

**VA**



U.S. Department  
of Veterans Affairs

# Gulf War Research Update and Strategic Plan

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Department of Veterans Affairs

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# VA Office of Research and Development

## **MISSION:**

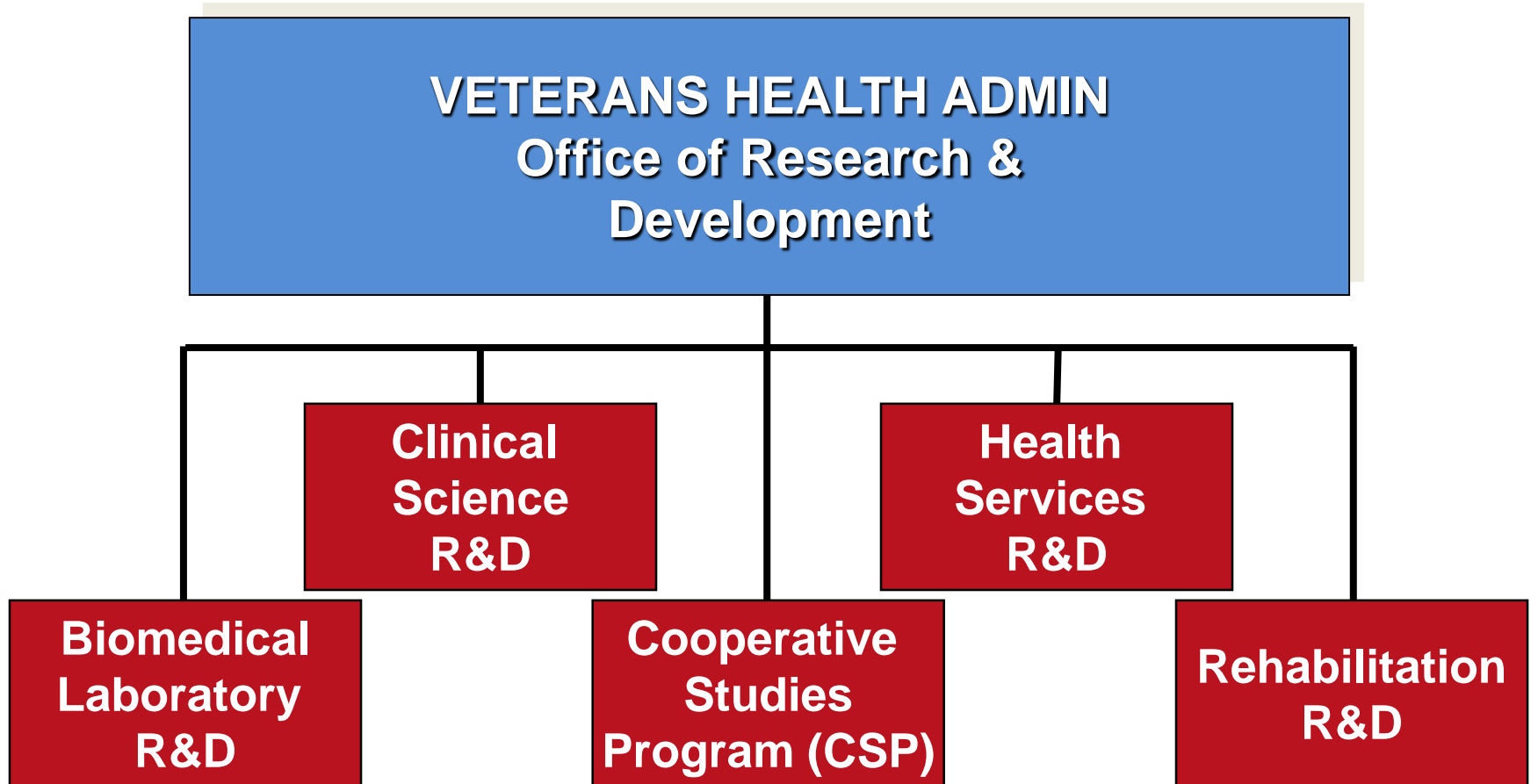
**To discover knowledge and create innovations that advance health care for our Veterans and our Nation**

## **VISION:**

**To be the premier research organization leading our Nation's efforts to enhance the health and well-being of Veterans by developing evidence-based clinical care and delivery systems improvements**



