CDMRP
Department of Defense

Gulf War Illness Research Program

Strategic Plan

INTRODUCTION

The Congressionally Directed Medical Research Programs (CDMRP) represents a unique partnership among the U.S. Congress, the military, and the public to fund innovative and impactful research in targeted program areas. In 2015, an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine (NASEM) [formally the Institute of Medicine (IOM)] was assembled to evaluate the CDMRP. This evaluation represented the fourth time the CDMRP was evaluated by the NASEM and included a review of the CDMRP two-tier review process as well as CDMRP's coordination of research priorities with the National Institutes of Health (NIH) and the Department of Veterans Affairs (VA). The committee found overall that "the CDMRP review process is effective in dispensing research funding across its programs and is not in need of extensive revisions." However, the committee's report provided considerations for how the process of reviewing and selecting studies may be improved. Among these was the following recommendation:

"Each CDMRP research program should develop a strategic plan that identifies and evaluates research foci, benchmarks for success, and investment opportunities for 3–5 years into the future. The plan should be re-evaluated and updated as necessary at the end of that interval. Each strategic plan should specify the mission of the program, coordination activities with other organizations, research priorities, how those priorities will be addressed by future award mechanisms, how research outcomes will be tracked, and how outcomes will inform future research initiatives."

This Strategic Plan builds on extensive past work by the GWIRP and is the GWIRP's response to these NASEM report recommendations. Although much progress has clearly been made in Gulf War Illness (GWI) research, significant work remains to be done. The GWIRP Strategic Plan has been formulated to accelerate progress. This Strategic Plan will be reviewed during the annual GWIRP Vision Setting meeting.

GWIRP BACKGROUND AND OVERVIEW

Population-based studies indicate that approximately 25% to 32% of the men and women who served in the 1990-1991 Persian Gulf War continue to experience Gulf War Illness (GWI), characterized by chronic symptoms including debilitating fatigue, cognitive difficulties, widespread pain, gastrointestinal problems, headache, respiratory symptoms, and other abnormalities. Department of Defense (DoD)-funded GWI research began in 1994 with the establishment of the Gulf War Veterans' Illnesses Research Program (GWVIRP) to study the health effects of Service members deployed in the 1990–1991 Persian Gulf War. From Fiscal Year 1994 (FY94) to FY05, the GWVIRP was managed by the U.S. Army Medical Research and Materiel Command's Military Operational Medicine Research Program (MOMRP). Research pertaining to GWI also was funded intermittently through the CDMRP's Peer Reviewed Medical Research Program (PRMRP), which supports selected military health-related research topics each fiscal year. The MOMRP shared management responsibility for the GWVIRP with the CDMRP in FY06, with separate $5 million (M) appropriations. Although the GWVIRP did not receive funding in FY07, a $10M appropriation renewed the program fully under CDMRP in FY08 as the Gulf War Illness Research Program (GWIRP). Congressional directives for the GWIRP in FY08, which the program continues to follow today, included: (1) studies of treatments for the complex of symptoms known as GWI, (2) no studies based on psychiatric illness and psychological stress as the central cause, and (3) competitive selection and peer review to identify research with the highest technical merit and military value.

In 2010, an IOM report, *Gulf War and Health, Vol. 8*, agreed with the myriad of studies published in the medical literature that GWI is a multisymptom illness, is a diagnostic entity, is associated with service in the 1991 Gulf War, and that its symptoms cannot be ascribed "to any known psychological disorder" but instead "it

is likely that Gulf War illness results from an interplay of genetic and environmental factors." The report called for "a renewed research effort with substantial commitment to well-organized efforts to better identify and treat multisymptom illness in Gulf War veterans... to alleviate their suffering as rapidly and completely as possible." The report's preface emphasized the need "to speed the development of effective treatments, cures, and, it is hoped, preventions." Most significantly, the preface stated the encouraging and proscriptive views of the IOM committee with regard to future research direction: "We believe that, through a concerted national effort and rigorous scientific input, answers can likely be found."

