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14. ABSTRACT

It is estimated that 10% to 20% of warfighters who have served in Iraq and Afghanistan have PTSD 1-4. An important limitation of these estimates is the reliance on self-report screening measures and clinical interviews to make the diagnosis of PTSD. These methods are subject to a number of biases, including underreporting of PTSD symptoms because of stigma of mental illness and concerns about adverse effects on careers, and exaggeration of symptoms in those seeking compensation for service- connected disability5. Development of biomarkers of PTSD is critical for DOD and VA as objective indicators of PTSD for use in post-deployment medical screening, treatment selection, treatment outcome monitoring, disability evaluations, and for informing novel targets for treatment development.

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Table of Contents

INTRODUCTION:

It is estimated that 10% to 20% of warfighters who have served in Iraq and Afghanistan have PTSD [1-4]. An important limitation of these estimates is the reliance on self-report screening measures and clinical interviews to make the diagnosis of PTSD. These methods are subject to a number of biases, including underreporting of PTSD symptoms because of stigma of mental illness and concerns about adverse effects on careers, and exaggeration of symptoms in those seeking compensation for service- connected disability[5]. Development of biomarkers of PTSD is critical for DOD and VA as objective indicators of PTSD for use in post-deployment medical screening, treatment selection, treatment outcome monitoring, disability evaluations, and for informing novel targets for treatment development. Additionally, biomarkers hold great potential for explaining and mitigating the associations between war zone-related PTSD and physical health problems, including cardiovascular and metabolic disorders [6-10]. In order to address this critical gap we will perform a pilot study to determine feasibility for larger scale biomarker identification and biomarker informed intervention studies by carefully examining 200 OIF/OEF warfighters through an extensive biological protocol. The first phase will pilot the integration of methods across five leading research laboratories and identify the most promising biomarkers in preparation for larger scale studies. Given the sample size for the pilot and large number of biomarkers of interest, we will specify a limited set of biomarkers for hypothesis testing. It is predicted that compared with controls the PTSD group will have smaller dentate/CA3 hippocampal subfield volumes, lower ambient cortisol levels, and greater cortisol suppression following dexamethasone administration. It is also predicted that lower neuropeptide Y levels will be associated with smaller Dentate/CA3 volumes, and that APO E4 polymorphisms will be associated with smaller Dentate/CA3 volumes.

BODY:

According to the Statement of Work, the goal of the initial start-up and planning phase of this study was to focus on gaining regulatory approval, hiring staff, and preparing the study for launch. The primary accomplishments of this reporting period involved receipt of funding, execution subcontracts, full staffing of all study sites, initiation and completion of all pilot testing (bloods, neuroimaging), receipt of final regulatory approvals to launch study, and study launch. We were able to meet and exceed our goals for recruitment rates in these early phases of study launch and have successfully run some participants through all phases of the study. These accomplishments are detailed below.

In year 1 of the grant, Dr. Marmar transitioned to a new position as Chair of the Department of Psychiatry at New York University Medical Center (NYUMC). Hence, the effort and focus of year 1 of the grant was on relinquishment of this grant from the DOD and Northern California Institute for Research and Education (NCIRE) and the transfer of this grant to NYU. Funding was finally transferred to NYU at the start of this reporting period in June 2010 and subcontracts were executed so that all study sites could complete major start-up tasks such as staffing and piloting procedures.

The IRB protocol underwent several rounds of amendments in order to coordinate changes requested amongst the multiple institutions involved in the study and the DOD, as well as changes to accommodate requests for blood samples and data sharing from the basic science groups at Walter Reed, University of California San Francisco, and the Institute of Systems Biology, who are involved in the larger collaborative effort that aims to apply a systems biology approach to PTSD. A final version of this protocol was fully approved across all performance sites (NYU, MSSM, JJPVAMC, UCSF, and SFVAMC) in October 2010. The final protocol was then approved by the DOD IRB in November 2010.

Dr. Clare Henn-Haase PsyD, co-investigator and a licensed Clinical Psychologist, accepted a faculty position at NYUMC in June 2010 and started the planning and start up phase for this project.

Recruitment materials were developed and study website was launched at the parent site. Recruitment materials were shared with the other recruitment sites (JJPVAMC/MSSM). A recruitment plan was developed to coordinate efforts between these sites. The study recruiter, who was hired in June 2010, continued

the outreach effort by contacting veteran organizations, VAs, and CBOCs within the boroughs of New York City, which will be the focus of recruitment efforts.

