AWARD NUMBER: W81XWH-13-1-0479

TITLE: Sleep-Disordered Breathing in Chronic SCI: A Randomized Controlled Trial of Treatment Impact on Cognition, Quality of Life, and Cardiovascular Disease

PRINCIPAL INVESTIGATOR: Shirin Shafazand, MD, MS

CONTRACTING ORGANIZATION: UNIVERSITY OF MIAMI
MIAMI FL 33136-1000

REPORT DATE: October 2015

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.
REPORT DOCUMENTATION PAGE

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.

1. REPORT DATE
   October 2015

2. REPORT TYPE
   Annual Report

3. DATES COVERED
   30 Sep 2014 - 29 Sep 2015

4. TITLE AND SUBTITLE
   Sleep-Disordered Breathing in Chronic SCI: A Randomized Controlled Trial of Treatment Impact on Cognition, Quality of Life, and Cardiovascular Disease

5. AUTHOR(S)
   Shirin Shafazand, MD, MS, FCCP, FAASM
   E-Mail: sshafazand@med.miami.edu

6. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
   UNIVERSITY OF MIAMI
   1400 NW 10 AVE RM 1007P
   MIAMI FL 33136-1000

7. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
   U.S. Army Medical Research and Materiel Command
   Fort Detrick, Maryland 21702-5012

8. DISTRIBUTION / AVAILABILITY STATEMENT
   Approved for Public Release; Distribution Unlimited

9. SUBJECT TERMS
   SDB, SCI, PAP, CV

10. SECURITY CLASSIFICATION OF:
    a. REPORT
       Unclassified
    b. ABSTRACT
       Unclassified
    c. THIS PAGE
       Unclassified

11. LIMITATION OF ABSTRACT
    Unclassified

12. NUMBER OF PAGES
    10

13. SUPPLEMENTARY NOTES

14. ABSTRACT
   This study addresses the widely recognized and heretofore incompletely managed cognitive, and cardiovascular (CV) secondary complications in military veterans and non-veterans with SCI. In this prospective randomized controlled trial, we will objectively measure sleep disordered breathing (SDB) in chronic SCI patients using portable sleep studies, and systematically evaluate the association between SDB, cognitive performance, mood, pain, and CV measures. We will randomize participants to 4 months of PAP or placebo. We will re-evaluate cognitive measures, quality of life, sleep quality, mood and CV outcomes after 4 months of therapy to determine whether PAP therapy has improved baseline impairments. There is minimal risk to study participants and significant potential for immediate and lasting benefits. In the first year of the study, we have completed the manual of study operations, designed a secure study database for data gathering, obtained local IRB approval at all study sites, and DoD approval for the University of Miami and Miami VA sites. Study equipment has been purchased. Research coordinators have been trained and we have enrolled 15 subjects at approved sites. Our first subject will be randomized shortly.

15. SPONSOR/MONITOR’S ACRONYM(S)

16. SPONSOR/MONITOR’S REPORT NUMBER(S)

17. LIMITATION OF ABSTRACT
    Unclassified

18. NUMBER OF PAGES
    10

19. NAME OF RESPONSIBLE PERSON
    USAMRMC

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18
1. **INTRODUCTION:**

   There is a paucity of information on the impact of sleep disordered breathing (SDB) and its treatment in chronic spinal cord injury (SCI). Despite the increased prevalence reported in the literature, screening for SDB and its treatment are not yet standard of care. To enable change in practice, well designed randomized placebo-controlled trials (RCT) are needed to demonstrate the importance of SDB and its treatment on the health of this population. The central hypothesis of this study is that the treatment of SDB with positive airway pressure (PAP) will improve cognitive impairment, sleep quality, quality of life, and cardiovascular disease (CVD) surrogate measures in persons with chronic SCI. The Specific Aims are: 1) Determine the associations between SDB and cognitive impairment and evaluate the impact of PAP therapy on cognitive measures, and 2) Determine the impact of PAP therapy on surrogate CV biomarkers, sleep quality, quality of life, mood, and pain, in a cohort with chronic SCI and SDB.

   This is a four year multi-center double blinded, placebo controlled RCT. We will objectively measure SDB in chronic SCI participants using portable unattended polysomnography, and randomize those with SDB to four months of therapeutic PAP vs. sham PAP (placebo). We will measure cognitive performance (memory, attention, and executive function) using a battery of standardized neuro-cognitive tests (PASAT-primary outcome). Additionally, we will measure surrogate CVD biomarkers. All measurements will be done at baseline and four month follow-up.

