AWARD NUMBER:
W81XWH-17-1-0368

TITLE: Persistent Hormonal Changes in Veterans with Gulf War Illness

PRINCIPAL INVESTIGATOR: Ricardo Jorge, MD

CONTRACTING ORGANIZATION: Baylor College of Medicine

REPORT DATE: October 2019

TYPE OF REPORT: Annual

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

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
Oct 2019	Annual Report	30 Sep 2018-29 Sep 2019

4. TITLE AND SUBTITLE
Persistent Hormonal Changes in Veterans with Gulf War Illness

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-17-1-0368

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

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

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The proposed cross-sectional, case-controlled study will assess the association of Gulf War Illness (GWI) with dysregulation of major hormonal systems. A total of 90 Veterans (45 Veterans with GWI and 45 Veterans of comparable age, gender, and military experience who deployed but did not develop GWI) will be recruited from clinical and community sources. Endocrine disorders can be effectively treated by pharmacological interventions currently available, thus, reducing the time it would take for Veterans to access treatment. Consequently, treatment may result in a significant reduction of Veterans' symptomatic burden.

15. SUBJECT TERMS
IRB, HRPO, Gulf War Registry

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	9	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION:

The proposed cross-sectional, case-controlled study will assess the association of Gulf War Illness (GWI) with dysregulation of major hormonal systems. The study will assess hormone measures (including the frequency of hormone deficiencies) between Gulf War Veterans with and without GWI and evaluate the relationship between endocrine measures and neurocognitive function. A total of 90 Veterans (45 Veterans with GWI and 45 Veterans of comparable age, gender, and military experience who deployed but did not develop GWI) will be recruited from clinical and community sources. Assessing hormonal dysregulations in the population has major therapeutic implications because endocrine disorders can be effectively treated by pharmacological interventions currently available, thus, reducing the time it would take for Veterans to access treatment. Consequently, treatment may result in a significant reduction of Veterans' symptomatic burden and maximizing their recovery and quality of life.

2. KEYWORDS:

Endocrine measures; hormonal dysregulation; HPA axis; Gulf War Illness.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Major Task 1	Target Date	% Complete
Subtask 1: Prepare regulatory documents for IRB submission	12/30/17	100%
Subtask 2: Submit IRB-approved human use protocol and documentation to the DoD HRPO for review and approval	12/31/17 to 3/31/18	100%
Subtask 3: Order medications and materials needed for assessments	12/31/17 to 3/31/18	100%
Subtask 4: Train research team on protocol	12/31/17 to 3/31/18	100%
Major Task 2		
Subtask 1: Identify, recruit, screen, and consent eligible participants	4/1/18 to 4/30/20	Ongoing
Subtask 2: Assess endocrine function at baseline and after stimulation tests	4/1/18 to 4/30/20	Ongoing
Subtask 3: Collect medical, background, neuropsychological, and psychiatric data from subjects in both groups	4/1/18 to 4/30/20	Ongoing

What was accomplished under these goals?

Major Goal 2: Collect Data for Analysis

Efforts during the second year of the study were focused on identification, recruitment, and data collection. The target enrollment across the three years is 90 participants. To date, 68% of the total participants have been enrolled.

Several setbacks encountered during the first year affected our ability to recruit participants. To overcome the deficit, we proposed to increase our recruitment goal every month by one or two patients for the remainder of the study. We estimated it would take eight quarters to compensate for the deficit; however, we successfully enrolled one additional participant during the fourth and fifth quarter, four additional participants during the sixth quarter, and four additional participants during the seventh quarter. We surpassed our expected enrollment rate and reached our enrollment goal sooner than expected.

During the last quarter of year two, several personnel changes and Tropical Storm Imelda hindered our ability to reach our quarterly goal. We enrolled 61 participants (4 below the quarterly target). We continue to recruit, enroll, and collect data.

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.

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

The first two quarters of the third year will have a heavy emphasis on recruitment and enrollment. It is our goal to conclude enrollment by the 8th month of the third year and complete endocrine stimulation tests (data collection) no later than the 9th month. The last quarter will be reserved for data analysis and reporting.

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

There were no significant changes in the project or its direction.

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

Several setbacks were encountered during the second year:

Personnel Changes: The research nurse responsible for conducting endocrine stimulation tests moved at the beginning of the grant's second year. We had been cross-training, and the graduate research assistant was able to cover the responsibilities when she left. During the last quarter of year two, several major changes occurred. Mr. Jeevan, one of the research coordinators assisting with the study left. Mr. Elammari, graduate research assistant, reduced his hours from full-time to 16 hours per week. Ms. Hendrickson, research coordinator, was out several weeks for personal reasons.