A Research Assistant was hired in July 2010. The Research Assistant completed preparing packets of the clinical interview and the self-report materials and manualizing all study procedures into an operation manual. The operation manual was distributed across sites to standardize procedures.

A database manager was hired and trained in September 2010. The database manager developed a secure tracking database for recruitment sites at NYU, MSSM and JJPVAMC to track participants' study information and progress. Remote access/VPN connection was provided to the JJPVAMC site to access the tracking database and SQL server.

A Project Manager, a licensed Clinical Psychologist, two hourly licensed clinical psychologists, and one postdoctoral trainee were hired in November 2010. Five Training sessions for all study clinicians were conducted.

A master's level Biostatistician was hired for this project in April 2011. The Biostatistician was trained with the senior consultant Biostatistician on this project.

Neuroimaging piloting was completed. Six healthy volunteer pilot participants were run on the imaging protocol at NYU's Center for Biomedical Engineering. Images were sent to UCSF/SFVAMC. The image processing team at UCSF/SFVAMC worked with the NYU team to work out signal-to-noise issues in data acquisition, to finalize parameters, and to finalize procedures for sharing of data.

Clinical data from the interview and self-report measures were digitized so that they could be completed at a computer and the data set will be saved directly into the study secure SQL database server. All data transfer protocols to the cores (i.e. MRI scans, blood, and urine) were finalized.

A data transfer agreement was approved to transfer data between the JJPVAMC/NYUMC and UCSF/NYUMC.

The implementation and data collection phase started in late November 2010 after getting the IRB approvals from all sites and from the DOD. All logistics and regulatory approvals were in place with the phlebotomy clinics at MSSM and NYU to launch Visits 2 and 3 blood draws in early January 2011. Neuroimaging Visit 4 was initiated in February 2011 after the completion of pilot testing.

Recruitment of subjects started at a high rate, with one participant recruited per day. As of June 2nd, 2011, a total of 59 subjects have been enrolled in the study and found to be eligible after completing the clinical interview (meeting all inclusion criteria for PTSD + or PTSD -). Blood draw procedures and MRI imaging are completely operational. Forty one subjects completed all procedures for this study. Neuroimaging core is receiving successfully de-identified raw data of the MRI scans from NYU. Blood samples are being shipped from the JJPVAMC to the Metabolism and Genetic cores at UCSF on regular bases.

Weekly meetings, through teleconference calls, have continued to take place between PIs at each site (JJPVAMC, SF VAMC, UCSF, Mt Sinai, and NYU). Calibration between clinicians at both recruitment sites has been conducted on weekly bases.

The table below includes details of the study recruitment numbers for the past year:

Biomarkers Recruitment and Enrollment As of 6/2/2011	
	Total for Both Sites (NYU/JJPVAMC)
Recruitment	
Screened	374
Scheduled	233
Hold by Screen	23
Ruled Out by Screen	96
Pending Scheduling	22
BCI Evaluation	
Consented	168
Visit 1 Evaluations Completed	153

Biomarkers Recruitment and Enrollment As of 6/2/2011	
Eligible by Evaluation	59
PTSD+	27
PTSD-	32
Ineligible by Evaluation or drop outs	80
Pending Clinical Consultation and Calibration	14
Cognitive Testing	
Completed	50
Scheduled	4
Self-Report Questionnaire	

Biomarkers Recruitment and Enrollment As of 6/2/2011	
Completed	52
Scheduled	4
Visit 2 Blood Draw (1)	
Completed	51
Scheduled	3
Visit 3 Blood Draw (2)	
Completed	51
Scheduled	3
MRI	
Completed	41

Biomarkers Recruitment and Enrollment As of 6/2/2011	
Scheduled	6
Refused	1
Ineligible (bullet fragment, Pregnancy)	2

KEY RESEARCH ACCOMPLISHMENTS:

Start Up & Planning Phase:

- Hired and trained all personnel and staff for the study.
- Developed recruitment materials and launched study website.
- Developed a manual of operation for the study to standardize procedures across sites.
- Completed neuroimaging pilot and finalized imaging parameters, protocols and raw transfer of data.
- Obtained regulatory and IRB approvals across all sites and the DOD.
- Obtained data transfer agreements between NYUMC/ JJPVAMC and NYUMC/UCSF.
- Completed database construction and remote access/VPN connection was set up for the collaborating sites to access the database.
- Clinical data from the baseline interview, Neurocognitive testing and Self-report measures were digitized for easier data management. The digital forms can be completed at a computer and the data set will be saved directly into the study secure SQL database server.
- Completed a number of shipments of blood samples from JJPVAMC to UCSF (Metabolism & Genetic cores)

Implementation and Data Collection Phase:

- Started recruitment and data collection for all study procedures.

