

VA-ORD GULF WAR RESEARCH : Research Program Overview

Presented to:

Research Advisory Committee on Gulf War Veterans' Illnesses

VHA OFFICE OF RESEARCH AND DEVELOPMENT / Victor Kalasinsky and Robert Jaeger

April 20, 2017

Boston, MA

VA Office of Research and Development Strategic Plan

MISSION:

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

VISION:

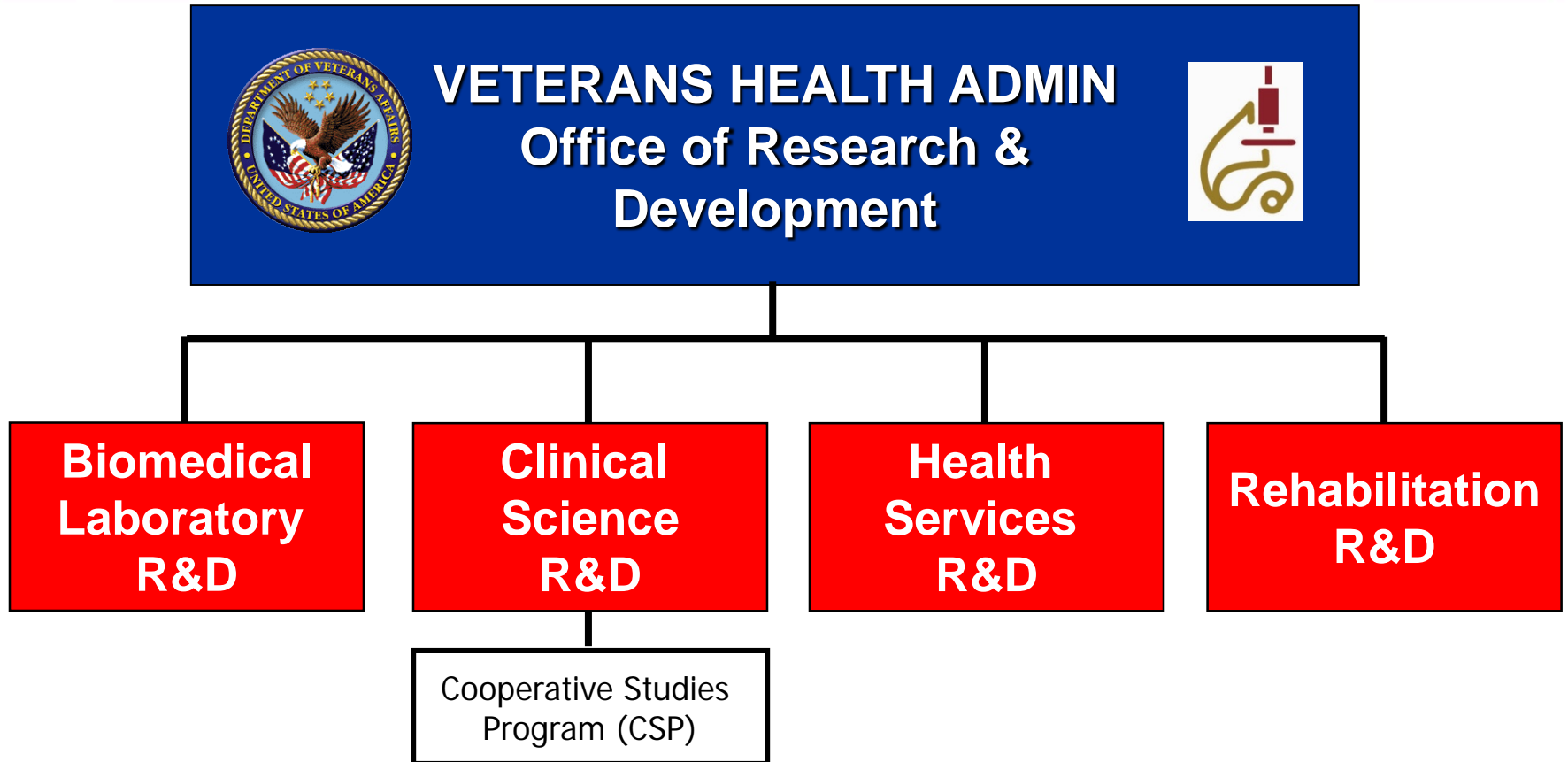
To be the premier research organization leading our Nation's efforts to enhance the health and well-being of Veterans by developing evidence-based clinical care and delivery systems improvements

http://vaww.va.gov/VHAOPP/POPlans/ORD_StrategicPlan2012.pdf

Nationwide VA Intramural Research Program Office of Research and Development

- **116 VAMCs have capacity for research**
 - **More than 90 are funded by VA at any time**
- **More than 2,400 Office of Research and Development (ORD)-funded projects**
- **Community of more than 3,000 VA researchers with a long history of significant research**
- **Broad, extensive research portfolio that balances the needs of all Veterans**

