleaning: Ongoing

• 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. We are now up to date on all actigraph processing.

• Now that baseline interviews have been completed, the baseline dataset integrating the interview and actigraph data will be compiled for final data cleaning.

• Regular quality control checks are ongoing for our questionnaire data.

Major task 6: Data analysis and manuscript preparation: Ongoing

• Analysis of the baseline data will begin as soon as the baseline dataset is released, expected in October 2021. First analyses will focus on addressing the cross-sectional components of the study aims.

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 will continue the follow-up assessments. We will resume in-person visits if possible, however, our participants are still reluctant to attend in-person research visits, so we do not expect any in-person visits to occur. We intend to complete follow-up visits by the end of July 2023, which will allow a 10-month follow-up period for all participants. This is later than originally proposed, due to delays caused by the COVID-19 pandemic.

• We will assemble a cleaned baseline dataset, merging all data from questionnaires, actigraphs, and cognitive assessments. A merged dataset for all follow-up data will be compiled as data collection is completed.

• As participants complete follow-ups, we will review their electronic health records to collect information about their disease status during the study period.

• We will submit at least one abstract to the 2022 American College of Rheumatology meeting (abstracts due in June 2022). Other abstract venues (e.g., lupus-specific conferences) will be considered as they are available.

• Manuscript preparation will begin during the next year, beginning with analysis of the baseline data. We had originally allowed for the last several months of the funding period to complete data analyses. Now, we anticipate that analyses and manuscript preparation will continue beyond the funding period, primarily because of delays in data collection. We are committed to completing at least the primary manuscripts outlined in the proposal.

• We have linked the baseline data to the parent cohort, matching to the interview closest in time to the sleep study collection period.

• We are at the stage of data analysis and manuscript preparation, and anticipate having a draft manuscript(s) for the baseline data completed in the first quarter of 2023.

• We are still conducting data cleaning and linking to the parent cohort for the follow-up data. We anticipate that being completed in December 2022. Longitudinal analyses will follow.

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 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. This process has been very successful and has permitted us to meet our recruitment goal.

• We modified the follow-up time from 12 months to 10 months to compensate for the study delays caused by the COVID research hold. We do not believe that this will have an appreciable change on the study results.

• We made the decision to recruit only participants who receive their clinical lupus care at UCSF so that we could obtain information about their disease activity from their electronic health records. This decision was made because we were not able to assess disease activity during in-person research visits.

• No additional changes have been made.

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 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.

• Because of delays in data collection, we anticipate that manuscript preparation will extend beyond the 3-year study period. We are, however, committed to ensuring that manuscripts addressing the primary study hypotheses are submitted for publication.

• As noted previously, manuscript preparation will extend beyond the 3-year project period, and we are committed to preparing manuscripts to address the primary study hypotheses. Now that all data collection has been completed, we are turning to completing data cleaning and dataset compilation. Manuscript preparation is the next step.

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 have been 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.

• No changes in addition to those previously reported.

Significant changes in use or care of human subjects

Nothing to report

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 Access 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, cleaning, and scoring 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