# VA Office of Research and Development





# Gulf War Research – Requests for Applications

## **Biomedical Laboratory Research & Development (BLR&D):**

BX-18-011

Award for Research on Gulf War Veterans' Illnesses (GWVI)

BX-18-012

Pilot Projects for Research on Gulf War Veterans' Illnesses (GWVI)

BX-18-007

Collaborative Merit Review Award for Research

## **Clinical Science Research & Development (CSR&D):**

CX-18-011

Award for Research on Gulf War Veterans' Illnesses (GWVI)

CX-18-012

Pilot Projects for Research on Gulf War Veterans' Illnesses (GWVI)

CX-18-013

Award for Research on Treatments for Gulf War Veterans' Illnesses (GWVI) – (clinical trial)

## **Health Services Research & Development (HSR&D):**

HX-18-014

Targeted Solicitation for Service-Directed Research Award on Health Services Research on the Care of Gulf War Veterans



# VA Office of Research and Development

- **VA research is driven by improving health care for all Veterans**
  - Investigator-initiated research (Clinician Researchers)
    - Pilot projects
    - Merit review
    - Clinical Trials
    - Career Development Awards
  - Service-directed research
  - Cooperative Studies Program (CSP)
- **Public Access to Information about VA/ORD funded research**
  - <http://clinicaltrials.gov> Information on current and past clinical trials
  - <http://projectreporter.nih.gov/> Information on current and previously funded research projects
  - <http://www.ncbi.nlm.nih.gov/pubmed> Published results of research studies
  - <http://www.rehab.research.va.gov/jour/jourindx.html> Official Journal of ORD



# VA/ORD-Based FACA Committees

- **National Research Advisory Council (NRAC)**
  - To provide advice to the Under Secretary for Health and the Secretary of Veterans Affairs on research and development sponsored and/or conducted by the Veterans Health Administration, to include policies and programs of the Research and Development Office
- **Research Advisory Committee on Gulf War Veterans' Illnesses (RACGWVI)**
  - To provide advice and make recommendations to the Secretary of Veterans Affairs on proposed research plans and strategies related to understanding and treating the health consequences of military service in the Southwest Asia theater of operations during the 1990 - 1991 Gulf War
  - Mandated by Congress in 1998; first chartered in January, 2002
- **Genomic Medicine Program Advisory Committee (GMPAC)**
  - To provide advice to the Secretary on the scientific and ethical issues related to the establishment, development, and operation of the Program in order to further VA's medical research in providing Veterans with Medical care and treatment.



# VA-ORD Funding - Gulf War Research (2008-2017)

| Fiscal Year (FY) | VA Merit Review | Contract   | FY Total    |
|------------------|-----------------|------------|-------------|
| 2008             | \$ 6.93 M       | \$ 15.00 M | \$ 21.93 M  |
| 2009             | \$ 9.63 M       | \$ 6.97 M  | \$ 16.60 M  |
| 2010             | \$ 11.57 M      | \$ 2.29 M  | \$ 13.86 M  |
| 2011             | \$ 5.54 M       | \$ 0.03 M  | \$ 5.57 M   |
| 2012             | \$ 6.72 M       |            | \$ 6.72 M   |
| 2013             | \$ 7.94 M       |            | \$ 7.94 M   |
| 2014             | \$ 9.73 M       |            | \$ 9.73 M   |
| 2015             | \$ 11.63 M      |            | \$ 11.63 M  |
| 2016             | \$ 12.34 M      |            | \$ 12.34 M  |
| 2017             | \$ 13.56 M      |            | \$ 13.56 M  |
| Total 2008-2017  | \$ 95.59 M      | \$ 24.29 M | \$ 119.88 M |



# VA-ORD Gulf War Research Funding

|                         | <b>Proposals<br/>Received</b> | <b>Projects<br/>Funded</b> | <b>Funds<br/>Approved</b> |
|-------------------------|-------------------------------|----------------------------|---------------------------|
| <b>Spring/Fall 2011</b> | 26                            | 3                          | \$ 4.0 M                  |
| <b>Spring/Fall 2012</b> | 32                            | 7                          | \$ 11.4 M                 |
| <b>Spring/Fall 2013</b> | 35                            | 7                          | \$ 12.6 M                 |
| <b>Spring/Fall 2014</b> | 40                            | 5                          | \$ 7.5 M                  |
| <b>Spring/Fall 2015</b> | 33                            | 8                          | \$ 13.2 M                 |
| <b>Spring/Fall 2016</b> | 26                            | 4                          | \$ 2.5 M                  |
| <b>Spring 2017</b>      | 16                            | 3                          | \$ 2.8 M                  |
| <b>Fall 2017</b>        | 13                            | 2                          | \$ 2.5 M                  |





