

**VA**



U.S. Department  
of Veterans Affairs

# **NIH-VA Gulf War Illness Deep Phenotyping Study**

## **RAC Meeting**

**Ft Lauderdale, FL**

**March 20, 2018**

**Matthew Reinhard, PsyD, Director, DC WRIISC**



# NIH PI-ME/CFS PROTOCOL

## Post-Infectious – Myalgic Encephalomyelopathy/Chronic Fatigue Syndrome (PI-ME/CFS)

Principal Investigator: **Avindra Nath, MD**

Lead Associate Investigator: **Brian Walitt, MD, MPH**

*Primary objective:* To explore the clinical and biological phenotypes of PI-ME/CFS.

*Secondary objective:* To explore the pathophysiology of fatigue and post-exertional malaise (PEM)

### *Design*

- **Phenotyping Visit, 2-5 days outpatient or inpatient admission at the NIH Clinical Facility** Phase 1 of an exploratory, cross sectional deep phenotyping study of PI-ME/CFS. Participants attend a 2-5 day inpatient phenotyping visit at the NIH Clinical Center in Bethesda, MD.
- A case adjudication process confirms case status.
- **Exercise Stress Visit, 5-10 day inpatient admission (up to 12 months after the phenotyping visit)** Adjudicated patients meeting inclusion criteria are invited back to participate in a 5-10 day inpatient exercise stress visit. Detailed subjective and objective measurements and biological specimens are serially collected before and up to 96 hours after a peak exercise test intended to induce post-exertional malaise during the test visit





# GWI PROTOCOL: VA “SISTER” PROTOCOL

## Gulf War Veterans Illness (GWI) at NIH

VA Study Chairs: **Nancy Klimas, MD** and **Mathew Reinhard, PsyD**

NIH PI: Avindra Nath, MD and NIH Lead Investigator: Brian Walitt, MD, MPH

**VA** Screening Visit:  
Phone, web and 1  
day in-person  
assessment

VA sites lead Veteran  
recruitment,  
screening and  
selection

**NIH** Phenotyping and  
Exercise Visit:  
10 days outpatient  
or inpatient  
admission at the  
NIH Clinical Facility



# GW I PROTOCOL-- STUDY OBJECTIVES

## Primary objective

- To explore the clinical and biological phenotypes of GWI in Veterans of ODS/S.

## Secondary objective

- To explore the pathophysiologies of fatigue and post-exertional malaise (PEM). PEM will be explored using an exercise stress and measuring the symptomatic and biological alterations that occur before and afterwards

## Study Outcomes

- This study will analyze the collected data in an exploratory manner. **The goal of these analyses is to identify physiological alterations for the purpose of hypothesis generation.**
- Results from this study will guide the design of future studies to elucidate the biologic mechanisms underlying GWI as well as identify potential mechanisms for intervention. On completion of the primary analyses, a repository of data/specimens will be created to engage the wider scientific community in GWI research.
- This study will also leverage ongoing work in ME/CFS at the NIH. The GWI in Veterans of ODS/S study will utilize a complementary research structure that will allow for additional comparisons with the ME/CFS patients and Healthy Volunteers that are enrolled in this 'sister' study.



# VA STUDY TIMELINE - ACTUAL

Ongoing

- Weekly leadership meetings, special topic workgroups, specialty subgroups, Co-Chair protocol development mtgs
- **Scientific protocol development**
- Background work: comparability with NIH, review process, research existing cohorts, communication with CRADO and regulatory team, veteran engagement activities

Oct

- Identify leadership, roles, planning committee
- Determine planning/review process and timeline, study team logistics

Nov

- Establish contacts at NIH for clinical facility, IRB and regulatory questions
- Obtained NIH MOU templates for VA review

Dec

- Workgroup 1: Computational statistics and comparability across studies
- Meeting with NIH Clinical Facility Director and VA regulatory team

Jan

- Workgroup 2 and 3: Define the study population, recruitment approach, study sites, process for veteran engagement
- Preliminary meeting with VA and NIH regulatory teams

Feb

- Workgroup 4: Exposures/toxicology. Workgroup 1 follow-up: adding VA methods and computational bio plan to NIH exercise visit. Workgroup 5: GW surveys and exposures/toxicology/mitochondria
- Clarify VA recruitment and enrollment plan, create and submit synopsis for VA and NIH pre-review