2. **KEYWORDS:** Spinal cord injury, Sleep disordered breathing, Positive airway pressure, Randomized controlled Trial, Cognition, Quality of life, Sleep Quality, Polysomnography

3. **ACCOMPLISHMENTS:**

   - What were the major goals of the project?
     
     Study Tasks
     
     Task 1. Regulatory Approval (months 1-6)
     
     1a. Obtain IRB approval University of Miami and Miami VA (months 1-3) **Completed**
1b. Obtain IRB approval Wayne State University and Detroit VA (months 1-3) Completed
1c. Obtain DoD regulatory approval (months 1-6) Miami site Feb 25, 2014; Miami VA site April 11, 2014, Wayne State and Detroit VA: Dec 11, 2014
1d. Obtain final project approval (month 6) Completed for Miami site and Detroit site

Task 2. Elaborating Study Protocol, Training, Purchasing Equipment, and Database Design (months 1-5)
2a. Finalizing a detailed study manual explicitly outlining inclusion/exclusion criteria, protocols for recruitment, questionnaire administration, performing portable polysomnography, scoring of questionnaires, and scoring of sleep studies (months 1-5) Completed
2b. Design of study database (months 1-2) Completed
2c. Training of Research Associates in study protocol, recruitment strategies, administration of sleep and cognitive questionnaires, hook up of portable sleep study, and maintaining database (months 3-5) Completed
2d. Purchasing portable PSG units, auto PAP units, testing, and ensuring accurate operation (month 4-5) Completed for University of Miami and Miami VA sites; Completed for Detroit sites March 2015.

3a. Screening and recruitment of participants (months 6-40) ongoing at Miami sites, ongoing at Detroit sites
3b. Portable polysomnography completion (months 6-40) ongoing at Miami sites, ongoing at Detroit sites
3c. Polysomnography scoring and interpretation (months 6-40) ongoing at Miami sites, ongoing at Detroit sites
3d. Computer generated randomization (months 6-40) Completed
3e. Completion of baseline sleep and neuro-cognitive questionnaires (months 6-40) ongoing at Miami sites, ongoing at Detroit sites
3f. Scoring of questionnaires (months 6-40) *ongoing at Miami sites, not started at Detroit sites*

3g. Medical record review to determine participant co-morbidities, and medications (months 6-40) *ongoing at Miami sites, ongoing at Detroit sites*

3h. Obtaining baseline blood and urine samples (6-40) *ongoing at all sites*

3i. Processing and storing of samples (6-40) *ongoing at all sites*

3j. Entry of results into de-identified study database (months 6-40) *ongoing at Miami sites, not started at Detroit sites, awaiting University of Miami approval of centralized access for Detroit sites*

Task 4. Cognitive, Sleep, Quality of Life, and Cardiovascular Outcomes (months 7-44) *ongoing at all sites*

4a. Completion of follow-up sleep, HRQoL, and neuro-cognitive questionnaires at 1 month (selected measures) and 4 month follow-up (months 7-44)

4b. Obtaining blood and urine samples at four month follow-up (months 10-44)

4c. Processing and storing of follow-up samples (months 10-44)

4e. Entry of follow-up results into de-identified study database (months 7-44)

Task 5. Data Analysis, Presentations, and Manuscripts (months 40-48) *These tasks are for years 3 onwards.*

5a. Interim baseline data accuracy and safety review (quarterly, months 6-44) *Baseline data on patients enrolled to date has been reviewed for safety and accuracy*

5b. Final data analysis (months 40-48)

5c. Manuscript preparation and presentations (months 44-48)

- **What was accomplished under these goals?** Study procedure manual, training of research associates, creation of secure study database, and purchasing of equipment (for Miami and Detroit site) has been completed. To date, we have enrolled 35 subjects from the University of Miami and Miami VA sites. All baseline questionnaires and cognitive evaluations have been completed. Baseline portable polysomnography has been completed for 30, 2 have been scheduled for polysomnography, 3 had incomplete tests and did not wish to continue. Of the 30 with baseline polysomnography completed, 17 have obstructive sleep apnea and
14 have undergone randomization, 3 did not wish to continue. 11 of the 14 have completed 4 month study follow-up and are discharged from the study. Subject recruitment is ongoing at the Miami sites. The Detroit site had enrolled and randomized 2 subjects.

