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TITLE: Assessment of Diverse Biological Indicators in Gulf War Illness: Are They Replicable? Are They Related?

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14. ABSTRACT

The complex of multiple symptoms known as Gulf War Illness (GWI) continues to affect a substantial number of veterans who served in the 1990-1991 Gulf War. Despite considerable research, the biological processes underlying veterans' symptoms have not been clearly elucidated. To develop useful diagnostic tests and effective GWI treatments, it is imperative to establish a more definitive and integrated understanding of GWI pathophysiology. This study utilizes a case-control design to evaluate diverse biological measures in a single, well-characterized sample of Gulf War veterans. Veterans with GWI are compared to healthy Gulf War veteran controls in a protocol that includes neuroimaging (MRI, fMRI, DTI), adrenal function tests, diverse immune, inflammatory, and coagulation measures, as well as physical and neuropsychological evaluations. Statistical analyses determine which objective measures significantly distinguish GWI cases from controls, and explore the extent to which biological findings are interrelated and are associated with identifiable veteran subgroups. Study progress has been limited during this period, owing to institutional, administrative and staffing challenges after the award was transferred to the PI's current institution. While study meetings and veterans' outreach activities have been initiated and regulatory requirements have been maintained, the project will not enroll its first subject until 2019. Therefore preliminary study results are not yet available.

15. SUBJECT TERMS
Gulf War illness, neuroimaging, biomarkers, central inflammation, immune function, hypothalamic-pituitary-adrenal testing

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
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Assessment of Diverse Biological Indicators in Gulf War Illness:
Are They Replicable? Are They Related?

TABLE OF CONTENTS

1. INTRODUCTION: Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

At least one in four military veterans who served in the 1990-1991 Persian Gulf War continue to suffer from a serious, often debilitating illness that is not explained by established medical or psychiatric diagnoses. This symptomatic illness is commonly known as Gulf War illness (GWI), and is characterized by a profile of concurrent symptoms that typically includes persistent headaches, memory and cognitive difficulties, widespread pain, unexplained fatigue, gastrointestinal problems, and other difficulties. Despite considerable research related to GWI, the precise pathophysiological underpinnings of veterans' symptoms have yet to be clearly elucidated. Studies have identified diverse biological differences between groups of GWI cases and healthy controls associated with neurological, endocrine, immune, and hematological measures. Most results, however, have been "one-off" findings. That is, most objective findings related to GWI have come from individual studies that have evaluated different questions, sometimes with limited samples or methodologies. The present study utilizes a case-control design to evaluate diverse biological measures in a well-characterized sample of 1990-1991 Gulf War veterans. Veterans with GWI, defined by Kansas GWI criteria (Steele 2000), are compared to healthy Gulf War veteran controls in a protocol that includes neuroimaging (MRI volumetric assessments, fMRI, diffusion tensor imaging), neuropsychological evaluations, assessment of hypothalamic-pituitary-adrenal function, standard diagnostic laboratory tests, and blood tests to evaluate immune, inflammatory, and coagulation parameters. Statistical analyses will determine which measures significantly distinguish GWI cases from controls, and will explore the extent to which findings are interrelated and/or are associated with subgroups of ill veterans distinguished by biological measures, deployment experiences/exposures, or illness severity and characteristics. The study protocol emphasizes the use of testing methods that, if found to successfully distinguish sick from healthy veterans, can most readily be developed for clinical application.

2. KEYWORDS

Gulf War illness, neuroimaging, biomarkers, central inflammation, immune function, hypothalamic-pituitary-adrenal testing, subgrouping

3. ACCOMPLISHMENTS: What were the major goals of the project?

Major Project Goals: Tasks	Target Date	% Complete
1. Prepare and Submit Regulatory Documents, Obtain Approvals	10/31/16	100%
2. Identify and Interview Sample of 1991 Gulf War Veterans for Study Eligibility and Recruit for Study Participation	9/30/17	20%
3. Conduct Clinical Evaluations, Data Collection, and Blood Assays	1/31/18	0%
4. Data Consolidation and Statistical Analyses	12/31/18	-
5. Preparation of Publications and Final Report	9/14/19	-

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements.