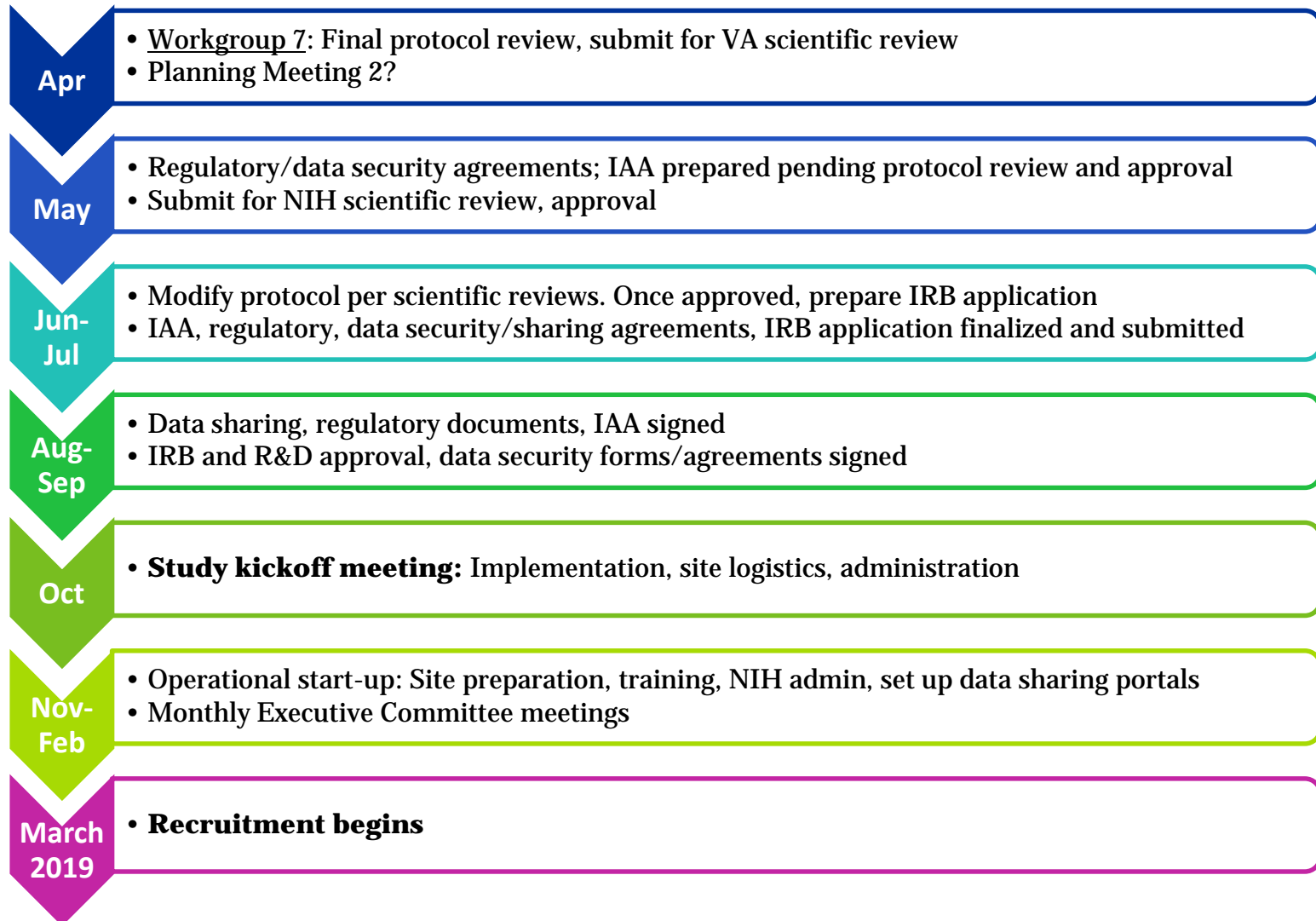
Mar

- Workgroup 6: Veteran Engagement, feedback from GW veterans on study methods and message. Common Data Elements for GWI, present to advisory boards, finalize protocol for planning mtg review
- **Planning Meeting 1, Wash DC**: Scientific protocol development, data management and security





# VA STUDY TIMELINE - PLANNED





# GWV PROTOCOL– VA SUBJECTS

- Up to 75 Veterans will be recruited to be part of 2 study groups:
  - 50 GWV Veterans deployed to ODS/S
  - 25 asymptomatic Veterans who were deployed to ODS/S.