Office of Research and Development Organizational Chart



Gulf War Research – Requests for Applications (RFAs)

Biomedical Laboratory Research & Development (BLR&D):

BX-17-011

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

BX-17-012

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

Clinical Science Research & Development (CSR&D):

CX-17-011

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

CX-17-012

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

CX-17-013

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

Health Services Research & Development (HSR&D):

HX-17-012

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

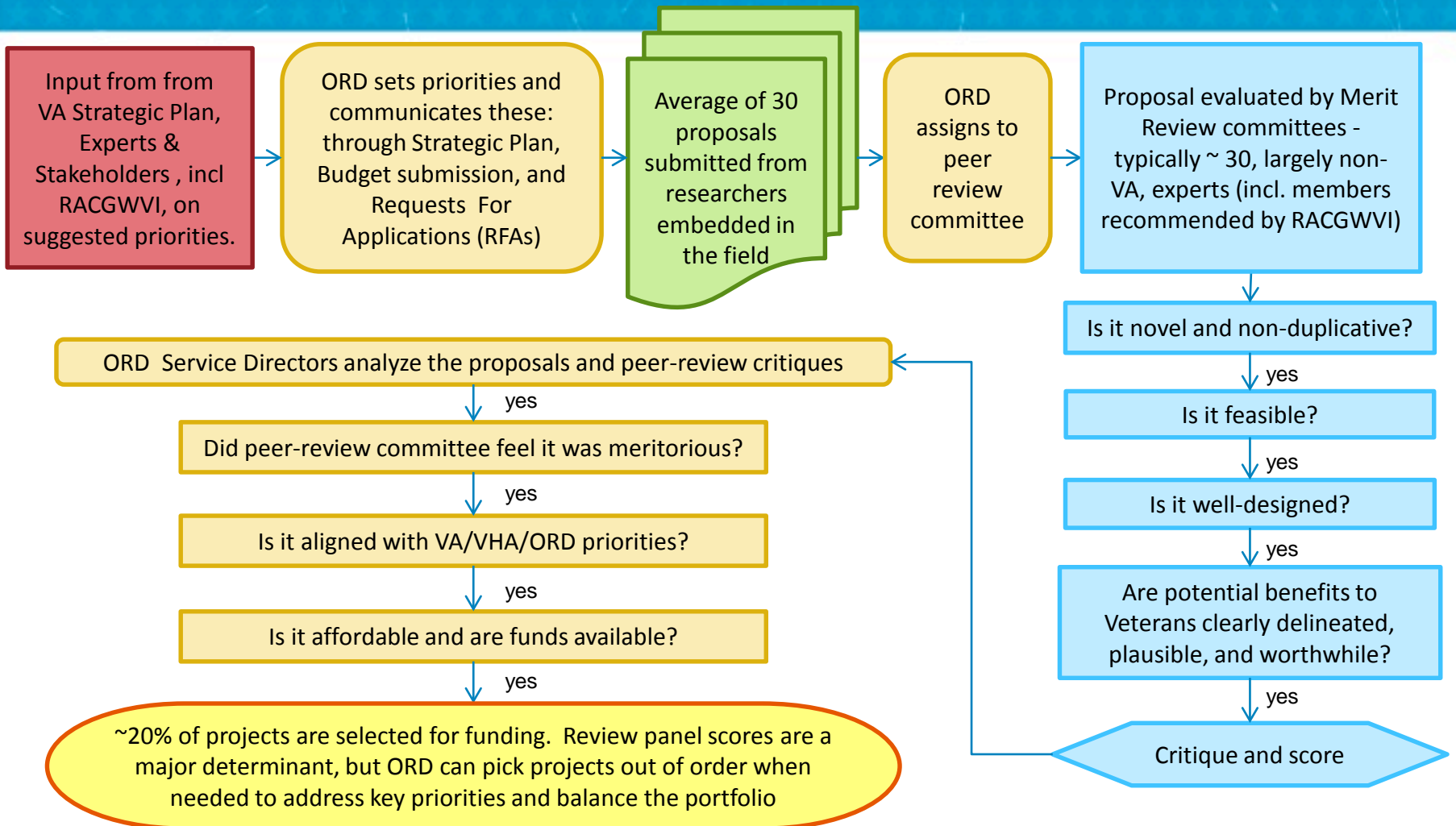
VA Office of Research and Development

- **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 Office of Research and Development Application Process

- The clinicians and researchers who treat and interact with ill Gulf War Veterans seeking care in VA Hospitals and Medical Centers are the best and most qualified individuals to propose the research that might be most beneficial to ill Gulf War Veterans.
- ORD invites VA intramural researchers to submit proposals for Gulf War research using the mechanism of “Requests for Applications” (RFAs).
- Since 2011, these RFAs have been issued by ORD twice per year on a consistent basis.
- VA/ORD has a specific Merit Review Panel, with expertise in Gulf War issues, to insure high quality, independent, and unbiased reviews of Gulf War research proposals submitted to ORD.

How ORD selects GWVI projects for funding



VA/ORD-Based FACA Committees (Federal Advisory Committee Act)

- **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.

RAC 2016 Recommendations - Status

- 1. Update GWRSP for 2018 – 2022
(IN PROGRESS)**
- 2. Establish coordinated system of centers within VHA
