

AWARD NUMBER: W81XWH-15-1-0216

TITLE: Vascular and Skeletal Muscle Function in Gulf War Veterans Illness

PRINCIPAL INVESTIGATOR: Scott Kinlay, MBBS, PhD

CONTRACTING ORGANIZATION: Boston VA Research Institute, Inc. (BVARI)  
Boston, MA 02130

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

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# REPORT DOCUMENTATION PAGE

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<b>6. AUTHOR(S)</b> Scott Kinlay, MBBS, PhD  E-Mail: <a href="mailto:Scott.Kinlay@va.gov">Scott.Kinlay@va.gov</a>						<b>5d. PROJECT NUMBER</b>			
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						<b>5f. WORK UNIT NUMBER</b>			
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<b>13. SUPPLEMENTARY NOTES</b>									
<b>14. ABSTRACT</b> Gulf War Illness (GWI) is a constellation of symptoms including fatigue, musculoskeletal pain, memory loss, and mood changes reported by Gulf War Veterans shortly after their return in 1991. Approximately 40% of Gulf War Veterans (over ¼ million Veterans) have GWI by the Center for Disease Control criteria for GWI (a recommended method for defining GWI). The underlying causes of GWI are poorly understood. The overall goal of our study is to determine if there are differences in blood vessels, skeletal muscle performance, and their controlling proteins and genes in Gulf War Veterans with and without GWI. Abnormalities in these factors may explain the symptoms of fatigue and muscle pain that are major parts of GWI. These insights could lead to new treatments for GWI as well as other illnesses with similar symptoms. Our pilot data show that we can assess blood flow to muscle, muscle strength and fatigue and examine proteins and genes from a specimen of muscle in Gulf War Veterans. We will assess if abnormalities in these factors are potential explanations for GWI. This study is seeking to enroll 70 Veterans (35 with GWI and 35 without GWI) and is currently open to enrollment.									
<b>15. SUBJECT TERMS</b> Gulf War Syndrome, Persian Gulf Syndrome/physiopathology, Veterans									
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**1. INTRODUCTION:** Gulf War Illness (GWI) is a constellation of symptoms including fatigue, musculoskeletal pain, and neurocognitive reported by Gulf War Veterans shortly after their return from deployment in 1991. The Center for Disease Control and Prevention (CDC)'s clinical diagnostic criteria for GWI is one of two recommended by an Expert Committee, and is based on symptoms in three categories: fatigue, mood/cognition, and musculoskeletal symptoms. Currently, approximately 40% of Gulf War Veterans (over ¼ million Veterans) have GWI by these criteria. The pathophysiological mechanisms underlying GWI are not understood and insights into these mechanisms could lead to new treatment interventions. Furthermore, abnormalities in peripheral blood flow related to endothelial function and muscle bioenergetics due to environmental toxins, such as those present in the Gulf War, are plausible mechanisms that could relate to the musculoskeletal symptoms of GWI. This study will determine the pathophysiology, and related genome and transcriptional mechanisms related to endothelial function and muscle mitochondrial biogenesis in Veterans with and without GWI through a case-control design of 70 Veterans who have served in the Gulf War and are participants of the ongoing Fort Devens Cohort. Specific aims include comparisons of: (1) microvascular endothelium-dependent and endothelium-independent function of the profunda femoral artery using techniques commonly used for peripheral endovascular interventions, (2) peak oxygen uptake and ventilator anaerobic threshold during cardiopulmonary exercise testing and other muscle functions, (3) expression of genes relevant to endothelial function and mitochondrial function in muscle biopsy samples, and (4) gene polymorphisms related to endothelial and mitochondrial respiratory function.

**2. KEYWORDS:**

Gulf War Syndrome  
 Persian Gulf Syndrome/physiopathology  
 Veterans

**3. ACCOMPLISHMENTS:**

**What were the major goals of the project?**

Major Tasks	Timeline (months)	Status
<b>Major Task 1: Institutional Review Board (IRB) Approval</b>		
Modify the current protocol to add new experiments and aim (microarray assays and next-generation RNA sequencing)	0.5	Completed
Submit final protocol to VA Boston Healthcare System (VABHS) IRB	0.5	Completed
<b>Milestone:</b> Achieve local IRB approval of protocol	1	Received VA Boston IRB approval for modified protocol amendment, Protocol Version 2.0 on 11-JAN-2016.  Submitted to and received HRPO Initial Approval for protocol (version 2/ dated 23-Dec-2015) on 09-FEB-2016.