Task 1. Prepare and Submit Regulatory Documents, Obtain Approvals

The study protocol received initial approval from Baylor College of Medicine (BCM) IRB Aug 1, 2016. An amended protocol was subsequently approved by BCM IRB and received initial Army HRPO approval Dec 16, 2016. Renewal/continuing review of the protocol has been maintained throughout the project period and was most recently approved by BCM IRB on May 20,2019, with HRPO acknowledging receipt of the continuing review documents on June 17, 2019.

Task 2. Identify and Interview Sample of 1991 Gulf War Veterans for Study Eligibility, Recruit for Study Participation

During previous project periods, efforts have focused on initial sample development activities, including steps taken to obtain data required for population-based sampling from DOD's Defense Manpower Data Center (DMDC). Although the PI reinstated her project account in DOD's DMDC data request system (DRS), we have still not been able to obtain DMDC data for this USAMRAA-funded project. The PI's VA WOC appointment was finalized in late 2017, but we have not yet been able to obtain access to VA's Gulf War Registry data.

As an alternate and backup recruitment strategy we have, in the current year, continued outreach to area Gulf War veterans potentially interested in study participation. This has included discussions with veterans who have contacted the program as well as presentations and meetings with Texas and national veterans' groups. This has allowed us to assemble a list of veterans who are interested in being contacted about possible participation in research projects in our program. As of May, 2019, we have screened 50 study-eligible Gulf War veterans who have indicated their interest in study participation.

Task 3. Conduct Clinical Evaluations, Data Collection, and Blood Assays

Nothing to report for the current period. Subject evaluation to be initiated in 2019.

Task 4. Data Consolidation and Statistical Analyses

Nothing to report for the current period. Data analyses to be initiated in 2019.

Task 5. Preparation of Publications and Final Report

Nothing to report for the current period. Publications and reports to be completed after data collection and analyses are complete.

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?

We will initiate data collection and analyses in the Summer of 2019. Preliminary results will be presented at DOD research meetings; final results will be submitted for publication in an appropriate peer reviewed journal.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to Report

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to Report

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to Report

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to Report

5. **CHANGES/PROBLEMS:** The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

No changes have been made during this period with respect to the scientific approach of the project or individual protocol activities. The primary change that has occurred during this project year relates to project delays that have pushed back milestone dates for completing major tasks. These are described below.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

The study has faced two major and ongoing problems/challenges for the first 2 years of the performance period: (1) Inability to obtain data from DOD DMDC to secure population-based sampling for recruiting veterans, and (2) Broad shortfalls in PI's ability to enlist institutional scientific and administrative resources for launching the study. <u>DMDC Data Acquisition Problem</u> When the PI was initially awarded funding for this project at her previous institution, she had long experience with obtaining DOD data from the Defense Manpower Data Center (DMDC) in order to develop a population-based sample of GWI cases and controls, the optimal design for this study. In particular, she was well familiar with requirements for obtaining and secure management of DMDC data. As our CDMRP GWIRP project officers know (and have assisted with at length), the regulations and requirements for accessing DMDC data changed after the current project was initiated, with specific elements of the revised DMDC policy not clearly worked out for some time. One of several reasons the PI opted to relocate to her current institution was her understanding that nonfederal, but DOD-funded, investigators could request access to DMDC data but would be required to have FISMA IT security controls in place. Prior to her institutional move, the PI was informed that BCM had the required FISMA credential.

After transferring the project, when the PI initiated the DMDC data request process, she was advised by DMDC personnel that obtaining the required DMDC data would be greatly facilitated if she requested it through a federal agency rather than her private institution. She therefore initiated the process of establishing a VA appointment in order to request DMDC data through a VA affiliation. Once her VA WOC appointment was approved in 2017, the PI's DMDC account was reestablished shortly thereafter, and the DMDC data request submitted. However, the requested population data have still not been obtained, owing partially to delays resulting from BCM-VA IRB requirements in relation to DMDC and partially to the PIs time constraints in managing the request and associated regulatory requirements, as described below.