(UNDER REVIEW)**
- 3. Seek strategic partnerships, collaboration with non-VA entities (IN PROGRESS)**
- 4. Form a Work Group to identify challenges and solutions to recruitment
(IN PROGRESS)**
- 5. Develop an approach to use ICD code(s) for GWI
(UNDER REVIEW)**

RAC 2015 Recommendations – Status (1 of 2)

- 1. Research and clinical sides of VA collaborate more interactively
(IN PROGRESS)**
- 2. VA physicians receive GWI training for uniformity of care
(IN PROGRESS)**
- 3. Make it easier for Veterans to volunteer for research studies and biobanks
(IN PROGRESS)**
- 4. Create a working group for a single case definition for GWI
(IN PROGRESS)**

RAC 2015 Recommendations – Status (2 of 2)

- 5. Re-categorize deployed and non-deployed cohorts recognizing that Operation Desert Storm ended April 11, not March 1, 1991
(IN PROGRESS)**
- 6. Undertake confirmation studies related to genomics (BChE variants; PON1, PON2, PON3; MVP; DoD serum; ALS)
(UNDER REVIEW)**
- 7. Follow Veterans closest to Khamisiyah and oil wells
(IN PROGRESS for Khamisiyah)**
- 8. Develop larger treatment trials from pilot studies (L-carnosine for IBS; CPAP treatment for GWI)
(IN PROGRESS)**

VA-ORD Gulf War Research Funding (2007 – 2016)

Fiscal Year (FY)	VA Merit Review	UTSW Contract	FY Total
2007	\$ 7.06 M	\$ 15.00 M	\$ 22.06 M
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
Total 2007-2015	\$ 89.09 M	\$ 39.29 M	\$ 128.38 M

Response Statistics for VA-ORD Gulf War Research Requests for Applications (RFAs)

	Proposals Received	Projects Funded	Funds Approved
Spring/Fall 2011	26	3	\$ 4.0 M
Spring/Fall 2012	32	7	\$ 11.4 M
Spring/Fall 2013	35	7	\$ 12.6 M
Spring/Fall 2014	40	5	\$ 7.5 M
Spring/Fall 2015	33	8	\$ 13.2 M
Spring/Fall 2016	26	4	\$ 2.5 M
Spring 2017	16	Jun 2017	

Gulf War Research Projects Active in 2017 (slide 1 of 3)