<b>Major Task 2: Recruitment of Subjects</b>		
Send batch invitations to 400 Gulf War Veterans who have completed the Fort Devens cohort study	1-24	<p>Dr. Maxine Krengel (Co-Investigator) helped initiate recruitment by sending Gulf War Veterans invitation letters to participate around 19-FEB-2016.</p> <p>As of 31-MAR-2018, we completed mailing at least 3 recruitment letters all 1107 Veterans from Dr. Krengel's Fort Devens Cohort. Additionally, we received approval from the VA Boston IRB committees on 13-Nov-2017 to mail a 4<sup>th</sup> letter accompanied by an opt-out card and to follow up by telephone call if no response is received.</p> <p>As of 31-MAR-2018, 160 Veterans have received a 4<sup>th</sup> letter and a follow up telephone call from a member of the study staff. We plan to continue this revised recruitment plan until enrollment is complete.</p> <p>Complete</p>
<b>Major Task 3: Endothelial Function Study and Muscle Biopsy</b>		
Schedule Visit 1 (Endothelial function studies and muscle biopsies)	1-24	All visit 1 appointments have been scheduled and completed as of 30-APR-2018
Complete endothelial function studies and muscle biopsies and measurement of intravascular ultrasound and flow data to assess microvascular and conduit endothelial function	1-28	<p>As of 30-APR-2018, 78 Veterans completed Visit 1 which includes endothelial function studies, muscle biopsies and measurement and intravascular ultrasound and flow data. Total of 78 is exclusive of 2 Veterans who were unable to complete Visit 1 due to extensive peripheral artery disease.</p> <p>Muscle biopsies for 76 Veterans have been collected.</p> <p>All of the intra-arterial IVUS</p>

		images have been measured (over 2600 images). Flow images are more than three quarters complete. The flow and IVUS measurements will be used to measure endothelial function. We have completed an analysis in 20 patients showing that our measurements are reproducible. This reproducibility data was presented at the Society for Vascular Medicine meeting and has been submitted for publication.
<b>Milestone:</b> Complete endothelial function data and muscle biopsies on 70 subjects	28	Complete
<b>Major Task 4: Exercise and Cardiopulmonary Stress Testing</b>		
Schedule Visit 2 (Exercise and cardiopulmonary stress tests)	3-28	Scheduling for Visit 1 continues to occur at least 2 weeks after completion of Visit 1, limited by Veteran's availability. There is 1 remaining subject who requires scheduling for this visit.
Complete exercise and cardiopulmonary stress studies and interpretation	3-28	As of 30-JUN-2018, 77 Veterans have successfully completed Visit 2. One subject remains to be scheduled.
<b>Milestone:</b> Complete exercise data on 70 subjects	28	As of 30-JUN-2018, 77 Veterans have successfully completed Visit 2. One subject remains to be scheduled.
<b>Major Task 5: Histopathology and Electron Microscopy</b>		
Prepare muscle biopsy specimens for histopathology and electron microscopy and image	4-30	Pending
Complete data on muscle analysis including histopathology	4-30	Pending
<b>Milestone:</b> Complete histopathological data and electron microscopy data on representative subjects	30	Pending
<b>Major Task 6: Gene and protein expression relating to mitochondrial biogenesis</b>		
Isolate DNA, RNA, and protein from muscle tissue samples. Prepare cDNA from RNA samples.	4-28	Pending
Complete qPCR and Western Blot to assess genes and proteins regulating mitochondrial biogenesis.	4-30	Pending
<b>Milestone:</b> Complete data on specific genes and proteins regulating mitochondrial biogenesis on 70	30	Pending