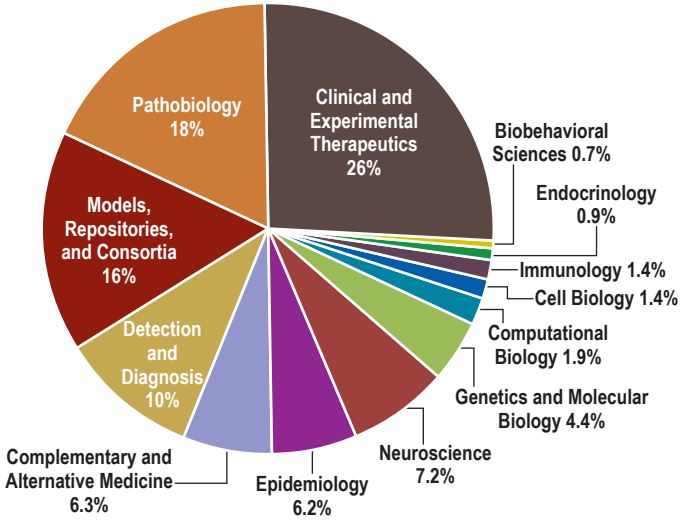
Since FY06, the GWIRP has been funding research to fill gaps and address program priorities. By applying advances in scientific knowledge in the implementation of annual Vision Setting meetings, the development of Areas of Emphasis, and the release of focused funding opportunity announcements, the GWIRP fosters a culture of collaboration, knowledge growth, accountability, vision aim, and mission focus. The vision and mission of the GWIRP are:

VISION: Improved health and lives of Veterans who have Gulf War Illness.

MISSION: Fund innovative Gulf War Illness research to identify effective treatments and accelerate their clinical application, improve definition and diagnosis, and better understand pathobiology and symptoms of disease

GWIRP INVESTMENT HISTORY

The program has built a broad research portfolio of 190 awards from FY06 to FY18. An additional 12 awards are anticipated in FY19. The GWIRP has funded research within public and private organizations, such as universities, colleges, hospitals, laboratories, and companies, the VA, the DoD, and the CDC. The research funded by the program is summarized by research topic in the figure to the right. Award data and abstracts of funded research proposals can be viewed on the CDMRP website (http://cdmrp.army.mil).



HISTORICAL FUNDING APPROACH

The GWIRP strategy has evolved over the history of the program. The figure to the right illustrates the funding priorities since the program's inception.

	FY06-FY11	FY12-FY14	FY15-FY16	FY17-FY18	FY19-FY20
Gap/Priority	• Treatment • Basic Research • Disease Models • Detection	• Treatment • Preclinical Research • Detection • Consortia	• Treatment • Clinical Translation • Focused Topics • Diagnosis • New Investigators	• Treatment • Quality of Life • Research Resources • Focused Topics	• Treatment • Diagnosis • Continued Discovery • Large scale replication and/or validation
Funding Opportunities Developed	• Clinical Trial • Innovative Treatment Evaluation • Investigator-Initiated Research	• Clinical Trial • Innovative Treatment Evaluation • Investigator-Initiated Research • Consortium	• Clinical Trial • Treatment Evaluation • Clinical Partnership • Investigator-Initiated Focused Research • Epidemiology • New Investigator	• Clinical Consortium • Qualitative Research • Biorepository • Investigator-Initiated Focused Research • New Investigator	• Idea • Research Advancement • Clinical Evaluation • Therapeutic/ Biomarker Trial • Patient-Provider and Health Communications Award • New Investigator
No. of Awards	51 awards	48 awards	56 awards	35 awards	12 awards*

*FY20 is TBD

In the early years of the GWIRP, the program focused funding on basic research under investigator-initiated research mechanisms as well as pilot clinical trials of symptoms-based treatments, including repurposed therapeutics. Variations of these standard mechanisms have been offered in nearly every year since then; however, in certain fiscal years, the program additionally emphasized specific GWI community needs including an increasing emphasis on large-scale clinical trials, replication, and validation building on previous findings.