# GW I PROTOCOL— VA RECRUITMENT

1995 National  
Health Survey

- **The 1995 National Health Survey of Persian Gulf Veterans and Their Families (NHS)**

Collected physical and psychological health and military exposure data on 11,441 Gulf War veterans soon after the exposure, with all veterans reporting at least one deployment exposure from a list of 14. A subset of deployed and nondeployed veterans who participated in the NHS were additionally recruited between 1999 and 2001 for in person medical evaluations (n=1061).

CSP 585 Gulf  
War Era Cohort

- **CSP 585 ‘The Gulf War Era Cohort and Biorepository’ (GWECB)**

Collected survey data, medical records and a linked biorepository of blood specimens on a nationally representative longitudinal cohort

Million Veteran  
Program

- **Million Veteran Program (MVP)**

Ongoing study that collects DNA samples with linkage to electronic health record information intended as an infrastructure for future research in multiple areas. The study includes a general questionnaire, *complete baseline* and optional lifestyle questionnaire.

- **CSP 2006 Genomics of Gulf War Illness in Veterans** sub-study of MVP examining single-nucleotide polymorphism (SNP) genotyping data and self-reported Gulf War environmental exposures



# GW I PROTOCOL– VA INCLUSION CRITERIA

## **Inclusion criteria for all Veterans**

1. Adult participants aged 45-65 years at the time of enrollment.
2. Veteran of Operations Desert Shield/Desert Storm (ODS/S, deployed August, 1990 – June, 1991)
3. Ability to speak, read, and understand English (all Veterans meet this).
4. Willing and able to complete all study procedures
5. Participant has a primary care physician at the VA at the time of enrollment.
6. Able to provide informed consent.

## **Additional inclusion criteria for participants with presumed GWI for the NIH referral**

1. A self-reported illness narrative of the development of GWI as the consequence deployment to ODS/S (1995 survey, 585 surveys, and SNAC)
2. The symptoms must have occurred within 2 years of deployment.
3. Medical documentation of absence of symptoms before ODS/S deployment (DoD evidence of trauma and exposure history before deployment)
4. Documentation of a medical evaluation of persistent symptoms since deployment (including civilian records).
5. Modified Kansas definition (includes CDC)
  1. Fatigue after exercise as predominant component (a history of exercise intolerance or exercise induced worsening of symptoms)
  2. Allowance for normal illnesses of aging, such as hypertension and diabetes if the conditions are treated and are in demonstrable stable and normal ranges at the time of screening and assessment.
  3. Allowance of stable comorbid conditions such as PTSD, MDD and TBI that have not required hospitalization in the 5 years prior to recruitment. Severe TBI would be excluded.



# **GW I PROTOCOL– VA RECRUITMENT AND SCREENING**

- 1. Contact potential subjects from prior cohort studies in catchment areas via prior IRB approved methods (phone or mail or both)**
- 2. Phone assisted on line informed consent - permission to review records, web based screening assessment platform and phone interview**
- 3. Web based screening and chart review performed by recruitment staff, scripted phone interview**
- 4. Schedule on site (VA ) visit for screening physical and laboratories**



# GWIPROTOCOL– VA RECRUITMENT AND SCREENING

5. On site repeat informed consent process then screening labs for inclusion and exclusion criteria (CBC, Chm 23, HIV, Hep C hep B, urine toxicology, u/a, pregnancy test (female), )
6. On site review of history, deployment, PE, medication review and taper planning, administer screening questionnaire to make sure they meet symptom criteria, MRI screening and documentation



# GWI PROTOCOL– NIH REFERRAL

- Eligible Veterans will be connected to the NIH study staff who will schedule phenotyping visit at the NIH Clinical Center (5 VA sites)
- The NIH Clinical Center GWI team will contain a mix of NIH and VA employees.
- DCVA WRIISC VA staff will have NIH credentials (special volunteer) and establish contact with Veteran that will be maintained throughout duration of study
  - These VA employees will establish the initial contact with Veteran and will continue to work with study participants throughout duration of study.



