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PRINCIPAL INVESTIGATOR: Lea Steele, Ph.D.

CONTRACTING ORGANIZATION: Baylor University  
Waco, TX 76706-1003

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<b>14. ABSTRACT</b> 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. In order to develop useful diagnostic tests and optimize the search for effective GWI treatments, it is imperative to establish a more definitive and integrated understanding of the pathophysiology of this problem. This study utilizes a case-control design to evaluate diverse biological measures in a single, well-characterized and population-based sample of 130 Gulf War veterans residing in Central Texas. Eighty veterans with GWI are compared to 50 healthy veteran controls in a protocol that includes physical and neuropsychological evaluations, neuroimaging (MRI, fMRI, DTI), adrenal function tests, and diverse immune, inflammatory, and coagulation measures. Statistical analyses will determine which objective measures significantly distinguish GWI cases from controls, and explore the extent to which biological findings are interrelated or are associated with identifiable veteran subgroups. Data collection has not yet begun, as we finalize the process of obtaining regulatory approvals. When complete, the study is expected to clarify many of the ambiguities currently associated with GWI and improve understanding of the biological processes that underlie veterans' symptoms. This will facilitate efforts to identify useful diagnostic tests and promising treatments.					
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**Assessment of Diverse Biological Indicators in Gulf War Illness:  
Are They Replicable? Are They Related?**

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## **Introduction**

A substantial proportion of 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. Studies consistently indicate that GWI is not a psychiatric disorder and is not the result of combat stress (Institute of Medicine 2010; Research Advisory Committee on Gulf War Veterans' Illnesses (RAC) 2008). Longitudinal studies indicate that few veterans who developed GWI during and after the 1991 Gulf War have recovered, or even substantially improved, with time (RAC 2008, Wolfe 2002, Kang 2008, Hotopf 2003).

Despite considerable research related to GWI, the pathophysiological underpinnings of veterans' symptoms have not yet been 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. Even studies evaluating abnormalities in the same biological system have used diverse methods and outcome measures, making comparison of results difficult or impossible. There are relatively few examples of specific GWI-related biological findings that have been replicated by a second team of investigators. There are also few instances in which measures related to different biological systems, for example, measures of brain function and immune function, have been evaluated in a single group of Gulf War veterans. It is therefore not possible to know whether findings in different biological systems occur in the same individuals, or in discrete subsets of ill veterans. And for many of the biological differences identified thus far, there is no clear rationale to explain why or how they relate to symptoms characteristic of GWI.

As a result, a relatively large body of suggestive evidence has accumulated that provides preliminary indications of biological processes that underlie veterans' symptoms. But the lack of replicated findings, the difficulty of comparing results from different groups, and the lack of information about the co-occurrence of findings in different systems presents an enormous barrier to developing a clear understanding of the biological nature of GWI. This limited understanding has slowed efforts to identify promising avenues for diagnostic tests and treatments.

The present study utilizes a case-control design to evaluate diverse biological measures in a well-characterized and population-based sample of 130 veterans, proactively recruited from among 1991 Gulf War veterans who currently reside in Central Texas. Eighty veterans with GWI, defined by Kansas GWI criteria (Steele 2000), are compared to 50 healthy Gulf War veteran controls in a protocol that includes physical examinations, 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.

This multidisciplinary study is being conducted by investigators at Baylor University in conjunction with collaborators at the Scott & White Healthcare System, Texas A&M Health Science Center, Columbia University School of Public Health, and the Minneapolis (MN) VA. Veterans are evaluated over two consecutive mornings using a protocol designed to address multiple questions at once in the most rigorous, comprehensive, and efficient way possible. 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 in the near term.

## **Body**

### **Task 1. Prepare and Submit Documents to Obtain Regulatory Approvals**

This project is obtaining data and tissue specimens from human subjects, and will involve research activities conducted at five institutions. This includes two primary institutions (Baylor University and Scott & White Healthcare) where investigators will interact directly with human subjects to obtain data and blood samples. It also includes three secondary sites (Texas A&M Health Science Center, Columbia School of Public Health, and Minneapolis VA), where research activities are limited to processing coded blood samples obtained at the primary sites. This multi-institutional project requires human subjects' determinations from five Institutional Review Boards (IRBs) and the Army's Office of Human Research Protections (HRPO). The majority of activities to date have focused on the somewhat complex regulatory issues and processes associated with the project. This has included submissions to all five IRBs and to HRPO, with resubmissions and additional reviews as needed at each institution to address changes requested by partnering IRBs, changes made to the study protocol, and changes requested by HRPO.