Enrollment: Our ability to enroll participants was hindered by several factors including Tropical Storm Imelda and staff changes. Despite the significant staff changes, we managed to enroll eight participants during the last quarter. As before, we hope to compensate for the deficit by increasing our quarterly enrollment by two participants until the enrollment goal is met.

Changes that had a significant impact on expenditures

There were no significant changes affecting expenditures.

Significant changes in use or care of human subjects

Nothing to Report.

Significant changes in use or care of vertebrate animals

There were no significant changes affecting expenditures.

Significant changes in use of biohazards and/or select agents

Not applicable.

6. PRODUCTS:

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)

Nothing to Report.

Technologies or techniques

Nothing to Report.

Inventions, patent applications, and/or licenses

Nothing to Report.

Other Products

Nothing to Report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Ricardo Jorge, MD
Project Role:	Principal Investigator
Nearest person month worked:	2.4
Contribution to Project:	Dr. Jorge oversees all aspects of the research protocol. He makes eligibility and termination decisions and assesses participants in the study. Dr. Jorge is also responsible for evaluating adverse events and submitting safety lab orders at the screen visit.

Name:	Marco Marcelli, MD
Project Role:	Co-Investigator
Nearest person month worked:	0.6
Contribution to Project:	Dr. Marcelli oversees the dynamic tests and interprets endocrine test results. He is also responsible for submitting endocrine lab orders, evaluating adverse events, and contacting patients whose laboratory results are out of range.

Name:	Lea Steele, PhD
Project Role:	Co-Investigator
Nearest person month worked:	0.6
Contribution to Project:	Provided consultation about diagnostic algorithms and chronology of symptoms in patients with Gulf War Illness.

Name:	Audri Villalon
Project Role:	Coordinator
Nearest person month worked:	2.5
Contribution to Project:	Ms. Villalon assists with regulatory documents and reports. She reviews invoices for accuracy and submits for processing.
Funding Source:	Unfunded

Name:	Jeanie Hendrickson
Project Role:	Research Coordinator
Nearest person month worked:	12
Contribution to Project:	Ms. Hendrickson screens candidates over phone and schedules appointments. She is primarily responsible for consenting, administering neuropsychological assessments and questionnaires, and processing payments for participants.

Name:	Mohamed Elammari
Project Role:	Research Assistant
Nearest person month worked:	7.5
Contribution to Project:	Mr. Elammari reviewed clinic lists and Gulf War Registry to identify participants who may be eligible for the study. He assisted with mailing recruitment letters to candidates, scheduling endocrine visit appointments, and specimen processing, as needed.

Name:	Sangeeth Jeevan
Project Role:	Research Coordinator
Nearest person month worked:	3
Contribution to Project:	Mr. Jeevan assisted with scheduling, recruitment calls, and questionnaire and neuropsychological test administration.
Funding Source:	Unfunded

Name:	Ruosha Li
Project Role:	Statistician
Nearest person month worked:	1.2 months
Contribution to Project:	Contributed to the design and organization of databases, as well as, quality monitoring.

Changes in the active other support of key personnel since the last reporting period

Ricardo Jorge, M.D.

Project Number (B9268-X) PI: Ricardo Jorge, MD Period: 01/01/2015 - 06/30/2024 5.0 Cal Mo
Supporting Agency: Department of Veterans Affairs
Title: Translational Research Center for TBI and Stress Disorders (TRACTS) Houston Total Level of Funding: $1,495,000 *(Renewal)*
Project goal: The Translational Research Center for TBI and Stress Disorders or TRACTS, originated at VA Boston Healthcare System, is developing a well characterized cohort of OIF/OEF/OND veterans needed to study how TBI impacts the evaluation and treatment of individuals who carry multiple physical and psychological diagnoses. TRACTS has built a strong and well-defined organizational structure that represents all core elements of the assessment program, including medical and genetic information, structural and functional neuroimaging, clinical, neuropsychological characterization, as well as state of the art data management tools.
Overlap: There is no overlap

Marco Marcelli, M.D. – no changes

Lea Steele, Ph.D.

1. Current Support: Continuing Baylor College of Medicine (BCM) project: "Assessment of MRI-Based Marker of Dopaminergic Integrity as a Biological Indicator of Gulf War Illness" (# W81XWH-14-1-0622; CDMRP Log #GW130063). Steele role changed from Co-I to PI for the project, effort increased from 5% to 20%.

2. Current Support: New BCM project: "Gulf Coast Center for Precision Environmental Health (GC-CPEH)" (PI: Cheryl Walker, PhD) Sponsoring agency: NIH/National Institute of Environmental Health Sciences. Steele role: CO-I, 5% effort (Dates: 4/1/2019-3/31/2024).