subjects		
<b>Major Task 7: Transcriptome microarrays comparing cases and controls</b>		
Run microarrays at Dana Farber Microarray Core Lab from cDNA samples	24-30	Pending
Interpret results and identify candidate genes related to Gulf War Illness	24-30	Pending
<b>Milestone:</b> Complete analysis of transcriptome microarray data on 70 subjects	30	Pending
<b>Major Task 8: SNP Microarray</b>		
Run MVP microarray at Dana Farber Microarray Core Lab	4-28	Pending
Identify candidate genetic polymorphisms related to GWI	4-30	Pending
<b>Milestone:</b> Complete data analysis of SNP microarray data on 70 subjects	30	Pending
<b>Major Task 9: Finalize data analysis, present results and meetings, publish results</b>		
Complete statistical analyses including comparisons of cases and controls and prepare for publication, presentation, and public release of de-identified data for other researchers.	24-36	Pending

**What was accomplished under these goals?** This report summarizes the research progress in the most recently completed budget period from July 1, 2017 to June 30, 2018. This time period corresponds to the third of this three-year project. The objectives of this study is to investigate the hypothesis that when compared to Veterans without Gulf War Illness (GWI), Veterans with GWI will have differences in arterial endothelial function, muscle function determined by cardiopulmonary exercise testing, and expression of genes responsible for mitochondrial function. This is a case control study of 2 visits looking to enroll 70 participants (35 with GWI and 35 without GWI) from a well characterized cohort of Gulf War Veterans (the Fort Devens study). Study Visit 1 consists of an endothelial function test performed using standard cardiac catheterization techniques used for peripheral artery interventions, and a muscle biopsy of the vastus lateralis muscle. Study Visit 2 consists of cardiopulmonary exercise testing and other tests of muscle strength and endurance.

The second budget period was heavily focused on participant recruitment (Major Task 2, 3, and 4). In the last year, 78 (100%; of expected 70) Veterans have completed Study Visit 1. More Veterans were recruited for the study as 2 were not able to provide Visit 1 data and 6 Veterans' data were not evaluable. Analysis of endothelial function is 75% completed and 100% of muscle biopsies have been collected. 77/78 Visit 2 appointments have been completed. We expect the last subject's Visit 2 to be completed in the next month.

**What opportunities for training and professional development has the project provided?**  
Nothing to Report.

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

We presented our data on the reproducibility of measuring endothelial function in the first 20 patients of this study as a poster at the Society of Vascular Medicine Annual Scientific Meeting in Chicago June 14-16, 2018. We have submitted this data for publication and it is currently under review in the peer-reviewed journal *Vascular Medicine*.

**What do you plan to do during the next reporting period to accomplish the goals?** We are generating the largest dataset of exposures, vascular function, exercise capacity, and genetic studies of Gulf War Veterans, and one of the largest studies to collect data of this type in any disease state. In spite of significant delays of about a year in starting this project we are close to completing the data collection for this study. In the next reporting period, we are planning to complete endothelial function analysis, complete exercise data analysis and begin muscle biopsy analysis. We have successfully obtained a no-cost extension for another year using remaining funds in this grant to support the muscle histopathological and gene analysis. Dr. Calum MacRae, has a large laboratory funded by the multimillion dollar One Great Idea grant to analyze gene expression and genomes in large population studies and has agreed to do the analyses we require for our Gulf War Illness study. Now that we have secured funding through the no-cost extension we are moving forward with negotiations for his lab to complete this work. The histopathological and genetic analyses of the muscle biopsies including the next generation RNA sequencing technology will use a large portion of the original grant budget. Remaining funds in this no-cost extension year will support salary to complete the endothelial function analysis, data management, and statistical analysis. The no-cost extension will allow us to complete these tasks within budget.

#### 4. **IMPACT:**

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

Fatigue and musculoskeletal symptoms are major components of GWI and could have an important impact on other symptoms associated with GWI. There are plausible reasons why endothelial function and mitochondrial biogenesis in muscle may be affected by exposure to environmental toxins during the Gulf War and lead to these symptoms.

In particular, pyridostigmine and nerve gases are anticholinesterase agents that potentially have long term effects on the balance of cholinesterases and acetylcholine, which could affect activity at the neuromuscular junction of skeletal muscle, muscarinic receptors affecting vascular smooth muscle tone, and damage mitochondrial structure and electron transport activity in several tissues including muscle.