# Active Gulf War Research Projects, 2017 (1 of 3)

## Treatments/Clinical Trials

- Impact of exercise training on pain and brain function in Gulf War Veterans
- Transcranial, Light-Emitting Diode (LED) Therapy to Improve Cognition in GWVI
- Complementary Neurosteroid Intervention in Gulf War Veterans' Illnesses
- Cognitive Rehabilitation Therapy for Gulf War Veterans
- Complementary and Alternative Medicine in Veterans with Gulf War Illnesses
- RCT of Duloxetine and Pregabalin for the treatment of GWI in Veterans
- Healthcare Utilization Patterns and Associated Costs for Gulf War I Era Veterans
- WRIISC as a Model of Care for Chronic Multisymptom Illness
- Novel Interventions for Gulf War Veterans' Illnesses
- Pilot Test of Telephone-Delivered Cognitive Behavioral Therapy for Insomnia for Veterans with Gulf War Illness
- Randomized, Double-blind Placebo-controlled Phase III Trial of Coenzyme Q10 in Gulf War Illness
- Evaluation of a Mindfulness-Based Intervention for Gulf War Illness
- Predictors of Response to Insomnia Treatments for Gulf War Veterans
- Listening to Gulf War Vets: A Qualitative Inquiry into the Health Experience and Treatment of those with Chronic Multisymptom Illness



# Active Gulf War Research Projects, 2017 (2 of 3)

## **Biomarkers/Mechanisms**

- Examination of Cognitive Fatigue in Gulf War Illness Using fMRI
- Longitudinal assessment of Gulf War veterans with suspected Sarin exposure
- Multimodal Biological Assessment of Gulf War Illness
- National Health Survey of Persian Gulf Veterans and their Families
- Somatic hypersensitivity in Veterans with IBS
- Women vs. Men with GWI: Differences in Computational Models and Therapeutic Targets
- Genomics of Gulf War Illness in Veterans
- Post Exertional Malaise in GWI: Brain Autonomic and Behavioral Interactions
- A Translational Medicine Approach to Gulf War Illness: From Cells to Therapy
- Mechanisms of Gulf War Illness



# Active Gulf War Research Projects, 2017 (3 of 3)

## Model Systems

- Central Mechanisms Modulating Visceral Sensitivity
- Immunoregulation of Myelin Specific T Lymphocytes
- Sleep Neurobiology and Circuitry
- Understanding Pain of Gastrointestinal Origin in Women that Serve in OEF/OIF
- Identification of Plasma Biomarkers of Gulf War Illness Using "omic" Technology
- Gulf War Exposures and the Molecular Mechanisms of Paternal Reproductive Risk
- Novel neurotrophic therapies in an optimized mouse model of GWVI
- Neuroinflammation, Oxidative Stress, and Hippocampal Defects in GWI
- Immune Basis for Hippocampal Cholinergic Deficits in Pyridostigmine-treated Rats
- Gulf War neurotoxicants and acquired cognitive and neuropsychological dysfunction
- Maintenance of Telomerase Activity as a Treatment for Gulf War Illness
- Treating GWI immune and metabolic disturbances by targeting lipid metabolism
- Neuroinflammation and abnormal behavior following combined chemical exposures and bacterial infection



# Gulf War Research Projects

## **Selected for Funding**

- Biomarkers in Gulf War Veterans
- Cytokines in Gulf War Veterans with IBS
- Gut microbiota in Veterans with Gulf War illness
- Exercise tolerance in ill Gulf War Veterans
- Cognitive fatigue in Gulf War Veterans (renewal)