#### **Human Subjects' Approvals**

We obtained initial approvals from our two primary IRBs (Baylor and Scott & White) in the Fall of 2012, and submitted all required human subjects' documentation to the Army's Office of Human Research Protections (HRPO) in November, 2012. An initial response was received from HRPO on March 27, 2013, which requested additional information and a limited number of changes to our protocol and informed consent form. Although the requested changes were easily addressed, we did not formally respond to HRPO until September 30, 2013, due to delays resulting from (1) a decision to move the MRI scanning portion of the study from the original intended site (the research-dedicated mobile MRI facility at VA's Center of Excellence for Returning War Veterans), and (2) Scott & White-requested changes to the study protocol and Informed Consent documents that were directly relevant to Human Subjects' issues. On the advice of the HRPO officer assigned to our project, we delayed submitting our formal response to HRPO until all project changes had been finalized and approved by IRBs for the institutions affected by the changes.

Research activities at the three secondary sites for the project (Columbia School of Public Health, Minneapolis VAMC, and Texas A&M Health Science Center) are limited to analyses of coded (de-identified) blood samples that Baylor will provide to laboratories at each site. In the past year, IRBs at all three secondary sites have designated the research activities conducted at their institutions for the project to be exempt from human subjects' review.

#### **Human Subjects Delays due to Change in Venue for the Neuroimaging Portion of the Study**

In April, 2013, we learned that it would not be possible for VA's Center of Excellence for Returning War Veterans (COE) to perform the brain scans (MRI, DTI, fMRI) for our project. This was due to equipment, administrative, and personnel problems at COE and the imaging facility. The COE was unable to obtain the needed research and service contracts to make the

mobile research MRI scanner usable for the project, essential personnel required to oversee and analyze the scans had resigned from COE, and the MRI itself subsequently “quenched” and was no longer functional for the degree of precision needed for the research scans.

With the advice and approval of our VA collaborators on the project, we sought an alternate venue for the MRI portion of the study. We were pleased that the Scott & White Imaging Facility agreed to our using their research MRI for the project. The facility is located in the same building as the clinical intake and evaluation portions of our project and houses a Siemens 3T magnet, which has all capabilities needed for our scanning protocol. Both Dr. Young and Dr. Deborah Little, the neuroimaging expert for the project, will continue to serve as Co-Investigators for this portion of the study, and will oversee collection and analyses of brain scanning data at Scott & White. Overall, this major change will maintain both the scientific integrity and total expenditures originally planned for the neuroimaging component of the project. It will also make the project more convenient and time-efficient for participating veterans, since all research activities will take place at one research site, rather than two. However, working out arrangements to implement this change has also imposed delays in finalizing the protocol and human subjects’ approvals for the project.

#### **Human Subjects Delays Resulting from Changes in Protocol and Informed Consent Requested by Scott & White**

Delays caused by moving the MRI scans to Scott & White were further extended when, in the course of revising the study protocol, Scott & White’s legal office and staff in their Division of Research asked us to revisit aspects of our protocol, primarily in relation to our use of research records for study data. Our research record system and extensive measures to protect the privacy of human subjects had previously been approved by both Baylor and Scott & White IRBs. However, some Scott & White research personnel now favored use of the healthcare system’s electronic medical records system (which includes personal identifiers) for the project’s research data. This precipitated a long series of meetings and discussions between Baylor and a number of offices at Scott & White, including Scott & White offices of General Council, Healthcare Administration, IRB, and Division of Research. Our HRPO human subjects’ officer was kept informed of the status of these discussions from April through August of 2013. In August, all project amendments were finalized and submitted to Scott & White’s IRB for review. Scott & White IRB approved all changes on September 19, 2013; Baylor approvals were obtained on September 24, 2013.

A comprehensive resubmission package that included responses to initial HRPO queries and comments, as well as all changes associated with venue and protocol changes approved by Baylor and Scott & White IRBs, was submitted to HRPO on September 30, 2013.