Insights on the pathogenesis of GWI could lead to new treatments for GWI, but also provide novel mechanistic insights into other exposure-related occupational health illness, such as pesticide exposure in the agricultural industry. Our study may also elucidate mechanisms of interest that require investigation as causes of other illnesses with muscle fatigue, pain, and abnormal muscle metabolism, such as peripheral artery disease and chronic heart failure, and advance our understanding of the pathophysiology of GWI and discover molecular pathways that could elucidate novel treatments for GWI. It may also direct future research into abnormalities

of important molecules that could form the basis of an improved diagnostic test, although establishing a diagnostic test is not the focus of this proposal.

As the study is still in progress, there are currently no findings 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:** Nothing to Report.

**Actual or anticipated problems or delays and actions or plans to resolve them:** There was a delay in approval of the no cost extension. This held up the subcontract with the Brigham and Women's Hospital for muscle biopsy analysis. However, now that the no-cost extension is approved this is moving forward and we expect to start this phase of the study shortly. In the meantime we are completing blood flow measurements for the endothelial function component and building spreadsheets of the data in preparation for statistical analysis of the key aims of the study.

**Changes that had a significant impact on expenditures:** Nothing to Report.

**Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents:** Nothing to Report.

6. **PRODUCTS:** Nothing to Report.

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

**What individuals have worked on the project?** Individuals who have worked on this project during the most recent budget period are described below with their efforts and contribution divided by each quarterly reporting period.

### July 1, 2016 to September 30, 2016

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<b>Name:</b>	Scott Kinlay, MBBS, PhD
<b>Project Role:</b>	Principle Investigator
<b>Research Identifier:</b>	0000-0001-7687-9136
<b>Nearest person month worked:</b>	1
<b>Contribution to Project:</b>	Dr. Kinlay is overseeing recruitment, ensuring that all Veterans meet study protocol eligibility criteria. He is also performing the peripheral catheterization and muscle

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biopsy in Visit 1.

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**Name:** Jacquelyn-My Do, MPH  
**Project Role:** Assistant Program Manager  
**Research Identifier:** N/A  
**Nearest person month worked:** 3  
**Contribution to Project:** Ms. Do is the new Project Manager for this study and has assumed the administrative project management responsibilities of Dr. Sara Jones. She is planning and tracking study recruitment, maintaining regulatory approval, and managing project resources and budget. She oversees mailing of recruitment letter, scheduling of patient appointments, and manages data collection.

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**Name:** Margot Quinn, BA  
**Project Role:** Research Assistant  
**Research Identifier:** N/A  
**Nearest person month worked:** 1  
**Contribution to Project:** Ms. Quinn performs research activities are described in the study protocol, including informed consent of participants and conduct of Visit 1. She also assisted the Project Manager in administrative duties.

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**October 1, 2016 to December 31, 2016**

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**Name:** Scott Kinlay, MBBS, PhD  
**Project Role:** Principle Investigator  
**Research Identifier:** 0000-0001-7687-9136  
**Nearest person month worked:** 1  
**Contribution to Project:** Dr. Kinlay is overseeing recruitment, ensuring that all Veterans meet study protocol eligibility criteria. He is also performing the peripheral catheterization and muscle biopsy in Visit 1.

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**Name:** Jacquelyn-My Do, MPH  
**Project Role:** Assistant Program Manager  
**Research Identifier:** N/A  
**Nearest person month worked:** 3  
**Contribution to Project:** Ms. Do continues in her role as Project Manager for this study. She continues to track study progress, maintains regulatory approval, and manages project resources and budget. She also oversees mailing of recruitment letter, scheduling of patient appointments, and manages data collection.

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**Name:** Margot Quinn, BA  
**Project Role:** Research Assistant  
**Research Identifier:** N/A  
**Nearest person month worked:** 1  
**Contribution to Project:** Ms. Quinn performs research activities are described in the study protocol, including informed consent of participants and conduct of Visit 1. She also assisted the Project Manager in administrative duties.