Treatments/Clinical Trials

- Impact of exercise training on pain and brain function in Gulf War Veterans (5.1)
- Transcranial, Light-Emitting Diode (LED) Therapy to Improve Cognition in GWVI (5.1)
- Complementary Neurosteroid Intervention in Gulf War Veterans' Illnesses (5.1)
- Cognitive Rehabilitation Therapy for Gulf War Veterans (5.1)
- Complementary and Alternative Medicine in Veterans with Gulf War Illnesses (5.1)
- RCT of Duloxetine and Pregabalin for the treatment of GWI in Veterans (5.1)
- Healthcare Utilization Patterns and Associated Costs for Gulf War I Era Veterans (5.1)
- WRIISC as a Model of Care for Chronic Multisymptom Illness (5.1)
- Novel Interventions for Gulf War Veterans' Illnesses (5.1)
- Pilot Test of Telephone-Delivered Cognitive Behavioral Therapy for Insomnia for Veterans with Gulf War Illness (5.1)
- Randomized, Double-blind Placebo-controlled Phase III Trial of Coenzyme Q10 in Gulf War Illness (5.1)
- Evaluation of a Mindfulness-Based Intervention for Gulf War Illness (5.1)

Gulf War Research Projects Active in 2017 (slide 2 of 3)

Biomarkers/Mechanisms

- Examination of Cognitive Fatigue in Gulf War Illness Using fMRI (5.5)
- Longitudinal assessment of Gulf War veterans with suspected Sarin exposure (5.4, 5.5)
- Multimodal Biological Assessment of Gulf War Illness (5.5)
- National Health Survey of Persian Gulf Veterans and their Families (5.2)
- Somatic hypersensitivity in Veterans with IBS (5.1)
- Women vs. Men with GWI: Differences in Computational Models and Therapeutic Targets (5.1, 5.4)
- Genomics of Gulf War Illness in Veterans (5.4)
- Post Exertional Malaise in GWI: Brain Autonomic and Behavioral Interactions (5.5)
- A Translational Medicine Approach to Gulf War Illness: From Cells to Therapy (5.5, 5.8)
- Mechanisms of Gulf War Illness (5.1, 5.4)

Gulf War Research Projects Active in 2017 (slide 3 of 3)

Model Systems

- Central Mechanisms Modulating Visceral Sensitivity (5.4, 5.6)
- Immunoregulation of Myelin Specific T Lymphocytes (5.4, 5.6)
- Neuroprotection and Myelin Repair Mechanisms in Multiple Sclerosis (5.4, 5.6)
- Sleep Neurobiology and Circuitry (5.4, 5.6)
- Understanding Pain of Gastrointestinal Origin in Women that Serve in OEF/OIF (5.5, 5.6)
- Identification of Plasma Biomarkers of Gulf War Illness Using "omic" Technology (5.5, 5.6)
- Gulf War Exposures and the Molecular Mechanisms of Paternal Reproductive Risk (5.6)
- Novel neurotrophic therapies in an optimized mouse model of GWVI (5.1, 5.6)
- Neuroinflammation, Oxidative Stress, and Hippocampal Defects in GWI (5.5, 5.6)
- Immune Basis for Hippocampal Cholinergic Deficits in Pyridostigmine-treated Rats (5.6)
- Gulf War neurotoxins and acquired cognitive and neuropsychological dysfunction (5.6)
- Maintenance of Telomerase Activity as a Treatment for Gulf War Illness (5.1, 5.6)

Gulf War Research Projects Selected for funding in 2017

- Treatments for Sleep Disorders in Gulf War Veterans (5.1)
- Treating Immune dysfunction in GWI (5.6)
- Gulf War Exposures and Neuroinflammation (5.6)
- Evaluating Treatments for Veterans with Chronic Multisymptom Illness (5.1)

Recently Completed Gulf War Research Projects

- Bacterial Overgrowth Associated with Chronic Multi-Symptom Illness Complex (5.1)
- Host Defense Mechanisms in Polyaromatic Hydrocarbon Carcinogenesis (5.5, 5.6)
- Prevention of Hippocampal Neurodegeneration Due to Age and Apnea (5.6)
- Epigenetic Mechanisms Relevant to the Pathogenesis of ALS (5.4, 5.6)
- Nanoparticle Coupled Antioxidants for Respiratory Illness in Veterans (5.1, 5.6)
- Memory and Mood Enhancing Therapies for Gulf War Illness (5.1, 5.6)
- MEG Synchronous Neural Interactions (SNI) in Gulf War Veterans (5.5)
- rTMS for the Treatment of Chronic Pain in GW1 Veterans (5.1)
- Diagnostic Utility of mtDNA Content and Exercise Challenge in Vets with GWI (5.1, 5.4)
- Vascular and Skeletal Muscle Function in Gulf War Veterans Illness (5.1, 5.4)

