U.S. Department of Veterans Affairs

Deep Phenotyping of Gulf War Illness: A VA-NIH Partnership

Presented to: Chronic Fatigue Syndrome Advisory Committee (CFSAC) to HHS
June 21, 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

Project IN-DEPTH

VA - NIH

INVESTIGATIVE DEEP PHENOTYPING STUDY

OF GULF WAR VETERAN HEALTH

PROJECT IN-DEPTH

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

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

VA VA sites lead Veteran recruitment, screening and selection

NIH Phenotyping Visit, 10 day inpatient admission at the NIH Clinical Facility

VA Post NIH follow-up visit debrief and review test results

PROJECT IN-DEPTH: SPECIFIC AIMS

Objectives of the VA Partner Protocol

- To provide an effective recruitment, screening, and monitoring process for the protocol by identifying representative GWI Veteran participants, documenting their health and GWI case status, and ensuring safety and health care coordination during study participation.
- To provide the VA infrastructure and scientific support for this VA/NIH collaboration.
- To use a machine learning algorithm to develop subgroup strategies for veterans with GWI based on all the screening data from both ill and non-ill deployed veterans.
- To provide the computational modeling of GWI using the NIH and VA data sets to provide targeted interventions through virtual modeling of the illness.

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 VA and non-VA 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.

PROJECT IN-DEPTH: TIMELINE

Ongoing
- Weekly leadership meetings, special topic workgroups, specialty subgroups, Co-Chair protocol development meetings
- **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: VA methods and computational biology
- 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

PROJECT IN-DEPTH: TIMELINE

Apr
- Protocol development post planning meetings, incorporating VA specific measures/additions at NIH

May
- Finalize protocol for VA scientific review, prepare review package, determine budget and needs of recruitment sites. Determine specimen storage and database tracking plans

Jun-Jul
- Submit for VA scientific review
- Prepare IAA, regulatory, data security/sharing agreements, IRB application
- Submit protocol for NIH Scientific Review

Aug-Sep
- Data sharing, regulatory documents, IAA signed upon NIH approval.
- Receive IRB and R&D approvals, data security forms/agreements signed

Oct
- **Study kickoff meeting:** Implementation, site logistics, administration

Nov-Feb
- Operational start-up: Site preparation, training, NIH admin, set up data sharing portals, tracking database
- Monthly Executive Committee meetings