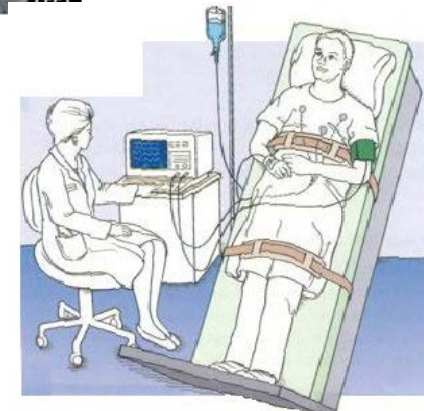
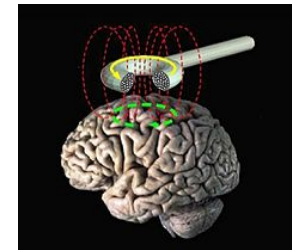
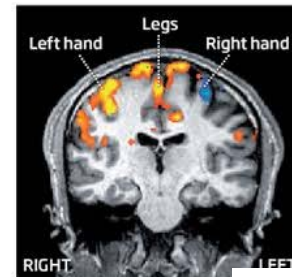




# GWI PROTOCOL– NIH PHENOTYPING

Designed to clearly define and document the characteristics of the study population and collect biological samples. Information collected is used to determine case status and eligibility for the exercise stress test.

1. Clinical assessment
2. Blood samples (includes heavy metal screening, immune and metabolic markers, genetic)
3. Urine collection for urine toxicology
4. Symptoms assessment (e.g. pain, sleep, fatigue, anxiety, depression, trauma, PTSD, global health, PROMIS)
5. Psychological assessment, Neurocognitive testing
6. OT eval, nutritional assessment
7. MRI – lower extremities, structured brain
8. Muscle strength testing
9. Activity monitor and fatigue diary, holter monitoring
10. Saliva sample, Buccal swab sample, stool samples (microbiome)
11. Lumbar puncture to collect cerebrospinal fluid
12. Optional: Autonomic testing, Immune cell collection
13. Exposure history and toxicology





# GWV PROTOCOL– NIH EXERCISE STRESS

Post-exertional malaise (PEM) will be explored using an exercise intervention designed to induce the symptoms. Cardiopulmonary exercise testing (CPET) using a cycle ergometer until patient reaches volitional fatigue is a validated method for inducing PEM. Measurements of participant's subjective experience, objective physiological function and biological specimens will be collected over 72 hours after CPET. Measurements are made immediately prior to CPET and 15 minutes, 1 hour, 4 hours, 24, 48, and 72 hours after the exercise intervention

Serial measurements made during this period include:

- Qualitative interviews
- Symptom questionnaires
- Blood, saliva, and stool measurements
- Physical activity monitoring
- Whole body energy use (metabolic chamber)
- Cellular energy use (Seahorse mitochondrial assay)

Participants will also undergo several tests before and CPET:

- Transcranial magnetic stimulation to explore the motor circuitry of physical fatigue
- Functional magnetic resonance imaging to explore the neuronal aspects of physical and cognitive fatigue as well as functional connectivity and volume-based evaluations.
- Neurocognitive performance

Additional tests will also be performed including electroencephalographic measures of sleep and a lumbar puncture at 48 hours after CPET



# **GW I PROTOCOL— VA CASE ADJUDICATION**

- **After completion of NIH visit, a de-identified case packet will be created with 3 experts and chair**
- **Teleconference to review patient data and deliberate**
- **Unanimous agreement necessary to be considered a GWI case**



# GWV PROTOCOL-- STUDY OUTCOMES

## ***Analysis Approach:***

***The analysis approach will be exploratory in nature.***

## **Primary Analytic Objectives:**

1. Characterization of the immune system and inflammatory signaling in blood and cerebrospinal fluid (CSF)
2. Characterization of the pattern of microbiome in gut, blood and CSF
3. Characterization of physical and cognitive fatigue using functional magnetic resonance imaging and transcranial magnetic stimulation
4. Effect of maximal exertion on neurocognition
5. Effect of maximal exertion on brain function and connectivity
6. Effect of maximal exertion on markers of immune dysfunction and inflammation
7. Effect of maximal exertion on metabolic function
8. Effect of maximal exertion on autonomic function
9. Effect of maximal exertion on gene expression profiles in blood and CSF



# **GW I PROTOCOL-- STUDY OUTCOMES**

## ***Computational Biology:***

***Cross-sectional comparative approach and serial PEM approach. Use of ME/CFS cohort to develop the data architecture and statistical modelling tools prior to availability of GWI data.***

## ***VA-NIH Data and Sample Repository:***

***NIH will exist as initial data and sample repository. When the initial planned analyses are completed, a combined VA-NIH repository will be created on NIH campus (perhaps with own freezers, etc). A combined VA-NIH data oversight committee will be created to evaluate applications for data use and sample access. A VA-NIH lab manager will be responsible for maintaining the sample repository and ensuring shipping integrity.***