3. Pending Support (primary award finalized, subaward pending): "Defining and Characterizing GWI Pathobiology Using Longitudinal Brain Imaging Biomarkers of White Matter Integrity and Hemodynamic Response". Primary award to Boston University, PI: Kim Sullivan, PhD. Steele role: Co-I, 5% effort in Years 2-3 (Dates: 9/30/19 – 9/29/22).

4. Recently Completed Project: "Brain-Immune Interactions as the Basis of Gulf War Illness: Gulf War Illness Consortium (GWIC)." Multisite consortium grant to Boston University Medical Campus; PI: Kim Sullivan, PhD. Steele role: Co-I, Texas Site PI (Dates: 10/1/2013 – 9/29/19).

Ruosha Li, Ph.D.

Title: Dynamic Prediction of Time to Next Failure Event
Supporting agency: NSF
Name/contact info of agency's procuring Contracting/Grants Officer: Nandini Kannan (nakannan@nsf.gov)
Performance Period: 9/1/2016-8/31/2019
Level of effort (in percentage or calendar months): 1.0 cal. Month (8.3% FTE)
Brief description of project goals: This project focuses on the development of novel statistical methods to conduct dynamic prediction of disease outcomes, on the basis of patients' post-baseline longitudinal biomarker trajectories.
PI: Xuelin Huang, PhD. Ruosha Li, PhD.
Role: co-PI.
Potential Overlap: no-overlap

What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A

QUAD CHARTS: N/A

9. APPENDICES:

Safety Monitor Report
01/11/2019

IRB Protocol Number	H-41120
Title	Persistent Hormonal Changes in Veterans with Gulf War Illness
Principal Investigator (PI)	Ricardo Jorge, MD
Study Sponsor	DoD
Proposal Number	GW160106
Award Number	W81XWH-17-1-0368
HRPO Log Number	A-20301.a and A-20301.b
Reporting Period	October 1, 2018 – December 31, 2018

Sanjay N Mediwala MD

Independent Safety Monitor:
Sanjay Mediwala, MD
Board Certified Endocrinologist
Michael E. DeBakey VA Medical Center

H-41120 Summary

Year 2 Quarter 1 (October 2018 – December 2018)

# who completed endocrine tests:	14
# of patients with AE:	1
# of patients with UPIRTSO:	0

Protocol Evaluation

The purpose of this study is to assess hormonal dysregulation in Gulf War veterans and evaluate the association of Gulf War Illness in major hormonal systems. The dynamic tests used in this study (Glucagon Stimulation Test for growth hormone deficiency and the ACTH stimulation test for adrenal insufficiency) are routine endocrine tests. The testing protocol used in this study is consistent with clinical guidelines and standard publications.

The risks of adverse events (AE) from stimulation tests in Gulf War veterans is the same as general population.

Adverse Events

Of the 14 patients who underwent testing, one patient reported dizziness, nausea, and vomiting. The symptoms were mild in nature. The patient vomited one time after the 150 min sample was drawn. Patient was allowed to break fast after the sample was collected. Symptoms resolved after patient had something to eat. The research nurse monitored the patient, and the patient was allowed to leave once she was asymptomatic. The team followed-up with the patient over phone the following day and week after; no further symptoms reported.

Reporting Requirements

Reporting requirements met. The AE was documented in the patient's study folder and reviewed by the endocrinologist and PI. The event does not require IRB reporting since it is not a serious adverse event nor unanticipated problem.

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

There were no unanticipated problems (in terms of nature, severity, or frequency) involving risks to subjects or others. There is no new literature or findings suggesting that the research places subjects or others at greater risk of harm than was previously known or recognized.

Safety Monitor Report
04/09/2019

IRB Protocol Number	H-41120
Title	Persistent Hormonal Changes in Veterans with Gulf War Illness
Principal Investigator (PI)	Ricardo Jorge, MD
Study Sponsor	DoD
Proposal Number	GW160106
Award Number	W81XWH-17-1-0368
HRPO Log Number	A-20301.a and A-20301.b
Reporting Period	January 1, 2019 – March 31, 2019

Sanjay N Mediwala MD.

Independent Safety Monitor:
Sanjay Mediwala, MD
Board Certified Endocrinologist
Michael E. DeBakey VA Medical Center

H-41120 Summary

Year 2 Quarter 2 (January 2019 – March 2019)

# who completed endocrine tests:	5
# of patients with AE:	0
# of patients with UPIRTSO:	0

Protocol Evaluation

The purpose of this study is to assess hormonal dysregulation in Gulf War veterans and evaluate the association of Gulf War Illness in major hormonal systems. The dynamic tests used in this study (Glucagon Stimulation Test for growth hormone deficiency and the ACTH stimulation test for adrenal insufficiency) are routine endocrine tests. The testing protocol used in this study is consistent with clinical guidelines and standard publications.