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**January 1, 2017 – March 31, 2017**

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**Name:** Scott Kinlay, MBBS, PhD  
**Project Role:** Principle Investigator  
**Research Identifier:** 0000-0001-7687-9136  
**Nearest person month worked:** 2  
**Contribution to Project:** Dr. Kinlay is overseeing recruitment, ensuring that all Veterans meet study protocol eligibility criteria. He is also performing the peripheral catheterization and muscle biopsy in Visit 1. Additionally, he is actively recruiting for a Project Manager to replace Ms. Do.

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**Name:** Jacquelyn-My Do, MPH  
**Project Role:** Assistant Program Manager  
**Research Identifier:** N/A  
**Nearest person month worked:** 1  
**Contribution to Project:** Ms. Do continues in her role as Project Manager for this study until 20-JAN-2017. She continues to track study progress, maintains regulatory approval, and manages project resources and budget. She also oversees mailing of recruitment letter, scheduling of patient appointments, and manages data collection. As of 20-JAN-2017, she has left the Boston VA Research Institute and VA Boston. She continues a temporary assignment with the project to help gather and analyze data from Visit 1, slated to end at 30-APR-2017.

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**Name:** Margot Quinn, BA  
**Project Role:** Research Assistant  
**Research Identifier:** N/A  
**Nearest person month worked:** 1  
**Contribution to Project:** Ms. Quinn performs research activities are described in the study protocol, including informed consent of participants and conduct of Visit 1. She also assisted the Project Manager in administrative duties.

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**April 1, 2017 – June 30, 2017**

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**Name:** Scott Kinlay, MBBS, PhD  
**Project Role:** Principle Investigator  
**Research Identifier:** 0000-0001-7687-9136  
**Nearest person month worked:** 1  
**Contribution to Project:** Dr. Kinlay is overseeing recruitment, ensuring that all Veterans meet study protocol eligibility criteria. He is also performing the peripheral catheterization and muscle biopsy in Visit 1. He continues to actively recruit for a Project Manager to replace Ms. Do, but has hired a new research assistant to replace Margot Quinn.

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**Name:** Margot Quinn, BA  
**Project Role:** Research Assistant  
**Research Identifier:** N/A  
**Nearest person month worked:** 1  
**Contribution to Project:** Ms. Quinn continues to performs research activities as described by study protocol, including informed consent of participants and conduct of Visit 1. As of 30-JUN-2017, she will be leaving her appointment with BVARI and will not longer be working on this project.

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**Name:** Melissa Chin, BS  
**Project Role:** Research Assistant  
**Research Identifier:** N/A  
**Nearest person month worked:** 1  
**Contribution to Project:** Ms. Chin has a Bachelor of Science in Biochemistry from Boston College and has extensive bench lab experience. She started on this project on 26-JUN-2017 and will be replacing Ms. Quinn's position as research assistant, responsible for recruitment and activities of study visit 1.

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**July 1, 2017-September 30, 2017**

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**Name:** Scott Kinlay, MBBS, PhD  
**Project Role:** Principle Investigator  
**Research Identifier:** 0000-0001-7687-9136  
**Nearest person month worked:** 1  
**Contribution to Project:** Dr. Kinlay is overseeing recruitment, ensuring that all Veterans meet study protocol eligibility criteria. He is also performing the peripheral catheterization and muscle biopsy in Visit 1. Additionally, he has been actively recruiting for Project Manager

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**Name:** Melissa Chin, BS  
**Project Role:** Research Assistant  
**Research Identifier:** N/A  
**Nearest person month worked:** 1  
**Contribution to Project:** Ms. Chin continues to perform research activities as described by the study protocol, including informed consent of participants and conduct of Visit 1 under the direction of Dr. Kinlay

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**Name:** Mariah Bundy, BS  
**Project Role:** Senior Research Assistant  
**Research Identifier:** N/A  
**Nearest person month worked:** 1  
**Contribution to Project:** Ms. Bundy was assigned to this project on 01-AUG-2017 to help collect and perform repeated measurement analysis on the intra-arterial IVUS images. She will provide blinded intra-arterial diameter measurements for this study.