Plans to address these issues, for recruitment purposes, have been underway throughout 2019 at the time this report is being prepared and submitted. As it became clear that DMDC data would not be available for developing a population-based sample in the necessary timeframe, we developed outside contacts and methods for recruiting by more conventional means. That is, the PI held meetings with veteran and community leaders and provided presentations to veterans' groups in the region to inform them of our research and enlist their help in reaching out to Gulf War veterans who were interested in participating in our studies. As a result of these efforts, we have already assembled an initial list of Gulf War veterans in the Houston area who have indicated their interest in study participation and have completed screening with 50 veterans who are eligible to participate. We also have initiated the IRB submissions required to utilize the Houston-area VA Gulf War Registry as an additional recruiting resource. We therefore expect a quick-launch of the study in the Summer of 2019 as the initial project period winds down. If the data obtained from this initial sample appear promising we will apply for a no cost extension of the performance period to allow us to complete data collection in the coming year.

Research Support Issues

This project was transferred to the PI's current institution with the expectation that, as per terms of her recruitment, she would have access to the resources needed—most prominently the availability of office and clinical research space, administrative support, and the capacity for bringing in faculty and research staff to cover major aspects of organizing, launching, and managing the studies in her research program. Unfortunately, this has not been the case. During 2017-2018, the PI was unable to bring in faculty associates to assist with the studies in her program, and was able to hire only one research support staff person to assist in study execution. In addition, the lack of administrative support for handling project business had far-reaching implications, e.g., lack of regulatory assistance, inability to access information about project accounts and expenditures to allow appropriate project management. These challenges occurred in connection with multiple senior leadership and administrative departures and related changes within her Division and Department, and extensive staffing and faculty turnover.

As a result, by necessity the PI has personally handled scientific, regulatory, and administrative responsibilities for all funded studies in her program through 2018, and consequently fell behind in some required activities. Alongside workplace challenges, two pressing family medical situations required that she take personal and family leave intermittently through 2017-2018. Given the heavy time demands and limited research support during this period, the PI opted to prioritize establishing recruitment and data collection for another CDMRP GWIRP study, the multisite GWIC consortium project (GW120037), since the success of clinical research from two other sites depended on the Texas/BCM site's successful enrollment and evaluation of Gulf War veterans.

For the present study, during the 2018 project year covered by this annual report, the PI has continued to be the only person working on the current project. She has personally handled all scientific, regulatory, and administrative activities during this period, but has only had time available to maintain ongoing efforts related to DOD and VA requests for data acquisition, for other recruitment activities, and for regulatory submissions for the study. As previously described, problems associated with limited research and administrative support has produced a long delay in achieving key study tasks and objectives.

However, at the time this report is being prepared in 2019, meaningful changes have occurred in recent months that give us confidence that the project can move forward with data collection in the Summer of 2019. In early 2019, after completion of the period covered by this annual report, the PI was able to hire two additional research staff. We have also screened a sizable number of 1990-91 Gulf War veterans who are eligible and willing to participate in the study. Personnel and many of the resources and processes put in place for the GWIC study will be available in Summer 2019 for the present project, allowing for rapid project start up and data collection. This includes study collaborators (e.g. neuropsychologist, MRI expert), study sites (e.g., MRI center, phlebotomy and biospecimen handling, testing facility, clinical reference lab), research support staff, and specific processes required for smooth study execution. In short, despite the long delay in meaningful study start-up, we are finally in a good position at the time this report is being prepared, to initiate data collection for this project. Of note, the research questions to be answered with these data continue to be as important and urgently needed as when this project was originally proposed.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Because of the extended delays previously described in relation to providing faculty support, hiring research staff, and data collection, research expenditures for the project are significantly lower than expected for this period, and a substantial balance remains for future use.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects.

Significant changes in use or care of human subjects

None of the delays is expected to affect use or care of human subjects.

Significant changes in use or care of vertebrate animals

Not applicable/nothing to report.