Gulf War Research Biorepositories

- **Gulf War Veterans' Illnesses Biorepository (5.2, 5.4, 5.5)**
 - Began operations – July, 2012
 - Enrolling Veterans to obtain medical records
 - Brain and spinal cord tissue to be collected post-mortem
 - Review of pilot project in November, 2014
 - http://www.research.va.gov/programs/tissue_banking/gwvib/default.cfm
- **CSP #585 Gulf War Era Cohort and Biorepository (5.2, 5.4, 5.5)**
 - Deployed and non-deployed Veterans
 - Users of VA health care and non-users
 - Surveys and blood collection
 - September, 2014 – May 2016: enrolled 1276 participants
 - <http://www.research.va.gov/programs/csp/585/default.cfm>

Gulf War Research Activities

National Academy of Medicine (NAM) Reports (formerly, Institute of Medicine)

- **Assessment of the Department of Veterans Affairs Airborne Hazards and Open Burn Pit Registry**
 - Jan 2015 – Jan 2017 (First meeting Mar 13, 2015)
 - NAM report, Feb 28
 - <https://www.nap.edu/catalog/23677/assessment-of-the-department-of-veterans-affairs-airborne-hazards-and-open-burn-pit-registry>
- **Gulf War and Health, Volume 11: Generational Health Effects of Serving in the Gulf War**
 - Sep 2016 – Sep 2018 (First meeting Jan 12, 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)**
 - <http://www.research.va.gov/pubs/GulfWarRpt14.cfm>
- **Joint VA/DoD Working Groups (Deployment Health and Medical)**
- **Participation in CFS Conference and GWI Workshop in Ft. Lauderdale, October 2016**

Post-Deployment Research – VA-DoD Coordination Individual Longitudinal Exposure Record (ILER)

- **ILER - A complete record of every Service member's occupational and environmental exposures over the course of their careers**
- **Pilot project – currently underway**
 - Demonstrate feasibility
 - Develop a prototype
- **Link DoD exposure databases to a Service member's location and dates**
 - Available to VA and DoD health care providers
 - Available to VBA adjudicators

Gulf War Research Activities

QUESTIONS ?

Gulf War Research Strategic Plan

VA/ORD Gulf War Research Strategic Plan 2013-2017 (2015 Update)

<http://www.research.va.gov/pubs/docs/GWResearch-StrategicPlan.pdf>

VA/ORD Gulf War Research Strategic Plan (2013-2017)

Table of Contents

- 1.0 EXECUTIVE SUMMARY
- 2.0 INTRODUCTION AND BACKGROUND
- 3.0 EVOLUTION OF THE GULF WAR RESEARCH STRATEGIC PLAN
- 4.0 SUMMARY OF GULF WAR RESEARCH RESULTS AND PAST FEDERAL RESEARCH SUPPORT
- 5.0 GULF WAR RESEARCH STRATEGIC OBJECTIVES 2013-2017
 - 5.1 Symptomatic and Specific Treatments
 - 5.2 Databases and Continued Surveillance
 - 5.3 Establish an Evidence-Based Case Definition ...
 - 5.4 Genetics/Genomics/Systems Biology
 - 5.5 Biomarkers
 - 5.6 Animal Models
 - 5.7 Improve Coordination and Communication with Stakeholders
 - 5.8 Translate Research Findings to Practice

VA/ORD Gulf War Research Strategic Plan (2018-2022)

- **SECTION 1: EXECUTIVE SUMMARY**
- **SECTION 2: INTRODUCTION AND BACKGROUND**
- **SECTION 3: GOALS AND OBJECTIVES** (*or 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**
 - 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 (2018-2022)

- **SECTION 3: GOALS AND OBJECTIVES (*or Vision and Mission*)**
 - **Goals (*or Vision*)**
 - Improve the health and well-being of Gulf War Veterans.
 - Utilize emerging knowledge to prevent similar war-related illnesses in the future.
 - **Objectives (*or Mission*)**
 - Develop effective treatments for ill Gulf War Veterans
 - Identify biomarkers and improve diagnosis for conditions affecting Gulf War veterans
 - Continue surveillance/health monitoring

VA/ORD Gulf War Research Strategic Plan (2018-2022)