## ***VA-NIH Publication Committee:***

***All presentations and publications of novel findings based on analysis of the GWI data and samples will be submitted for review to a joint VA-NIH publication committee.***





# VA STUDY WORKGROUP: COMPUTATIONAL STATISTICS

## Subject Matter Experts and Expert Advisors and Study Leadership Team

- Travis Craddock, PhD
- Gordon Broderick, PhD
- Kory Johnson, PhD, NIH

12/19/17 NIH and VA share computational approaches

2/16/18 VA modifications to the NIH exercise stress protocol

**Outcome:** Team develops a VA approach building on the existing model, syncing the exercise protocol / blood draw schedule to allow group-wise comparisons with other ongoing studies of GWI. Rather than creating an amendment to the NIH ME/CFS protocol, a VA sister protocol will be created adding VA modules.

- The NIH protocol collects xxxx at 1, 4-6, 24, 48 and 72 hours after CPET, corresponding timepoints with symptoms and questionnaires. The importance of adding a 15 minute timepoint was discussed. This timepoint allows targeting of biological subgroups even in small numbers, and information on mediators that may be occurring before symptoms appear. This information further allows for symptom based interventions instead of modeling? interventions.
- VA suggested doing 10 flexion exercises (10 reps) before collecting mitochondrial sample as the gold standard for seahorse assays.
- NIH plans to handle all data analyses with state of the art techniques at the end of the study. The VA protocol will include rolling analyses looking at preliminary data along the way.



# VA STUDY WORKGROUP: STUDY POPULATION/RECRUITMENT /VETERAN ENGAGEMENT

## Subject Matter Experts and Expert Advisors and Study Leadership Team

- Wes Ashford, MD, PhD, WRIISC-Palo Alto
- Michael Falvo, PhD, RCEP, WRIISC-NJ
- Drew Helmer, MD, MS, Director, WRIISC-NJ
- Stephen Hunt, MD, Director, Post-Deployment Integrated Care Initiative
- Kristy Lidie, PhD, Program Manager, DoD-CDMRP
- Jeffrey Nast, JD, RAC GWVI member

1/12/18 Redefine the study population, inclusion criteria, veteran engagement

1/26/18 Eligibility criteria, veteran engagement continued *\*Biweekly recurring meetings set*

**Outcome:** Following more information from CRADO, the team redefined the veteran population within the study time period and budget. The team decided on deployed study groups with broader entry criteria and allowing comparability to the NIH CFS protocol. Discussed ideas for veteran engagement and recruitment drawing on experience from existing GW studies and clinical expertise.

### Study population

75 GWI subjects –  
50 GWI Veterans deployed to Gulf War 1  
25 asymptomatic Veterans deployed to GW1

### 5 Sites selected

East Orange NJ WRIISC, Palo Alto WRIISC,  
Wash DC WRIISC, Seattle VAMC, Miami VA

### Inclusion Criteria for Veterans with presumed GWI

- Age 45-65 years and Veteran deployed to Gulf War 1
- Participant has a VA primary care physician at the time of enrollment
- Self-reported GWI developed as consequence of deployment to ODS/S within 2 years of deployment
- Med documentation of no sx's before deployment, persistent sx's since deployment
- Modified Kansas definition with fatigue after exercise predominant component
- Stable comorbid conditions not requiring hospitalization in past 5 years allowed

### Subjects will be recruited from the following sources

1. The 1995 National Health Survey of Persian Gulf Veterans and Their Families (NHS)
2. CSP 585 'The Gulf War Era Cohort and Biorepository' (GWECB)
3. MVP / CSP 2006 Genomics of Gulf War Illness in Veterans sub-study



# VA STUDY WORKGROUP: EXPOSURES AND TOXICOLOGY/ MITOCHONDRIA

## Subject Matter Experts and Expert Advisors and Study Leadership Team

- Wes Ashford, MD, PhD, WRIISC-Palo Alto
- Michael Falvo, PhD, RCEP, WRIISC-NJ
- Drew Helmer, MD, MS, Director, WRIISC-NJ
- Stephen Hunt, MD, Director, Post-Deployment Integrated Care Initiative
- Kristy Lidie, PhD, Program Manager, DoD-CDMRP
- Jeffrey Nast, JD, RAC GWVI member
- Jim O'Callaghan, PhD, CDC-NIOSH
- Kim Sullivan, PhD, GWI Research Consortium
- Karen Block, PhD, VACO

2/9/18 Long term measurable toxins, instruments available bioassays, adding microtoxins to the NIH protocol

2/23/18 Existing survey instruments reviewed, toxicology and mitochondrial experts

**OUTCOME:** Existing surveys that have included GW era exposures will be adapted for use 27 years since deployment. 15 minute after peak exercise stress test blood sample added to measure...