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**Name:** Samantha Ly, MA  
**Project Role:** Program Manager  
**Research Identifier:** N/A  
**Nearest person month worked:** 1  
**Contribution to Project:** Ms. Ly is responsible for training Ms. Chin in study procedures and Ms. Bundy with image analysis. She is also helping Dr. Kinlay with additional personnel recruitment and helping with the project's administrative tasks (e.g. maintenance of study regulatory binders, tracking study equipment inventory, and revising case report forms) until a Project Manager is hired.

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#### **October 1, 2017-December 30, 2017**

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**Name:** Scott Kinlay, MBBS, PhD  
**Project Role:** Principle Investigator  
**Research Identifier:** 0000-0001-7687-9136  
**Nearest person month worked:** 1  
**Contribution to Project:** Dr. Kinlay is overseeing recruitment, ensuring that all Veterans meet study protocol eligibility criteria. He is also performing the peripheral catheterization and muscle biopsy in Visit 1. Additionally, he has been actively recruiting for Project Manager/Coordinator

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**Name:** Melissa Chin, BS  
**Project Role:** Research Assistant  
**Research Identifier:** N/A  
**Nearest person month worked:** 1

**Contribution to Project:** Ms. Chin continues to perform research activities as described by the study protocol, including informed consent of participants and conduct of Visit 1 under the direction of Dr. Kinlay

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**Name:** Mariah Bundy, BS  
**Project Role:** Senior Research Assistant  
**Research Identifier:** N/A  
**Nearest person month worked:** 1  
**Contribution to Project:** Ms. Bundy was assigned to this project on 01-AUG-2017 to help collect and perform repeated measurement analysis on the intra-arterial IVUS images. She will provide blinded intra-arterial diameter measurements for this study.

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**Name:** Samantha Ly, MA  
**Project Role:** Program Manager  
**Research Identifier:** N/A  
**Nearest person month worked:** 1  
**Contribution to Project:** Ms. Ly continues to assist Mr. Chin with study procedures and Ms. Bundy with image analysis as necessary. She is also helping Dr. Kinlay with additional personnel recruitment and helping with the project's administrative tasks (e.g. maintenance of study regulatory binders, tracking study equipment inventory, and revising case report forms) until a Project Manager/Coordinator is hired.

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**January 1, 2018-March 30, 2018**

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**Name:** Scott Kinlay, MBBS, PhD  
**Project Role:** Principle Investigator  
**Research Identifier:** 0000-0001-7687-9136  
**Nearest person month worked:** 1  
**Contribution to Project:** Dr. Kinlay is overseeing recruitment, ensuring that all Veterans meet study protocol eligibility criteria. He is also performing the peripheral catheterization and muscle biopsy in Visit 1. Additionally, he has been actively recruiting for Project Manager/Coordinator

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**Name:** Melissa Chin, BS  
**Project Role:** Research Assistant  
**Research Identifier:** N/A  
**Nearest person month worked:** 1  
**Contribution to Project:** Ms. Chin continues to perform research activities as described by the study protocol, including informed consent of participants and conduct of Visit 1 under the direction of Dr. Kinlay

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**Name:** Mariah Bundy, BS  
**Project Role:** Senior Research Assistant  
**Research Identifier:** N/A  
**Nearest person month worked:** 1  
**Contribution to Project:** Ms. Bundy was assigned to this project on 01-AUG-2017 to help collect and perform repeated measurement analysis on the intra-arterial IVUS images. She will provide blinded intra-arterial diameter measurements for this study.

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**Name:** Samantha Ly, MA  
**Project Role:** Program Manager  
**Research Identifier:** N/A  
**Nearest person month worked:** 1  
**Contribution to Project:** As of 13-FEB-2018, Ms. Ly no longer works on this project. The new Project Manager/Coordinator will assume her responsibilities of managing project progress and data analysis

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**Name:** Desiree Tobin, MPH  
**Project Role:** Research Assistant  
**Research Identifier:** N/A  
**Nearest person month worked:** 1  
**Contribution to Project:** Ms. Tobin was assigned to this project 01-AUG-2017 to help with measuring of the flow-map data blinded to patient details and infusion stage

