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

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**CONTRACTING ORGANIZATION:** Baylor College of Medicine, Houston, TX

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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 the nearly 700,000 U.S. veterans who served in the 1990-1991 Gulf War. Despite considerable research, the biological processes underlying veterans' symptoms have not yet 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 was designed to evaluate diverse previously-identified and hypothesized biological alterations associated with GWI in a single, well-characterized sample of Gulf War veterans. Using a case-control design, the protocol included physical and neuropsychological evaluations, brain imaging (MRI, fMRI, DTI), adrenal function tests, and diverse immune, inflammatory, and coagulation measures. Despite ongoing good-faith attempts to operationalize and implement the project over an extended period, data collection was not initiated and there are no study results to report, owing to a variety of internal and external challenges that we were unable to successfully address. For the most recent period of performance, all study updates, preparations, and sample identification were in place for data collection, including protocol revisions to limit in-person contact and related COVID safety precautions. However, recruitment and data collection were not undertaken due to extended public health restrictions in place during the ongoing pandemic. It is therefore necessary, with great regret, that we close the project without performing the study. We acknowledge and extend our sincere appreciation to the USAMRAA CDMRP program for their support as we worked to address project challenges over the duration of the grant period.

**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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## 1. INTRODUCTION

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 project was designed to evaluate multiple biological measures—both those previously associated with GWI and innovative measures hypothesized to be associated with GWI—in a single, well-characterized sample of 1990-1991 Gulf War veterans. The study protocol included objective measures associated with physical evaluation, neuroimaging (MRI volumetric assessments, fMRI, diffusion tensor imaging), neuropsychological evaluations, assessment of hypothalamic-pituitary-adrenal function, standard diagnostic laboratory tests, and research tests to evaluate immune, inflammatory, and coagulation parameters. The study protocol emphasized the use of testing methods that, if found to successfully distinguish sick from healthy veterans, could most readily be developed for clinical application.

## 2. KEYWORDS

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

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

| Major Project Goals: Tasks | % Complete |
|---|---|
| 1. Prepare and Submit Regulatory Documents, Obtain Approvals | 100% |
| 2. Identify Sample of 1991 Gulf War Veterans for Study Eligibility and Recruit for Study Participation | sample identified, not recruited/enrolled |
| 3. Conduct Clinical Evaluations, Data Collection, and Blood Assays | 0% |
| 4. Data Consolidation and Statistical Analyses | 0% |
| 5. Preparation of Publications and Final Report | 0% |

**What was accomplished under these goals?**

Task 1. Prepare and Submit Regulatory Documents, Obtain Approvals

The study protocol was initially approved by the Baylor College of Medicine (BCM) IRB Aug 1, 2016 and by Army HRPO Dec 16, 2016. All protocol renewals, amendments, and related regulatory requirements were subsequently maintained in a timely fashion throughout the project period.

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

Throughout the project period, extensive efforts focused on a range of study sample development activities. Most prominently, this included repeated efforts to obtain data required for population-based sampling from DOD's Defense Manpower Data Center (DMDC). Requirements for accessing DMDC data changed substantially since the project was initially proposed. But despite multiple efforts to meet those requirements, including identifying collaborators at federal agencies and obtaining federal appointments and enhanced nonfederal data security capabilities, it was necessary to establish alternate strategies for sample development and recruitment that were not population-based. This included more conventional means of identifying veterans who were interested and eligible for study participation, including presentations and meetings with local, state, and national veterans' groups, and additional outreach via social media and veteran referrals. This allowed us to assemble a sizable list of 1990-1991 Gulf War veterans who indicated their interest in being contacted for the study and other projects in our program, with many screened or pre-screened for study eligibility. Once the sampling pool was assembled, however, final recruitment and scheduling for in-person study appointments were never undertaken. Initially, this was the result of program and staffing limitations that did not allow us to successfully complete data collection concurrently for this and other studies in the program, and later was due to public health safety concerns and research restrictions in place in early 2020 as a result of the COVID-19 pandemic. We were therefore never able to complete this task or collect data for this study, as hoped, in the final year of the project period.

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

Clinical evaluations and data collection was not initiated; no outcomes or achievements to report.

Task 4. Data Consolidation and Statistical Analyses

Data were not collected or analyzed; no results to report.

Task 5. Preparation of Publications and Final Report

No data collection or study results; no publications to report.

**What opportunities for training and professional development has the project provided?**

Opportunities for training and professional development on this project were limited to the capabilities in online survey programming, neuropsychological testing methods, and offsite data collection afforded our research coordinator that supported her development as a psychology graduate student.

**How were the results disseminated to communities of interest?**

The project did not yield study results to report to interested communities of veterans and researchers.

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

Nothing to report (this is final report).

## 4. IMPACT:

**What was the impact on the development of the principal discipline(s) of the project?**

Nothing to report in this section.