The risks of adverse events (AE) from stimulation tests in Gulf War veterans is the same as general population.

Adverse Events

None of the patients who underwent stimulation tests reported adverse events.

Reporting Requirements

There were no adverse events reported during this quarter.

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

There were no unanticipated problems (in terms of nature, severity, or frequency) involving risks to subjects or others. There is no new literature or findings suggesting that the research places subjects or others at greater risk of harm than was previously known or recognized.

Safety Monitor Report
07/15/2019

IRB Protocol Number	H-41120
Title	Persistent Hormonal Changes in Veterans with Gulf War Illness
Principal Investigator (PI)	Ricardo Jorge, MD
Study Sponsor	DoD
Proposal Number	GW160106
Award Number	W81XWH-17-1-0368
HRPO Log Number	A-20301.a and A-20301.b
Reporting Period	April 1, 2019 – June 30, 2019

Sanjay Mediwala MD

Independent Safety Monitor:
Sanjay Mediwala, MD
Board Certified Endocrinologist
Michael E. DeBakey VA Medical Center

H-41120 Summary

Year 2 Quarter 3 (April 2019 – June 2019)

# who completed endocrine tests:	19
# of patients with AE:	2
# of patients with UPIRTSO:	0

Protocol Evaluation

The purpose of this study is to assess hormonal dysregulation in Gulf War veterans and evaluate the association of Gulf War Illness in major hormonal systems. The dynamic tests used in this study (Glucagon Stimulation Test for growth hormone deficiency and the ACTH stimulation test for adrenal insufficiency) are routine endocrine tests. The testing protocol used in this study is consistent with clinical guidelines and standard publications.

The risks of adverse events (AE) from stimulation tests in Gulf War veterans is the same as general population.

Adverse Events

Of the 19 patients who underwent testing, two reported adverse events. Both patients experienced nausea at GH 150 timepoint. The symptoms were mild in nature and resolved without intervention.

Event 1: The participant asked to use the restroom just before GH 150 sample was drawn. Upon return, the patient reported brief period of nausea while defecating. He also indicated a small amount of stomach acid was regurgitated. No nausea was observed prior to or after using the restroom. Symptoms were brief and resolved by the time the patient returned. No other symptoms or complications noted.

Event 2: The patient experienced nausea shortly after GH 150 blood sample was drawn. He attempted to gag but did not vomit. The patient reported feeling better after gagging. Nausea resolved completely; no other symptoms reported.

Reporting Requirements

Reporting requirements met. The AEs were documented in the participants' study folders and reviewed by the principal investigator. Neither event require IRB reporting because symptoms were mild and not unforeseen.

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Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

There were no unanticipated problems (in terms of nature, severity, or frequency) involving risks to subjects or others. There is no new literature or findings suggesting that the research places subjects or others at greater risk of harm than was previously known or recognized.

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Safety Monitor Report
10/11/2019

IRB Protocol Number	H-41120
Title	Persistent Hormonal Changes in Veterans with Gulf War Illness
Principal Investigator (PI)	Ricardo Jorge, MD
Study Sponsor	DoD
Proposal Number	GW160106
Award Number	W81XWH-17-1-0368
HRPO Log Number	A-20301.a and A-20301.b
Reporting Period	July 1, 2019 – September 30, 2019

Independent Safety Monitor:
Sanjay Mediwala, MD
Board Certified Endocrinologist
Michael E. DeBakey VA Medical Center

H-41120 Summary

Year 2 Quarter 4 (July 2019 – September 2019)

# who completed endocrine tests:	8
# of patients with AE:	0
# of patients with UPIRTSO:	0

Protocol Evaluation

The purpose of this study is to assess hormonal dysregulation in Gulf War veterans and evaluate the association of Gulf War Illness in major hormonal systems. The dynamic tests used in this study (Glucagon Stimulation Test for growth hormone deficiency and the ACTH stimulation test for adrenal insufficiency) are routine endocrine tests. The testing protocol used in this study is consistent with clinical guidelines and standard publications.

The risks of adverse events (AE) from stimulation tests in Gulf War veterans is the same as general population.

Adverse Events

None of the participants who underwent glucagon stimulation test and ACTH stimulation test during the fourth quarter of year two experienced adverse events.

Reporting Requirements

N/A

Unanticipated Problems Involving Risk to Subjects or Others (UPIRTSO)

There were no unanticipated problems (in terms of nature, severity, or frequency) involving risks to subjects or others. There is no new literature or findings suggesting that the research places subjects or others at greater risk of harm than was previously known or recognized.