## **NIH-VA Collaboration**

- Deep phenotyping of Gulf War illness



# RACGWVI Recommendations

## 2016 Recommendations

1. Update Existing “Gulf War Research Strategic Plan 2013-2017 (2015 Update)
2. Establish Post-Deployment Centers of Excellence – three tiers; hub-and-spoke
3. Increase Strategic Partnerships for GW Research (non-VA entities)
4. Identify Barriers to Recruiting Research Participants
5. Address (i) Limitations of ICD-9/10 for GWI & (ii) Comparison Group issue

## 2017 Recommendations

1. Partner with the National Institutes of Health to conduct a deep phenotyping study of Gulf War Illness and Chronic Fatigue Syndrome
2. Commit to piloting and establishing a coordinated system of centers and expertise focused on complex chronic conditions of post-deployment, and operationalize the beginning stages of such a system by 2019



# Gulf War Research Biorepositories

- **Gulf War Veterans' Illnesses Biorepository**
  - Enrolling Veterans to obtain medical records
  - Brain and spinal cord tissue to be collected post-mortem
  - [http://www.research.va.gov/programs/tissue\\_banking/gwvib/default.cfm](http://www.research.va.gov/programs/tissue_banking/gwvib/default.cfm)
  
- **CSP #585 Gulf War Era Cohort and Biorepository**
  - Deployed and non-deployed Veterans (1276 participants)
  - Users of VA health care and non-users
  - Surveys and blood collection
  - Genomic data
  - <http://www.research.va.gov/programs/csp/585/default.cfm>



# Gulf War Research Reports

- **Gulf War Illness: Improvements Needed for VA to Better Understand, Process, and Communicate Decisions on Claims (GAO 17-511)**
  - June 2017
  - <http://www.gao.gov/assets/690/685562.pdf>
- **Gulf War and Health, Volume 11: Generational Health Effects of Serving in the Gulf War**
  - Sep 2016 – Sep 2018 (First meeting Jan 12, 2017)
  - Closed meetings (Mar 16; Jul 18; Sep 18, 2017)
  - Open meeting (Nov 7, 2017)
  - <http://www8.nationalacademies.org/cp/projectview.aspx?key=49832>



# Gulf War Research – VA-DoD Coordination

- **Regular briefings/updates between Gulf War Program Managers in VA/ORD and DoD/CDMRP**
- **Periodic review of proposals submitted/funded between agencies**
- **Annual Report to Congress (jointly with DoD)**
  - <https://www.research.va.gov/pubs/GulfWarSummary15.cfm>
- **Joint VA/DoD Working Groups (Deployment Health and Medical)**
- **Participation in CFS Conference and GWI Workshop in Ft. Lauderdale, October 2016**
- **GAO recommendation – Case Definition for Gulf War illness**
- **Field-Based meeting to promote collaboration – September 2017 and March 2018**
- **NIH-VA Deep Phenotyping study**
- **Telephone calls with Canada, UK, Australia, and New Zealand**
- **Individual Longitudinal Exposure Record (ILER)**





# VA-ORD Gulf War Research Strategic Plan

- **Gulf War Research Strategic Plan, 2013-2107**
- <http://www.research.va.gov/resources/pubs/docs/GWResearch-StrategicPlan.pdf>
- **Gulf War Research Strategic Plan, 2013-2107 (2015 Update)**
- <http://www.research.va.gov/pubs/docs/GWResearch-StrategicPlan.pdf>
- **Gulf War Research Strategic Plan, 2018-2122**



# VA-ORD Gulf War Research Strategic Plan

## Gulf War Research Strategic Plan (2018-2022)

- SECTION 1: EXECUTIVE SUMMARY
- SECTION 2: INTRODUCTION AND BACKGROUND
- SECTION 3: GULF WAR PROGRAM VISION AND MISSION
- SECTION 4: PROGRESS, CHALLENGES and OPPORTUNITIES
- SECTION 5: CORE RESOURCES (Cohorts; Data Use and Management; Technology)
- SECTION 6: CROSS-CUTTING OBJECTIVES (Partnerships; Communication)
- **SECTION 7: SCIENTIFIC APPROACHES AND RESEARCH GOALS**
  - Genetics/Genomics
  - Molecular and Cellular Mechanisms
  - Systems Biology and Biological Circuits
  - Animal Models, Physiology, and Behavior
  - Clinical Research
  - Epidemiology/Continued Surveillance
- SECTION 8: CONCLUSIONS