**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

A number of changes were made to the study design and protocol over the course of the project period, with the input and approval of our grants officer. This included (1) a change in our planned sampling/recruitment approach, necessitated by the previously described challenges in obtaining the federal data required for population-based sampling. We instead assembled a less representative sample using a more conventional outreach and recruitment approach. The original challenges to population sampling were never satisfactorily resolved despite the PI's repeated efforts across two institutions and hands-on assistance from our CDMRP project team. (2) Change in laboratory collaborator and method for assaying blood TSPO levels in veteran subjects, owing to initial collaborator's inability to perform assays after transferring institutions. (3) Later project changes developed to enable us to enroll and evaluate veteran subjects in a manner that would limit the number and duration of in-person study visits, optimized to support safety precautions during the pandemic period. This included adoption of mail and telephone-administered informed consent and conversion of most data collection activities to be administered via a secure online platform. The overriding primary change to the project has been repeated project delays and failure to meet the planned timeline for sampling, data collection, and completion of the study, as described below.

### Actual problems or delays and actions or plans to resolve them

Throughout the project period, the study faced two major and ongoing problems/challenges: (1) Inability to obtain DOD DMDC data to enable population-based sampling for recruiting veterans, and (2) Broad shortfalls in PI's ability to enlist scientific, staffing, and administrative resources for implementing data collection according to the intended project timeline.

<u>Data Acquisition Problem</u>

Challenges related to acquisition of sampling data and actions taken to resolve them were summarized in relation to Task 2. 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, and was well familiar with requirements for obtaining and secure management of DMDC data. As our CDMRP GWIRP project officers know (and 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, the PI 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 appointment was approved, she was able to submit another DMDC data request. The requested data were never obtained, however. The PI therefore developed contacts and methods for recruiting by more conventional means. This involved meetings with veteran and community leaders and 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 assembled an extended list of Gulf War veterans in the Houston area and surrounding region who were interested in study participation and were eligible to participate.

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 required 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, continued challenges in bringing in faculty and staff left the program shorthanded and required the PI to perform all project activities until the final project year. Prior to that time, she personally handled all scientific, regulatory, and administrative activities, necessarily focusing on ongoing efforts related to federal data acquisition, other recruitment activities, and scientific planning and regulatory submissions for the study. These challenges occurred in connection with multiple senior leadership and administrative changes within her Division, and extensive staffing and faculty turnover during this period. The multiyear problems associated with limited research and administrative support produced ongoing delays in achieving key tasks and objectives. With personnel responsibilities spread thin, the PI opted to focus all staff efforts on completion of another study, the multisite GWIC consortium project (GW120037), in 2019 and then to reallocate personnel and other resources to complete the current project in 2020. Unfortunately, the emergence of the pandemic in March 2020 precluded our ability to conduct human subjects research and collect data for the study in our final project year.

**Changes that had a significant impact on expenditures**

Because of the extended delays described in relation to staff support and data collection, research expenditures for the project were much lower than the project budget, and a substantial balance remains for return to the sponsor. However, personnel costs accrued throughout the grant period to cover salary expenses for the PI and for collaborators and staff who participated in project planning and preparations.

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

**Significant changes in use or care of human subjects**

Several pandemic-related protocol changes were planned, and intended to reduce direct contact with and risk to human subjects during the final project period. However, no changes were implemented during the project that related to use, care of, or risk to 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.

## 6. PRODUCTS:

- **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**

  Nothing to Report.

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

  Not applicable; nothing to Report.

- **Other Products**

  Nothing to Report.

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

### What individuals have worked on the project?

| | |
|---|---|
| *Name:* | Lea Steele, Ph.D. |
| *Project Role:* | Principle Investigator |
| *Nearest person month worked:* | 3 |
| *Contribution to Project:* | Dr. Steele performed all project work related to project development, initial and revised study design, scientific and administrative arrangements for data acquisition, for contracting labs, phlebotomy services, and imaging center, scientific arrangements with in-house collaborators, regulatory submissions, sample acquisition and preparation |
| *Funding Support:* | In addition to the present award, additional funding support from Baylor College of Medicine/endowment for Yudofsky Chair in Behavioral Neuroscience |

| | |
|---|---|
| *Name:* | Vanesa Lerma, M.A. |
| *Project Role:* | Research Coordinator |
| *Nearest person month worked:* | 6 |
| *Contribution to Project:* | Programming for online versions of study questionnaires, training and preparation of psychological and neuropsychological testing materials and workbooks, veteran contacts and correspondence |
| *Funding Support:* | In addition to the present award, additional funding support from Baylor College of Medicine Program 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?

Changes in active "Other Support" for the PI during the most recent reporting period include:
1. Completion of BCM site subaward for "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: K. Sullivan; Steele role: Co-I, TX site PI)

2. EWOF approved for "Assessment of MRI-Based Marker of Dopaminergic Integrity as a Biological Indicator of Gulf War Illness". Funded by DOD/CDMRP (#GW130063) to Baylor College of Medicine (PI: L. Steele)

### What other organizations were involved as partners?

No other organizations to report.

## 8. SPECIAL REPORTING REQUIREMENTS

None applicable.

## 9. APPENDICES

No appendices attached.