March 2019
- **Recruitment begins**

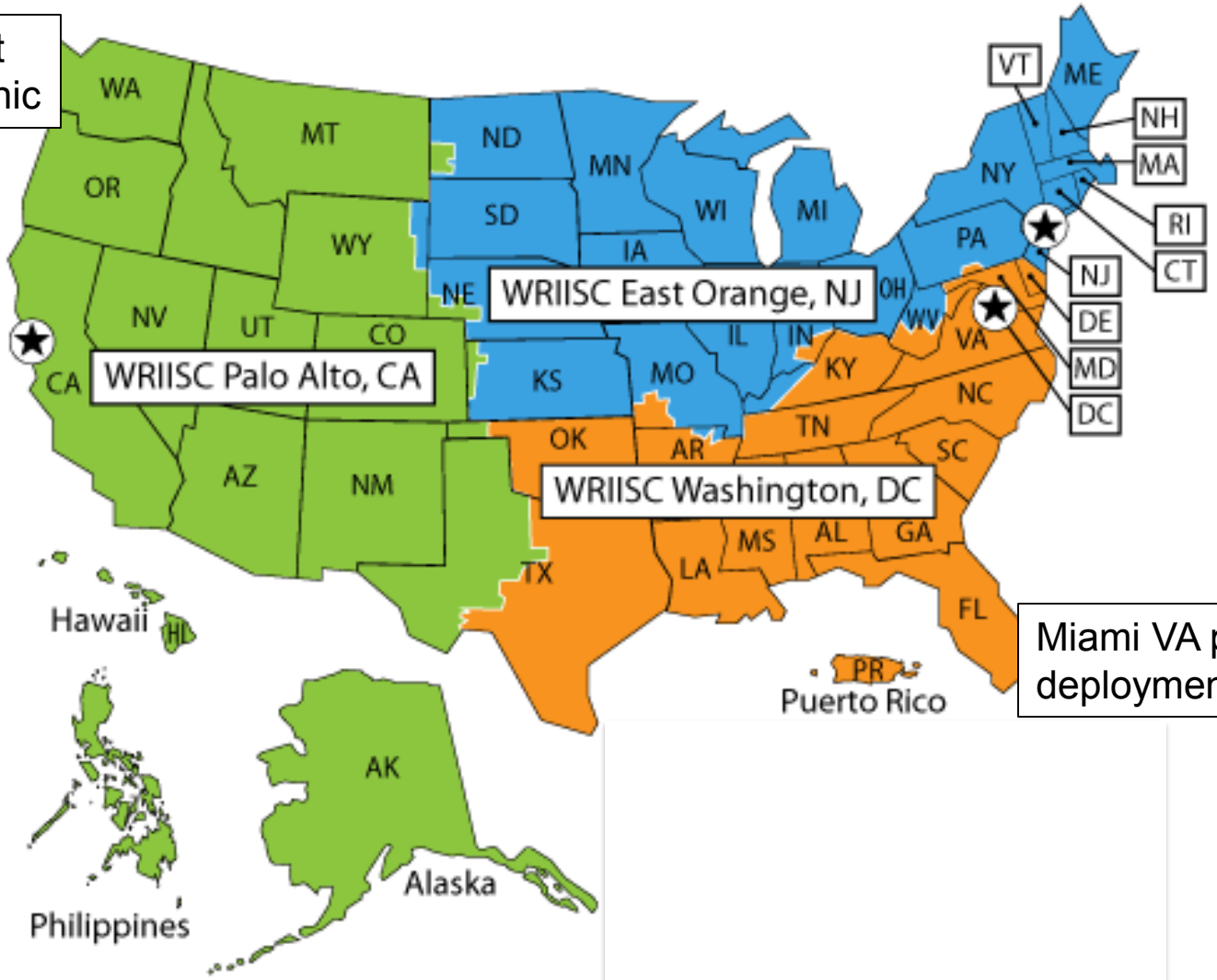
PROJECT IN-DEPTH: VA SUBJECTS

Up to 75 Veterans will be recruited to be part of 2 study groups:

- 50 GWI Veterans deployed to ODS/S
- 25 asymptomatic Veterans who were deployed to ODS/S

PROJECT IN-DEPTH: VA SITES

Seattle VA post deployment clinic



Miami VA post deployment clinic

PROJECT IN-DEPTH: 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).

Ft Devens Cohort

- **Longitudinal Health Survey of the Ft. Devens Cohort of 1991 Gulf War Veterans**
  A 20-year study of 2,949 veterans that returned from the Persian Gulf to Ft. Devens, MA assessed at several time points for self-reported combat exposure and psychological well-being upon return in 1991, a second survey in 1992-1994 adding functioning and health status, and collecting neuropsych evals and military history on a subset (n=220) from 1994-1996.

CSP 585 Gulf War Era Cohort

- **CSP 585 The Gulf War Era Cohort and Biorepositor' (GWECB)**
  A longitudinal research database and linked biorepository integrating epidemiologic, survey, clinical, and environmental exposure data from a nationally representative longitudinal cohort of 1276 1990-1991 Gulf War Era Veterans. GWAS is currently planned.

PROJECT IN-DEPTH: 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. 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 eval 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.

GWI PROTOCOL– VA RECRUITMENT AND SCREENING

- Identify potential participants from the cohorts and generate targeted outreach mailings (5 VA sites)
- Chart review (5 VA sites) --- depending on consent specifications of the different cohort studies, pre-review of patient data may occur. Review of medical evaluation of persistent symptoms since deployment.
- Phone review and web-based surveys of the entry criteria (5 VA sites)
- Ineligible Veterans will be referred to MVP or additional GW clinical or research resources if Veterans express interest

PROJECT IN-DEPTH: METHODS

Purpose: To determine case status and eligibility for the NIH deep phenotyping visit