Significant changes in use of biohazards and/or select agents

Not applicable/nothing to report. BCM

6. PRODUCTS: List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  Journal publications.

  Nothing to Report.

  Books or other non-periodical, one-time publications.

  Nothing to Report.

  Other publications, conference papers and presentations.

  Nothing to Report.

- **Website(s) or other Internet site(s)**

  PI's BCM Veterans Health Research Program Website:
  www.bcm.edu/vethealth

  PI's BCM Veterans Health Research Program on Facebook:
  https://www.facebook.com/bcmveteranshealth/

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

  Nothing to Report.

- **Inventions, patent applications, and/or licenses**

  Nothing to Report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project.

  Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort).

Name:	*Lea Steele, PhD*
Project Role:	*Principle Investigator*
Nearest person month worked:	*1*
Contribution to Project:	*Dr. Steele has performed all project work related to regulatory submissions, project design and implementation, data acquisition, and veterans outreach.*
Funding Support:	*In addition to the present award, additional funding support from Baylor College of Medicine endowment for Yudofsky Chair in Behavioral Neuroscience*

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission.

Changes in Active "Other Support" for the PI During Current Reporting Period

Added support from newly active project

1. Title: Gulf Coast Center for Precision Environmental Health (GC-CPEH). Funded by NIH/National Institute of Environmental Health Sciences. Award to Baylor College of Medicine, PI: Cheryl Walker. Steele role: Co-I, Effort: 5%. (2019 – 2024)

Discontinued support from projects no longer active

1. Title: Understanding Gulf War Illness: An Integrative Modeling Approach. Funded by DOD/CDMRP (#GW120045) Primary award to Nova Southeastern, PI: Mariana Morris. BCM subaward completed Sep 2017. Steele role: Co-I, Effort: 5%
2. Title: Gulf War Women's Health Cohort. Funded by DOD/CDMRP (#GW150116). Primary award to Augusta Univ, PI: S. Coughlin. BCM subaward never finalized; withdrew from project. Steele role: Co-I, Effort: 5%

Continuing support from previously-awarded projects

1. Title: Assessment of MRI-Based Marker of Dopaminergic Integrity as a Biological Indicator of Gulf War Illness. Funded by DOD/CDMRP (#GW130063) Award to Baylor College of Medicine. PI: Deborah Little. Steele role: Co-I, Effort: 5%
2. Title: Brain-Immune Interactions as the Basis of Gulf War Illness: Gulf War Illness Consortium (GWIC). Funded by DOD/CDMRP (#GW120037) Primary award to Boston University, PI: Kimberly Sullivan. Steele role: Co-I, site PI, Effort: 25%
3. Title: Examination of Plasma PON1 Paraoxonase Activity and Genotype in Gulf War Veterans. Funded by DOD/CDMRP (#GW150037) Primary award to Northern CA institute for Research and Education (NCIRE), PI: Linda Chao. Steele role: Co-I, Effort: 5%
4. Title: Persistent Hormonal Changes in Gulf War Veterans. Funded by DOD/CDMRP (#GW160106) Award to Baylor College of Medicine. PI: Ricardo Jorge. Steele role: Co-I, Effort: 5%
5. Title: Glutamate Receptor and Kynurenine Pathway Functioning in the Pathobiology of Gulf War Illness. Funded by DOD/CDMRP (#GW160077) Award to Baylor College of Medicine. PI: Marijn Liffijt. Steele role: Co-I, Effort: 2.5%
6. Title: Investigating Gene-Environment Interactions in Multiple Cohorts of 1990-91 Gulf War Veterans. Funded by DOD/CDMRP (#GW160013). Primary award to Boston University, PI: Patricia Janulewicz -Lloyd. Steele role: Co-I, Effort: 2.5%

What other organizations were involved as partners?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS (none applicable)

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating Principal Investigator (PI) and the Collaborating/Partnering PI. A duplicative report is acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to **https://ers.amedd.army.mil** for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on https://www.usamraa.army.mil) should be updated and submitted with attachments.

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

No appendices attached.