#### **Delays Related to Federal Office of Management and Budget (OMB) Submissions**

In addition to IRB and HRPO approvals, we had understood, through early 2013, that our data collection would require review and approval by the federal Office of Management and Budget (OMB) under the federal Paperwork Reduction Act (PRA). We were advised, by several offices within the Department of Defense (DOD), that our data collection would need OMB approval in order for DOD’s Defense Manpower Data Center (DMDC) to provide the project with names of

Gulf War veterans residing in Central Texas. These names were needed to identify and recruit the “gold standard” population-based sample required for the project. We had been informed by the DOD office that handles Army OMB submissions that the OMB approval process typically requires up to eight months. The project was therefore designed to allow nine months for the process of regulatory approvals, as indicated in the Statement of Work. After a series of startup delays at Baylor, OMB documentation was provided to the Army for submission to OMB in June 2012 and we expected OMB approvals would be available in late 2012/early 2013. We experienced a potentially serious setback, however, when we learned in December, 2012, that the Army and DOD information management offices still had not forwarded our PRA submission to OMB, potentially causing a serious delay in the project. In a December 17, 2012, telephone conference with officials from both the Army and DOD information management offices, we reviewed regulations in DOD Manual 8910.1-M, which indicated that our project was potentially exempt from OMB review and approval. We received confirmation, early in 2013, that the project could proceed without OMB approval, once the required human subjects’ approvals are in place.



## **Task 2. Identify and Interview Stratified Random Sample of Gulf War era Veterans for Study Participation**

Because of the extended time allowed in our initial timeline to obtain OMB approvals for this study, it was expected that data collection would begin in the second year of the project. However, due to delays stemming from the regulatory issues and venue changes previously described, we have not yet received final human subjects approvals from the Army, and no subject recruitment or data collection activities have been initiated at this time.

All institutional IRB approvals have been obtained for initial submissions and all amendments, and HRPO resubmissions were recently completed, so we hope to obtain final human subjects' approvals in the near term. This will allow us to formally submit our request to DMDC to obtain data on Gulf War veterans living in the Central Texas target area. We will then update veterans' contact information, mail advance letters to potential study subjects, and begin telephone screening and recruitment for the study.

Two activities outlined under Task 2 have been undertaken in the current year, however. These include CATI programming for the telephone interview and recruitment efforts, and discussions with DMDC to work out anticipated components of our data request, so that we can obtain data as quickly as possible once human subjects' approvals are in place.

### **Computer Assisted Telephone Interview (CATI) for Subject Screening and Recruitment**

The recruitment process for enrolling study subjects requires veterans to be contacted and screened by trained telephone interviewers working at the Computer Assisted Telephone Interview (CATI) facility at Baylor's Center for Community Research and Development (CCRD). Specialized CATI software was required for the project, to provide interviewers with real time determinations of Gulf War illness case/control status, using a complex algorithm to assist in identifying individuals who are or are not eligible to participate in the study. CATI project directors have completed initial CATI programming for the project and the program is being tested by research staff. This will allow us to mail out advance letters and initiate telephone screening and recruitment as soon as the study sample is identified and drawn. We have also obtained the toll-free telephone number to be used by veterans contacted for the project, and have laid out the project website, to be launched as we begin subject recruitment.

### **Defense Manpower Data Center (DMDC) Data Request**

After learning of the protracted delays in DOD's submission of our PRA package to OMB, we were concerned that, even in the best case scenario, we would be further delayed in submitting our data request to DMDC for at least eight additional months. On the advice of our CDMRP Science Officer for the project, we contacted DMDC to determine if it would be possible to initiate the process required for obtaining DMDC data for our sample. With our Science Officer's assistance, we were able to establish an account with the DMDC Data Reporting System (DRS), which will be used to submit our DMDC data request. We have also worked with the DMDC analyst/data manager who will be filling our data request, to outline the types of variables and sample information we will be requesting. Our discussions with DMDC's human

research protection official clearly indicate, however, that DMDC cannot take action on the data request until HRPO approvals are obtained.

### **Tasks 3 – 5.**

No activities completed or underway at this time.

## **Key Research Accomplishments**

Only regulatory submissions accomplished to date. Study data have not yet been collected.

## **Reportable Outcomes**

There are no manuscripts or other reportable outcomes at this time.

## **Conclusion**

No research results are yet available; no conclusions can be drawn at this time.

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