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**Name:** Samuel Davis  
**Project Role:** Research Assistant  
**Research Identifier:** N/A  
**Nearest person month worked:** 1  
**Contribution to Project:** Mr. Davis completed the DUAL-XRay-Absorption (DXA) studies on subjects, which is used to adjust the exercise parameters on aerobic thresholds

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#### **April 1, 2018-June 30, 2018**

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**Name:** Scott Kinlay, MBBS, PhD  
**Project Role:** Principle Investigator  
**Research Identifier:** 0000-0001-7687-9136  
**Nearest person month worked:** 1  
**Contribution to Project:** Dr. Kinlay is overseeing recruitment, ensuring that all Veterans meet study protocol eligibility criteria. He is also performing the peripheral catheterization and muscle biopsy in Visit 1. Additionally, he has been actively recruiting for Project Manager/Coordinator

<b>Name:</b>	Melissa Chin, BS
<b>Project Role:</b>	Research Assistant
<b>Research Identifier:</b>	N/A
<b>Nearest person month worked:</b>	1
<b>Contribution to Project:</b>	Ms. Chin continues to perform research activities as described by the study protocol, including informed consent of participants and conduct of Visit 1 under the direction of Dr. Kinlay. Ms. Chin has been helping with the project's administrative tasks (e.g. maintenance of study regulatory binders, and managing project progress) until a Project Manager/Coordinator is hired
<b>Name:</b>	Mariah Bundy, BS
<b>Project Role:</b>	Senior Research Assistant
<b>Research Identifier:</b>	N/A
<b>Nearest person month worked:</b>	1
<b>Contribution to Project:</b>	As of 27-APR-2018 Ms. Bundy no longer works on this project. Intra-arterial measurements have been completed
<b>Name:</b>	Desiree Tobin, MPH
<b>Project Role:</b>	Research Assistant
<b>Research Identifier:</b>	N/A
<b>Nearest person month worked:</b>	1
<b>Contribution to Project:</b>	Ms. Tobin was assigned to this project 01-AUG-2017 to help with measuring of the flow-map data blinded to patient details and infusion stage
<b>Name:</b>	Samuel Davis
<b>Project Role:</b>	Research Assistant
<b>Research Identifier:</b>	N/A
<b>Nearest person month worked:</b>	1
<b>Contribution to Project:</b>	Mr. Davis completed the DUAL-XRay-Absorption (DXA) studies on subjects, which is used to adjust the exercise parameters on aerobic thresholds

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?** Nothing to Report.

**What other organizations were involved as partners?** The analysis of muscle samples will include isolation and analysis of RNA and DNA, protein isolation expression, microchip arrays, and next generation RNA generation. We will work with our collaborator, Dr. Calum MacRae at the Brigham and Women's hospital to complete these analyses.

Organization Name: Brigham and Women's Hospital

Location of Organization: Boston, MA

Partner's contribution to the project: Collaboration

Until sample analysis commences, we current do not have any partner organizations.

8. **SPECIAL REPORTING REQUIREMENTS COLLABORATIVE AWARDS:** None.

9. **APPENDICES:** Please see the attached quad chart.

# Vascular and Skeletal Muscle Function in Gulf War Veterans Illness

Log Number: GW14003

Award Number: W81XWH-15-1-0216



PI: Scott Kinlay, MBBS, PhD

Org: Boston VA Research Institute, Inc. (BVARI)