- **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 year, we anticipate that the Detroit sites will increase their recruitment. We are also trying to increase enrollment at Miami sites by reaching out to support groups. We anticipate close to 50 subjects randomized by next reporting period.

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** Nothing to report
- **Actual or anticipated problems or delays and actions or plans to resolve them.** There was an initial delay in funding/project approval due to sequestration and changes in DoD regulatory personnel assigned to project. The project was approved for funding Sept 30, 2013. DoD approval of the University of Miami site occurred Feb 25, 2014 and Miami VA site April 11, 2014. Recruitment from the Miami VA is slower than anticipated and we are trying to rectify the situation by advertising study at support groups. We will also obtain IRB approval and DoD approval for going to subject’s home if necessary to perform home sleep study. One of the barriers to recruitment has been transportation difficulties for subjects.
- **The Detroit site started enrollment in October and will be increasing recruitment this year.**
- **Changes that had a significant impact on expenditures** Nothing to report
- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents** Nothing to report
- **Significant changes in use or care of human subjects** Nothing to report
- **Significant changes in use or care of vertebrate animals.** Nothing to report
- **Significant changes in use of biohazards and/or select agents** Nothing to report

6. **PRODUCTS:** Nothing to report

7. **PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

   - What individuals have worked on the project?

<table>
<thead>
<tr>
<th>Name:</th>
<th>Shirin Shafazand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project Role:</td>
<td>PI</td>
</tr>
<tr>
<td>Researcher Identifier (e.g.</td>
<td></td>
</tr>
<tr>
<td>ORCID ID):</td>
<td></td>
</tr>
<tr>
<td>Nearest person month</td>
<td>3 months</td>
</tr>
<tr>
<td>worked:</td>
<td></td>
</tr>
<tr>
<td>Contribution to Project:</td>
<td>PI, design study, responsible for</td>
</tr>
<tr>
<td></td>
<td>overseeing all aspects of study,</td>
</tr>
<tr>
<td></td>
<td>interpreting sleep studies</td>
</tr>
<tr>
<td>Funding Support:</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name:</th>
<th>Patricia Burns</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project Role:</td>
<td>Research Associate</td>
</tr>
<tr>
<td>Researcher Identifier (e.g.</td>
<td></td>
</tr>
<tr>
<td>ORCID ID):</td>
<td></td>
</tr>
<tr>
<td>Nearest person month</td>
<td>6 months</td>
</tr>
<tr>
<td>worked:</td>
<td></td>
</tr>
<tr>
<td>Contribution to Project:</td>
<td>Study coordinator, subject</td>
</tr>
<tr>
<td></td>
<td>recruitment, responsible for</td>
</tr>
<tr>
<td></td>
<td>conducting cognitive testing and</td>
</tr>
<tr>
<td></td>
<td>sleep studies, data entry</td>
</tr>
<tr>
<td>Funding Support:</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name:</th>
<th>Mark Nash</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project Role:</td>
<td>Co-investigator</td>
</tr>
<tr>
<td>Researcher Identifier (e.g.</td>
<td></td>
</tr>
<tr>
<td>ORCID ID):</td>
<td></td>
</tr>
<tr>
<td>Nearest person month</td>
<td>1 month</td>
</tr>
<tr>
<td>worked:</td>
<td></td>
</tr>
<tr>
<td>Contribution to Project:</td>
<td>Assisted in study design,</td>
</tr>
<tr>
<td></td>
<td>finalizing operations manual,</td>
</tr>
<tr>
<td></td>
<td>database design</td>
</tr>
<tr>
<td>Funding Support:</td>
<td></td>
</tr>
</tbody>
</table>
Name: Douglas Johnson Greene

Project Role: Co-investigator

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 1 month

Contribution to Project: Training of research associates in cognitive testing, overseeing accuracy of cognitive testing

Funding Support:

Name: Safwan Badr

Project Role: Co-investigator; Wayne state PI

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 1 month

Contribution to Project: responsible for overseeing regulatory overview at Detroit sites and coordinating study procedures with Miami sites

Funding Support:

- 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? Nothing to report. Wayne state University and Detroit VA were 2 other sites listed previously on this multi-site proposal and that has not changed.

8. SPECIAL REPORTING REQUIREMENTS
   - COLLABORATIVE AWARDS: Not applicable
   - QUAD CHARTS: attached

9. APPENDICES: Not applicable