REPORTABLE OUTCOMES:

The major development during this annual report of this project is that the start-up and planning phase has been completed. All study personnel were hired and trained, IRB and regulatory requirements were obtained from the DOD and all the participating cores, a manual of operation has been developed and distributed to other sites, study database was constructed and a data management system among sites was established.

The study is currently in the implementation phase, recruitment and data collection began in November 2010 and participants are completing all study procedures.

Tasks to complete for the next annual report include: (1) Continue to recruit and enroll subjects for the study. (2) Run study participants through all procedures. (3) Continue data collection and data management. (4) Analyze background and demographic data for enrolled participants. (5) Process and ascertain the majority of the biomarkers. (6) Test biomarkers for 50 cases/50 controls. (7) Replicate the most promising biomarkers. (8) Ship samples to Drs. Marti Jett and Lee Hood for analysis.

CONCLUSION: The study has received IRB approval from all sites and from the DOD. The study has achieved high rate of recruitment. Data collection and data management is running smoothly.

We will start data analysis when a sample size of 50 cases/50 controls is achieved. The most promising biomarkers will be replicated.

The original award for this project is to study 100 PTSD + and 100 PTSD – OIF/OEF service members. A BAA was submitted for additional funding to include 40 PTSD+ OIF/OEF and 40 PTSD- OIF/OEF female veterans. Female mouse model will also be developed for this supplemental work.

We also have obtained a no cost extension for this study until February, 19th, 2013.

REFERENCES:

1 K.H. Seal, et al., Getting beyond "Don't ask; don't tell": an evaluation of US Veterans Administration postdeployment mental health screening of veterans returning from Iraq and Afghanistan. *Am J Public Health* **98**, 714-20 (2008).

2 C. W. Hoge, A. Terhakopian, C. A. Castro et al., Association of posttraumatic stress disorder with somatic symptoms, health care visits, and absenteeism among Iraq war veterans *Am J Psychiatry* **164** (1), 150-3 (2007).

3 C. W. Hoge, C. A. Castro, S. C. Messer et al., Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care *The New England journal of medicine* **351** (1), 13-22 (2004).

4 K.H. Seal, Bertenthal, D., Miner, C.R., Sen, S. & Marmar, C., Bringing the war back home: mental health disorders among 103,788 US veterans returning from Iraq and Afghanistan seen at Department of Veterans Affairs facilities. *Arch Intern Med* **167**, 476-82 (2007).

5 P. B. Watson and B. Daniels, Follow up of post-traumatic stress disorder symptoms in Australian servicemen hospitalized in 1942-1952 *Australas Psychiatry* **16** (1), 18-21 (2008).

6 J.A. Boscarino, Psychobiologic predictors of disease mortality after psychological trauma: implications for research and clinical surveillance *Journal of Nervous and Mental Disease* **196** (2), 100-07 (2008).

7 M.J. Mancino, J.M. Pyne, S. Tripathi et al., Quality-adjusted health status in veterans with posttraumatic stress disorder *Journal of Nervous and Mental Disease* **194** (11), 877-79 (2006).

8 W. V. Vieweg, D. A. Julius, J. Bates et al., Posttraumatic stress disorder as a risk factor for obesity among male military veterans *Acta Psychiatr Scand* **116** (6), 483-7 (2007).

9 B. I. O'Toole and S. V. Catts, Trauma, PTSD, and physical health: an epidemiological study of Australian Vietnam veterans *J Psychosom Res* **64** (1), 33-40 (2008).

10 J.A. Boscarino, A prospective study of PTSD and early-age heart disease mortality among Vietnam veterans: implications for surveillance and prevention *Psychosomatic Medicine* **70** (6), 668-76 (2008).

SUPPORTING DATA: N/A