# VA-ORD Gulf War Research Strategic Plan

## GENETICS AND GENOMICS (1 of 3)

- Continue the effort to establish reliable and accessible genomic resources from Gulf War Veterans (database and biospecimens)
  - Improve the clinical characterization of GWI patients (illness severity, whether or not multi-morbidity is involved, disease progression history)
  - Determine patients' exposure histories
  - Conduct twins and siblings studies, to understand the impact on next generations
  - Increase Gulf War-era Veteran enrollment for MVP and other repositories
  - Explore and identify MVP participants that have served in GW, and have GWAS/other genomic data
  - Develop survey materials that would help better address data unique to the investigators' needs
  - Epigenetic markers that may be unique to GWI will need separate analysis



# VA-ORD Gulf War Research Strategic Plan

## GENETICS AND GENOMICS (2 of 3)

- Establish various genomic data collection and analysis technical platforms
  - Utilize large scale sequencing, transcriptome, copy number variations, GWAS, monitoring genomic instability, single cell genomics, candidate gene approaches.
  - Study gene/genome-environment interaction, including the epigenome
  - Explore requirements to perform epigenome analyses from MVP samples of GW participants
  - Explore requirements to perform epigenome analyses on GW participants that would have familial lineage (e.g., parent-child-grandchild)



# VA-ORD Gulf War Research Strategic Plan

## GENETICS AND GENOMICS (3 of 3)

- Establish data exchanges, integration, and translational research
  - Establish networks across investigators and centers for data comparison and integration
  - Select a set of patient cohorts (with good clinical profiles) to compare multiple technological platforms
  - Study comparisons with data from animal models
  - Apply genomic profiles to translational research
  - Develop data requirements that would benefit the entire VA Investigator community studying GW Veterans



# VA-ORD Gulf War Research Strategic Plan

## MOLECULAR AND CELLULAR MECHANISMS

- In animal models of GWI, elaborate the downstream effects of adverse changes in inflammation, mitochondrial function, oxidative stress and other molecular pathways on cell function and gene expression
- In studies of humans with and/or without GWI, corroborate or refute the changes in cell structure, function, or gene expression identified in animal models
- In studies in humans with and without GWI, establish whether there are differences in molecular pathways, and gene and protein expression in different tissues
- In studies in humans with and without GWI, establish whether there are differences in nerve conduction, motor-endplate dysfunction in skeletal muscle, or other nerve-tissue function (e.g. gastrointestinal)
- In studies in humans with and without GWI, link exposures associated with GWI in epidemiological studies to changes in molecular pathways, and gene and protein expression.
- In studies in humans with and without GWI, assess genotypes associated with GWI after accounting for exposures associated with GWI.



# VA-ORD Gulf War Research Strategic Plan

## SYSTEMS BIOLOGY AND BIOLOGICAL CIRCUITS

- Conduct systems biology studies using proteomics, lipidomics, genomics, and metabolomics to study dysregulation of pathways involved in immune function, inflammation, lipid metabolism, and mitochondria dysfunction.
- Determine whether the biome can be used as a biomarker, to implicate susceptibility pathways/genes/variants, in GW Veterans.
  - Conduct biome profiling in existing cohorts, and consider new therapies based on biome profiles.
  - Improve methods for expression evaluation (RNA-sequencing).
- Use exome, genome, and transcriptome sequencing in a systems-biology approaches combined phenotype/genotype approaches to understand the microbiome in GW Veterans.
  - Explore the effect of exposure conditions on the microbiome via various platforms (exome, genome, and transcriptome, etc.) in validated animal models.
- Conduct computational modeling of the brain-gut-immune axis to integrate knowledge and provide a rapid testing bed for hypotheses as well as for hypothesis generation.
- Investigate new clinical interventions based on restoring the microbiome environment to that resembling typical health.



# VA-ORD Gulf War Research Strategic Plan

## ANIMAL MODELS, PHYSIOLOGY, AND BEHAVIOR (1 of 2)

- Develop/improve animal models to capture the chronic and persistent clinical presentation of GWI even after the cessation of pathogenic GW exposures.
  - Use animal models to delve deeper into the molecular pathways associated with global changes in immune function, inflammation, lipid metabolism, mitochondria dysfunction, and other difficulties in Gulf War Veterans.
- Validate animal models by examining biological profiles from animal and human studies, including gender.
  - Better characterize the innate and adaptive immune responses in GW Veterans using animal models and clinical samples from the Veterans.
  - Explore the co-occurrence of biomarkers in human patients and in animal models as validation of their relevance for translational research.