Consider aggravated DNA damage from lifelong exposure, fat biopsy, autoantibodies from CSF and repair capacity of mitochondria, energy questions, exercise intervention and analytes, muscle tissue, PBMC in Seahorse assay, motor protein via scanning EM, consider length in addition to number of mitochondria per cell in imaging data

### Surveys and Patient Questionnaires Reviewed

- 1995 National Health Survey
- CSP 585 GW Era Veteran's Survey
- Structured Neurotoxicant Assessment Checklist (SNAC)
- Airborne Hazards and Open Burn Pit Registry self-reported questionnaire
- The Quick Environmental Exposure and Sensitivity Inventory (QEESI)
- Systemic sclerosis risk factor interview
- WRIISC intake packet
- CSP 2006 Survey



# VA STUDY WORKGROUP: VETERAN ENGAGEMENT

## **Subject Matter Experts, Expert Advisors and Study Leadership Team**

- Wes Ashford, MD, PhD, WRIISC-Palo Alto
- Michael Falvo, PhD, RCEP, WRIISC-NJ
- Drew Helmer, MD, MS, Director, WRIISC-NJ
- Stephen Hunt, MD, Director, Post-Deployment Integrated Care Initiative
- Kristy Lidie, PhD, Program Manager, DoD-CDMRP
- Jeffrey Nast, JD, RAC GWVI member
- Kim Sullivan, PhD, GWI Research Consortium
- Karen Block, PhD, VACO
- Peter Greene, Veterans of Modern Warfare, CDMRP GWI Consumer Reviewer
- Vera Roddy, USAF, GW Veteran, CDMRP GWI Consumer Reviewer

- 1/12/18 Discussed CDMRP GWI research program veteran outreach and engagement paper/video, GW Registry, use of personal letters, focus groups, recruiting from military units vs VA users
- 1/26/18 Considered Khamisiyah population, national recruitment vs recruitment at specific sites, civilian population in Miami as source of healthy controls, consider active duty veterans getting ready to retire
- 3/9/18 Critical components of existing surveys compiled into one structured interview, GW veteran feedback, inclusion and exclusion criteria

## **OUTCOME:**



# VA STUDY LEADERSHIP TEAM

## **Principal Proponents / Study Co-Chairs**

Nancy Klimas, MD

Matthew Reinhard, PsyD

## **Co-Investigators**

Brian Walitt, MD, MPH, NIH ME/CFS Study Lead

Vic Kalasinsky, PhD, Gulf War Research Program Manager

Michelle Costanzo, PhD, DC WRIISC

Karen Block, PhD, Gulf War Research Program Manager

## **Coordinating Center: CSPEC - Durham**

Dawn Provenzale, MD, MS, Director

Beth Hauser, MD, Statistical Geneticist

Lin Gu, MS, Biostatistician

Marsha Turner, MS, Project Manager

Brian Han, Research Assistant





# PLANNING COMMITTEE

## **VA ADVISORS**

Vicky Davey, PhD, MPH  
Jon VanLeeuwen, PhD

## **NIH ADVISORS**

Brian Walitt, PhD, MPH  
Vicky Whittemore, PhD

## **SUBJECT MATTER EXPERTS**

Stephen Hunt, MD  
Bill Meggs, MD, PhD  
Jeffery Nast, JD  
Jim O'Callaghan, PhD  
Kim Sullivan, PhD

## **COMPUTATIONAL BIOLOGY CO- INVESTIGATORS**

Gordon Broderick, PhD  
Travis Craddock, PhD

## **SITE INVESTIGATORS**

Wes Ashford, MD, PhD, Palo Alto  
WRIISC  
Michael Falvo, PhD, RCEP, NJ  
WRIISC  
tbd, DC WRIISC  
tbd, Miami VAMC  
Steven Hunt, MD, Seattle VAMC

## **UNDIAGNOSED DISEASE**

### **NETWORK**

David Adams,  
Cynthia Tift, MD

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Peter Greene, Veterans of  
Modern Warfare  
Vera Roddy, USAF  
David Winnett, USMC (Ret)

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# QUESTIONS?