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

Presented to: Research Advisory Committee on Gulf War Veterans’ Illnesses
September 18, 2018

Matthew Reinhard, PsyD, Director, DC WRIISC, Washington DC VA Medical Center
Nancy Klimas, MD, Director, Institute for Neuro-Immune Medicine, Nova Southeastern University, Gulf War Illness Research Program Miami VA Medical Center
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.
Project IN-DEPTH

VA - NIH

INVESTIGATIVE DEEP PHENOTYPING STUDY

OF GULF WAR VETERAN HEALTH
VA Study Co-Chairs: Nancy Klimas, MD and Mathew Reinhard, PsyD

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

VA sites lead Veteran recruitment, screening and selection

NIH Phenotyping Visit, 10-18 day inpatient admission at the NIH Clinical Facility

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

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<th>Month</th>
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| 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 |

**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
PROJECT IN-DEPTH: TIMELINE

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

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

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

Sep-Oct
- Finalize regulatory documents, data security/data sharing agreements, IAA signed upon NIH approval
- IRB and R&D preparation and submission

Nov-Jan
- Attend VA CSSEC review
- Operational start-up: Site preparation, training, NIH admin, set up data sharing portals, tracking database

Jan-Mar
- Study kickoff meeting: Implementation, site logistics, administration
- Monthly Executive Committee meetings

Mar-April
- Recruitment begins
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
• **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).

• **Longitudinal Health Survey of the Ft. Devens Cohort of 1991 Gulf War Veterans**

• **CSP 585 The Gulf War Era Cohort and Biorepository' (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.
Inclusion criteria for all Veterans

1. Adult participants aged 45-65 years at the time of enrollment
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.
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<th>CDC</th>
<th>KANSAS</th>
<th>MODIFIED KANSAS</th>
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<td>One symptom required in at least two of the following domains:</td>
<td>Multiple moderately severe symptoms (&gt;=6 months) in at least 3 of the 6 symptom domains:</td>
<td>Kansas definition that also meets the CDC case definition, and includes the following modifications / allowances:</td>
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<tr>
<td>1) Fatigue</td>
<td>1) fatigue and sleep problems</td>
<td>1) Fatigue: Predominant component is fatigue after exercise (a history of exercise intolerance or exercise induced worsening of symptoms)</td>
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<td>2) mood and cognition (feeling depressed, difficulty remembering/concentrating, feeling moody, anxious, trouble finding words, difficulty sleeping)</td>
<td>2) somatic pain symptoms</td>
<td>2) Common diseases of aging, such as hypertension and diabetes, if the conditions are treated, demonstrably stable, and within normal range at the time of screening and assessment.</td>
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<td>3) musculoskeletal (joint pain, joint stiffness, muscle pain)</td>
<td>3) neurologic/cognitive/mood symptoms</td>
<td>3) Stable comorbid conditions, such as PTSD, MDD and mild TBI, that have not required hospitalization in the five years prior to recruitment.</td>
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<td>No exclusions.</td>
<td>Exclusions: Any serious medical or psychiatric diagnosis that accounts for symptoms, or prevents accurate symptom reporting.</td>
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<td>Severity not included in determining case.</td>
<td>Must have at least 1 moderately severe symptom or 2 or more symptoms within each symptom domain.</td>
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IOM 2014 CMI Case Definition Report recommended VA use CDC and Kansas case definitions because they capture the most commonly reported symptoms of Gulf War Illness (National Academies Report, 2014).

Clinical evaluation requires a thorough physical exam, mental status exam, minimum battery of lab tests. Symptoms should be assessed systematically using standardized instruments that assess functional status and symptom domains. Some medical conditions Some medical conditions will resolve or are adequately managed with treatment and should therefore be considered temporary exclusions (Reeves et al., 2003).
Gulf War

Modified Kansas
Includes the following allowances:
- Fatigue after exercise as predominant component.
- Common diseases of aging (e.g., HTN and DM) if treated, stable, and within normal range at screening.
- Stable comorbid conditions (e.g., PTSD, MDD, mTBI) that have not required hospitalization in past 5 years.

Kansas Criteria
Multiple moderately severe sx (≥6 months) in at least 3 of 6 sx domains:
- fatigue and sleep problems
- somatic pain symptoms
- neurologic/cognitive/mood symptoms
- gastrointestinal symptoms
- respiratory symptoms
- skin symptoms

Exclusions: Any serious med/psych dx that accounts for sx, or prevents accurate sx reporting.
Must have at least 1 moderately severe sx or 2 or more sx within each symptom domain.
Sx developed as a consequence of deployment to ODS/S, August, 1990 – June, 1991.
• 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
**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
Additional phone screening
Web-based screening surveys
Medical record review
In-person clinical assessment
Medication washout planning

Qualitative interviews

Warm handoff to NIH
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

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= Metabolic Chamber
10-18 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
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.
**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
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.
Principal Proponents / Study Co-Chairs
   Nancy Klimas, MD
   Matthew Reinhard, PsyD

Co-Investigators
   Brian Walitt, MD, MPH, NIH ME/CFS Study Lead
   Michelle Costanzo, PhD, DC WRIISC
   Drew Helmer, MD
   Wes Ashford, MD

Coordinating Center: CSPEC - Durham
   Dawn Provenzale, MD, MS, Director
   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
Travis Craddock, PhD, Computational Biologist
Gordon Broderick, PhD, Computational Biologist
Beth Hauser, MD, Statistical Geneticist
Erin Dursa, PhD, MPH, Post-Deployment Health
Katherine Bloeser, PhD, Qualitative Investigator
PROJECT IN-DEPTH: PLANNING COMMITTEE

VA ADVISORS
Vicky Davey, PhD, MPH
Jon VanLeeuwen, PhD

NIH ADVISORS
Avi Nath, MD
Vicky Whittemore, PhD

EXPERT ADVISORS
Jim Breeling, MD
Erin Dursa, PhD, MPH
Steve Hauser, MD
Joe Holston, MBA
Grant Huang, PhD, MPH
Karen Jeans, PhD, CCRN, CIP
David Kearney, MD
Kristy Lidie, PhD
Avindra Nath, MD
Kristy Lidie, PhD
Aaron Schneiderman, PhD, MPH, RN
Marc Simard, MD
Lea Steele, PhD
Jon Vanleeuwen, PhD
Nick Verne, MD

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

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

UNDIAGNOSED DISEASE NETWORK
David Adams,
Cynthia Tifft, MD