# VA-ORD Gulf War Research Strategic Plan

## **ANIMAL MODELS, PHYSIOLOGY, AND BEHAVIOR (2 of 2)**

- Use validated animal models to perform preclinical testing of potential therapeutic compounds in order to minimize translational failures for identifying treatments for GW Veterans.
- Use animal models to investigate different combinations of GW exposures for identifying areas of overlap and distinction in response to these exposures.



# VA-ORD Gulf War Research Strategic Plan

## CLINICAL RESEARCH

- Improve the translation of basic laboratory findings into evidence-based treatments for Gulf War Veterans.
  - Follow-up on promising basic laboratory findings that can be turned into treatments that are tested through clinical research studies such as RCTs.
- Improve the implementation of evidence-based practice for Gulf War Veterans
  - Evaluate the best models of care and improve implementation of evidence-based treatments.
- Ensure that treatments and delivery of care for Gulf War Veterans are patient-centered.
  - Develop treatments and implement treatments that are responsive to individual Gulf War Veterans' preferences, needs, and values.
- Improve measurement, recruitment, and design issues that impede clinical research for Gulf War Veterans.
  - Study operational approaches to improve methodological impediments.



# VA-ORD Gulf War Research Strategic Plan

## EPIDEMIOLOGY AND CONTINUED SURVEILLANCE (1 of 4)

- Use data driven approaches to refine the current case definitions for GWI
  - Determine the data sources that are available within VA that can be linked and used to refine case definition for GWI.
    - Work with colleagues in PDHS to compile a list of all databases that have information pertinent to GWI, as well as the owners, locations, and permissions.
  - Bring together a panel of experts to determine the best possible method for refining and promoting a case definition that will be used for VA funded research moving forward for those who served in the Gulf in 1990-1991.
    - Create a GWI case definition workgroup including VA and DoD personnel as well as membership from RAC.
  - Promote and fund projects that will employ data driven methods to refine research case definitions for GWI.



# VA-ORD Gulf War Research Strategic Plan

## EPIDEMIOLOGY AND CONTINUED SURVEILLANCE (2 of 4)

- Enhance cancer surveillance among Gulf War Veterans.
  - Determine whether deployed versus non-deployed GW era Veterans have differing incidence rates of cancer.
    - In the absence of a national cancer registry, link a Gulf War era Veterans database to cancer registries in the largest states.
  - Determine whether deployed versus non-deployed GW era Veterans who use the VA medical system have differing incidence rates of cancer.
    - Conduct a medical records search of VA records to determine the incidence of cancer in the GW era Veterans.
  - Determine whether deployed GW era Veterans have higher cancer mortality rates than non-deployed GW era Veterans.
    - Link a Gulf War era Veterans database to the National Death Index to identify cancer deaths.



# VA-ORD Gulf War Research Strategic Plan

## EPIDEMIOLOGY AND CONTINUED SURVEILLANCE (3 of 4)

- Enhance surveillance of diseases of systems most likely affected by Gulf War deployment exposures such as neurological and respiratory/pulmonary.
  - Use traditional (longitudinal studies) and novel ways to conduct disease surveillance in the Gulf War cohort.
    - Re-examine the existing Epidemiology Program's GW cohort with longitudinal re-assessment of members and their data.
    - Investigate novel ways to conduct surveillance for disease incidence anomalies among VHA healthcare users via the electronic health record
  - Use VA electronic medical records (including linked Medicare data) to regularly monitor ([3] year intervals) incidence and prevalence of diseases (such as Parkinson's disease, Alzheimer's, COPD, and cancers) in Gulf War Veterans compared to a non-deployed control population.
    - Develop RFA for establishing protocol, procedure, and initial reports



# VA-ORD Gulf War Research Strategic Plan

## EPIDEMIOLOGY AND CONTINUED SURVEILLANCE (4 of 4)

- Continue to improve methods for deployment-related exposure assessment metrics.
  - Determine the feasibility of using satellite data modeling of particulate matter exposures in the Gulf region during the 1990-1991 period.



# VA-ORD Gulf War Research Strategic Plan

Questions?