Recruitment

Send Invitation Letters to Potential GW Study Subjects

Subjects may opt out or call in

↓

Contact by Veteran National Recruiter

Provide study details, determine initial interest and eligibility

↓

Screening

Referral to Local Site Research Team

Phone screening

Web-based screening surveys

Medical record review

In-person clinical assessment

Medication washout planning

↓

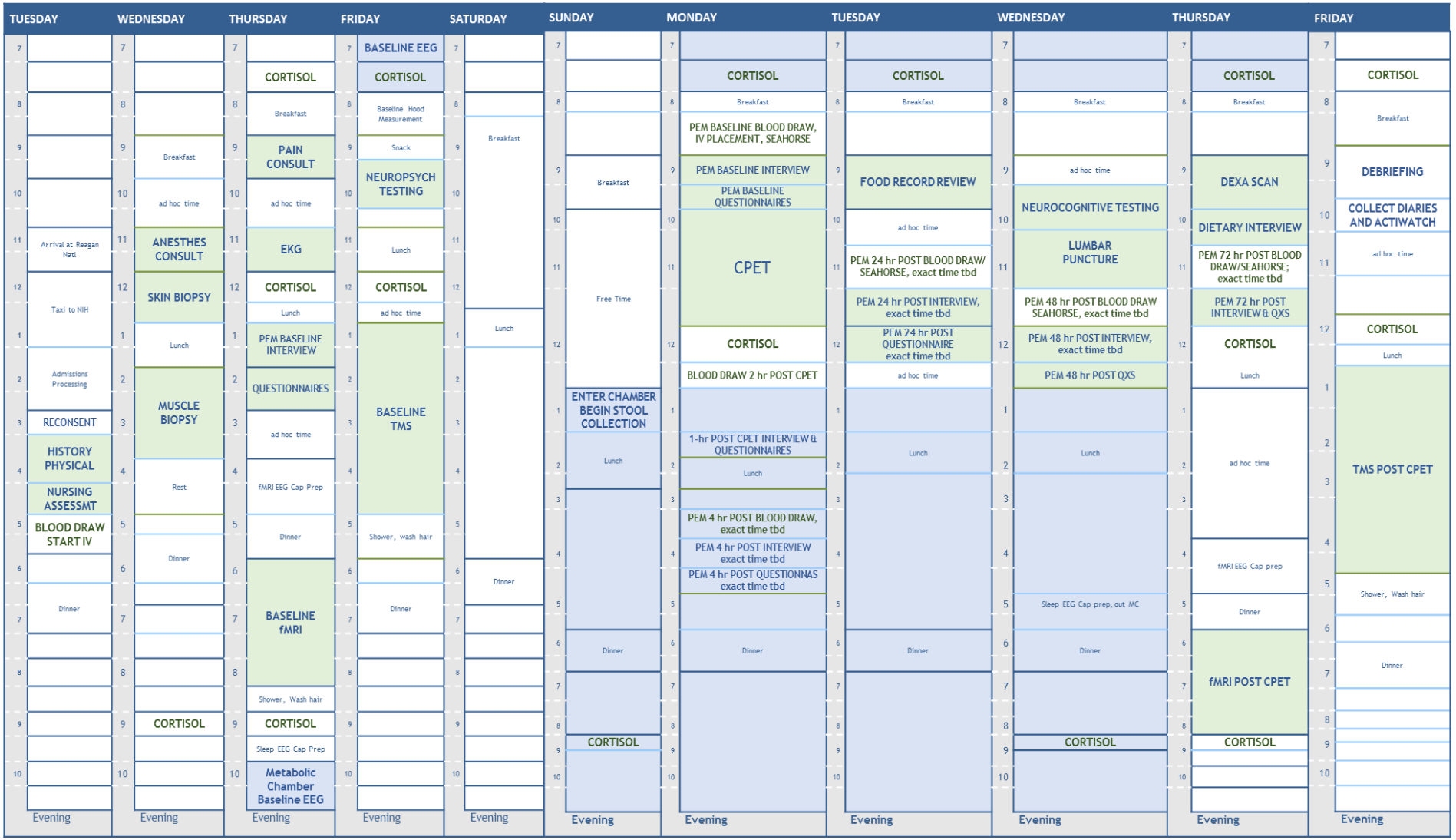
Warm handoff to NIH

PROJECT IN-DEPTH: NIH REFERRAL

- Eligible Veterans will be connected to the NIH study staff who will schedule the deep phenotyping visit at the NIH Clinical Center
- The GWI team at the NIH Clinical Center will contain a mix of NIH and VA employees
- DCVA WRIISC VA staff will have NIH credentials (special volunteer)