- **SECTION 7: SCIENTIFIC APPROACHES (or Research Goals) - each with Background, Objectives/Aims (and sub-Aims, if needed), Strategies, Targets/Metrics, and relevant Cross-cutting Objectives/Goals.**
 - **Genetics/genomics**
 - **Molecular and cellular mechanisms**
 - **Systems biology and biological circuits**
 - **Animal models, physiology, and behavior**
 - **Clinical research**
 - **Epidemiology/Continued surveillance**

VA/ORD Gulf War Research Strategic Plan (2018-2022) Structure Crosswalk

<u>OLD</u>	<u>NEW</u>	<u>Notes</u>
I. Executive Summary	I. Executive Summary	
II. Intro and Background	II. Intro and Background	Less information about plan development process
III. Overall Goals	IIIa. Goals (or Vision)	
Improve health of GW vets	Improve health of GW vets	
Prevent similar illnesses	Prevent similar illnesses	
IV. Two branches	IIIb. Objectives (3) (or Mission)	
1. Monitor health	1. Treatments	Elevating treatments to the top priority
2. Biomarkers and treatments	2. Biomarkers and diagnosis	Made biomarkers distinct from treatments in new
	3. Monitor health	
	IV. Progress, Challenges, Opportunities	
	V. Core Resources (3)	
	1. Cohorts	
	2. Data use and management	Data could stand alone, surveillance could be part of epidemiology (see below)
	3. Technology	Missing in old structure, could also be "cross-cutting"
	VI. Cross-cutting Objectives (2)	or Cross-cutting Strategic Goals (2)
	1. Partnerships	
	2. Communication	
V. Strategic Goals/Objectives (8)	VII. Scientific Approaches (6)	or Research Goals (6)
1. Treatments	--	Redundant with "branches"; just in "objectives" in new
2. Databases and Surveill.	--	Moved to "core resources"
3. Case definition	--	NAM report; to be noted as a "challenge" in intro
4. Genetics and systems bio	1. Genetics/genomics	"Systems bio" broken out and included below
	2. Mol. & Cellular Mechanisms	Missing in old structure
5. Biomarkers	--	Redundant with "branches"; just in "objectives" in new
	3. Systems bio and bio circuits	Can include areas like microbiome and neural circuits
6. Animal models	4. Animal models/phys/behav	Expanded to be more encompassing
7. Communication w/ stakeholders	--	In new, made into a "cross-cutting objective" (see above)
8. Translate research to practice	5. Clinical research	Expanded to be more encompassing
	6. Epidemiology & Surveill.	Epi. missing in old structure, combining w/ surveillance
VI. Conclusions	VIII. Conclusions	

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VI. Conclusions	Conclusions	

VA/ORD Gulf War Research Strategic Plan (2018-2022)

GENERAL TEMPLATE for SECTION 7: SCIENTIFIC GOALS AND OBJECTIVES

A. Select one scientific area from Section 7 (Highlight your selected area):

Genetics/Genomics	Animal Models, Physiology, and Behavior
Molecular and Cellular Mechanisms	Clinical Research
Systems Biology and Biological Circuits	Epidemiology/Continued Surveillance

B. Progress:

What progress has been made in this scientific area as it relates to Gulf War research? Focus attention to recent years and advances since the current GWRSP.

-

C. Challenges:

What research-related challenges have hampered progress to-date and/or what challenges pose an impediment to future progress in this scientific area?

-

D: Opportunities:

What research directions offer the greatest opportunity to make progress in this scientific area as it relates to the GWRSP? Take into consideration timeframe and potential impact, as well as partnerships that may be needed.

-

E. Scientific Goal(s) and/or Objectives

What are the top goal(s) for your selected scientific area that are achievable by 2022?

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What might be some supporting objectives for each goal? Consider specific outcomes that are actionable and measurable.

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VA/ORD Gulf War Research Strategic Plan (2018-2022)

DRAFT TIMELINE

- Apr 11-19 Establish Writing Teams
- Apr 20 Briefing for RAC
- May First drafts from Writing Teams
- Jun Second drafts from Writing Teams
- Jul Combine and edit draft GWRSP
- Jul 24-28 Work Group discuss GWRSP
- Aug Briefing for RAC
- Aug-Sep Finalize and submit to VHA

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Gulf War Research Activities

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