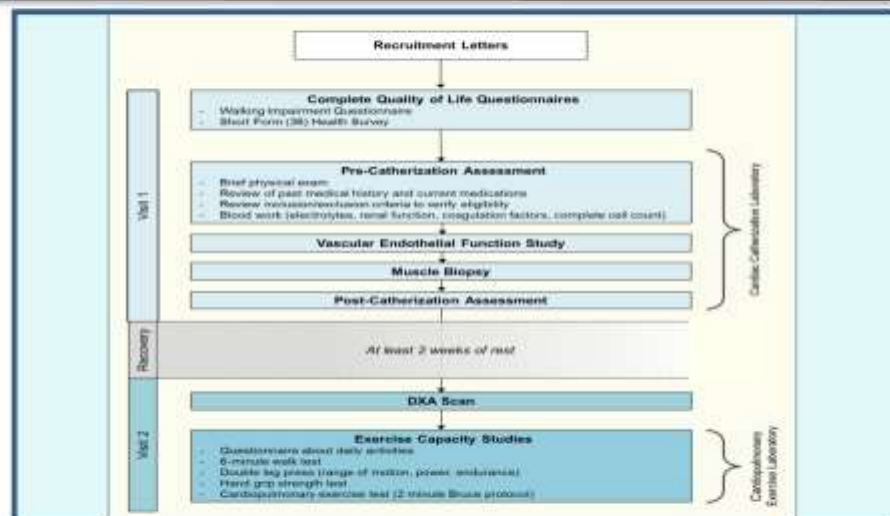
Award Amount: \$870,642.00

## Study/Product Aim(s)

- To determine if microvascular endothelium-dependent and endothelium-independent function of the profunda femoral artery is impaired in subjects with Gulf War Veterans Illness (GWVI) compared to deployed Veterans without GWVI.
- To determine if peak oxygen uptake and ventilatory anaerobic threshold during cardiopulmonary exercise testing, and other muscle functions are impaired in subjects with GWVI compared to deployed Veterans without GWVI.
- To determine how the expression of genes relevant to endothelial function and mitochondrial function in muscle biopsy samples differs between subjects with GWVI compared to deployed Veterans without GWVI.
- To determine if polymorphisms to genes relating to endothelial function and mitochondrial respiratory function differ between subjects with GWVI compared to deployed Veterans without GWVI.

## Approach

Gulf War Illness (GWI) is a constellation of symptoms including fatigue, musculoskeletal pain, and neurocognitive dysfunction reported by Gulf War Veterans shortly after their return from deployment in 1991. There are plausible reasons why endothelial function and mitochondrial biogenesis in muscle may be affected by exposure to environmental toxins during the Gulf War and lead to GWI symptoms. We hypothesize that compared to Veterans without GWI, Veterans with GWI will have differences in arterial endothelial function, muscle function determined by cardiopulmonary exercise testing, and the expression of genes responsible of mitochondrial function.



Accomplishment: This IRB-approved prospective cross-sectional clinical trial consisted of 2 study visits. 78 of 70 Gulf War Veterans were enrolled. Analysis continues.

## Timeline and Cost

Activities	CY	15	16	17	18	19
Milestone 1: Achieve local IRB approval of protocol		█				
Milestone 2: Complete Visit 1 (endothelial function and muscle biopsies) on 70 subjects			█			
Milestone 3: Complete Visit 2 (exercise and cardiopulmonary stress test) on 70 subjects			█	█		
Milestone 4: Complete histopathology and electron microscopy analysis				█	█	
Milestone 5: Complete gene and protein analysis				█	█	
Milestone 6: Complete analysis on transcriptome microarray data				█	█	
Milestone 7: Complete analysis of SNP microarray data				█	█	
Finalize data analysis, present results and meetings, publish results				█	█	█
<b>Estimated Budget (\$K)</b>		<b>\$0</b>	<b>\$220</b>	<b>\$361</b>	<b>\$287</b>	<b>\$0</b>

Updated: 30-JUN-2018

## Goals/Milestones

### CY15 Goals – Institutional Review Board (IRB)

- Achieve local IRB approval
- Achieve HRPO approval

### CY16/17 Goals – Subject Recruitment

- Start recruitment with letters of invitations
- Schedule and conduct Visits 1 and 2

### CY18 Goals – Complete recruitment and data analysis

- Complete Visits 1 and 2 on 70 Subjects
- Complete histopathological data, electronic microscopy data, specific genes and proteins regulating mitochondrial biogenesis, analysis of transcriptome microarray data on samples collected

### CY19 Goal – Analyze and publish results

- Analyze, present, and publish results at DoD and scientific meetings

**Comments/Challenges/Issues/Concerns:** We anticipate that a majority of the expenditures will be used to cover costs of analysis.

### Budget Expenditure to Date

Projected Expenditure: \$870,642; Actual Expenditure: \$314,643