These DCVA employees will establish the initial contact with the Veteran and will continue to work with study participants throughout the duration of the study

PROJECT IN-DEPTH: NIH DEEP PHENOTYPING VISIT



= Metabolic Chamber

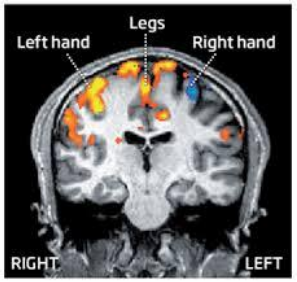
PROJECT IN-DEPTH: NIH PHENOTYPING VISIT

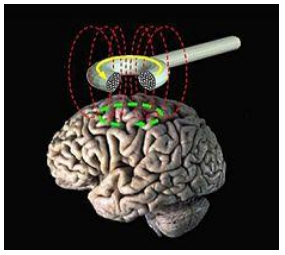
10 day inpatient admission at the NIH Clinical Facility

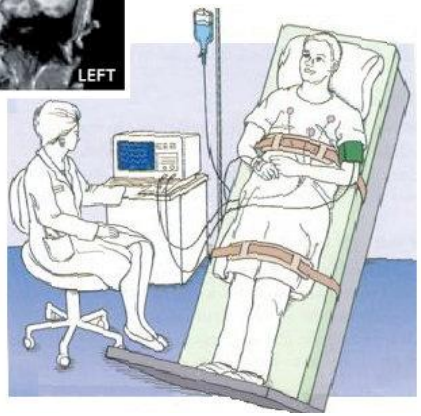
After case status and eligibility for the exercise stress test have been clearly determined through the VA GWI protocol.

Designed to clearly define and document the characteristics of the study population and collect biological samples.

1. Blood samples (includes heavy metal screening, immune and metabolic markers, genetic)
2. Urine collection for urine toxicology
3. Symptoms assessment (e.g. CFS symptom inventory, pain, sleep, fatigue, anxiety, depression, trauma, PTSD, global health, PROMIS, IBS)
4. Psychological assessment
5. 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







PROJECT IN-DEPTH: EXERCISE STRESS TEST

10 day inpatient admission for phenotyping and exercise stress test (up to 12 months after initial screening)

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
- fMRI to explore the neuronal aspects of physical and cognitive fatigue as well as functional connectivity and volume-based evaluations.
- Neurocognitive performance

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

PROJECT IN-DEPTH: 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

PROJECT IN-DEPTH: 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.

PROJECT IN-DEPTH: CASE ADJUDICATION

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

PROJECT IN-DEPTH WORKGROUP: COMPUTATIONAL BIOLOGY

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.

PROJECT IN-DEPTH 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 sxs before deployment, persistent sxs 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

PROJECT IN-DEPTH 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

PROJECT IN-DEPTH 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:

PROJECT IN-DEPTH: 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
Karen Block, PhD, Director of VA Gulf War Research
Michelle Costanzo, PhD, DC WRIISC

Coordinating Center: CSPEC - Durham

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Beth Hauser, MD, Statistical Geneticist
Lin Gu, MS, Biostatistician
Marsha Turner, MS, Project Manager/ VA Gulf War Program Manager
Kellie Sims, Data Manager
Brian Han, Research Assistant
Ashlyn Press, Research Coordinator
Blair Chesnut, Data Programmer

PROJECT IN-DEPTH: ADDITIONAL CO-INVESTIGATORS

Drew Helmer, MD, Local Site Investigator, NJ WRIISC

Michael Falvo, PhD, RCEP, Local Site Investigator, NJ WRIISC

Wes Ashford, MD, PhD, Local Site Investigator, Palo Alto WRIISC

Steven Hunt, MD, Local Site Investigator, Seattle VAMC

Erin Dursa, PhD, MPH, Post-Deployment Health

Travis Craddock, PhD, Computational Biologist

Gordon Broderick, PhD, Computational Biologist

PROJECT IN-DEPTH: PLANNING COMMITTEE

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Jon VanLeeuwen, PhD

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QUESTIONS?