In FY12, the CDMRP GWIRP funded the development of two diagnostic and treatment discovery research consortia to build strong partnerships and collaborations in the scientific community and to more effectively advance GWI treatment development. One consortium studied brain-immune interactions to understand the central roles of neurotoxic and neuroinflammatory reactions as underlying causes of the health problems in GW Veterans. The other consortium focused on a "systems biology" approach of combining basic research data with clinical results to identify biomarkers and possible treatments for GW Veterans. These multi-institutional organizations engaged the scientific community by addressing overarching issues in GWI research, combining and sharing resources, and fostering real-time communication of research results.

In FY15 and FY16, other innovative funding opportunities were announced including: a New Investigator Award to encourage the participation of investigators outside of the GWI community who might bring new or unique approaches to GWI research; an Expansion Award to expand upon previously funded high-impact research to move it along the pipeline toward clinical application; a Gulf War Illness Epidemiology Research Award to assess symptomatology and comorbidities over time; a Clinical Partnership Award to support a two-way continuum between clinicians and laboratory scientists and accelerate the movement of promising research hypotheses into clinical practice; and a Qualitative Research Award for the purpose of developing health communications materials for Veterans with Gulf War Illness and those who care for them, including healthcare providers, caregivers, and family members. Each of these award mechanisms added to the growing portfolio of GWIRP-funded research designed to help ill Gulf War Veterans.

In FY17, the GWIRP took a bold step by offering two large funding mechanisms supporting both clinical research and infrastructure. The first, a Clinical Consortium Award, was offered to support a group of institutions, coordinated through an Operations Center that conceived, designed, developed, and is now conducting collaborative Phase I and II clinical trials of promising therapeutic agents for the management or treatment of GWI. The treatments being tested have been identified by the earlier-funded diagnostic and treatment discovery consortia. The second, a Biorepository Resource Network Award, was offered to support development and maintenance of a GWI biorepository through a collaborative network to collect, process, annotate, store, and distribute both clinical specimens and clinical research data. These mechanisms build on the achievements of the previously established consortia to further promote collaboration and resource sharing.

In FY18, innovative supplemental funding was offered as an option, nested within the Investigator-Initiated Focused Research Award and the Clinical Trial Award mechanisms, to incentivize the contribution of samples and data to the Biorepository Network funded in FY17. The following year a similar supplemental funding option was added to clinical trial mechanisms encouraging collaboration with the Clinical Consortium funded in FY17.

In FY19, the GWIRP offered an innovative research pipeline composed of six new award mechanisms to address the overarching challenges in a step-wise and translational manner. The award mechanisms were aligned to the different phases of the research pipeline, from discovery through large-scale replication, verification and confirmation to dissemination of existing research. The Idea Award encouraged new ideas at their earliest stage of development, including for high-risk/high-reward ideas. The Research Advancement Award addressed the preclinical research already supported by preliminary or published data in the GWI field that is ready for validation through expansion, replication, or comparative studies. The Clinical Evaluation Award aimed at addressing clinical translation of concepts in GWI research previously validated through expansion, replication, or comparative studies. And the latest stage, the Treatment/Biomarker Trial Award, aimed at conducting large-scale confirmatory and pivotal clinical trials. Additionally, the program transitioned from the previously offered Qualitative Research Award to the Patient-Provider Health Communications Award mechanism, targeting tool development to effectively communicate GWI research and clinical recommendations. Finally, the New Investigator Award continued to encourage new ideas and investigators into the field.

FY20 and beyond, the GWIRP anticipates continuing this research pipeline composed of six award mechanisms to further address the overarching challenges in a step-wise and translational manner.

GWIRP RESEARCH ACCOMPLISHMENTS

The GWIRP has built a broad research portfolio of awards featuring clinical trials and mechanistic research as well as studies addressing Gulf War-relevant chemical exposures and GWI symptomatology. Significant treatment outcomes, objective findings, and exploratory avenues resulting from GWIRP-funded research are shown below. Additional outcomes can be gauged in part by the innovative collaborations, resulting follow-on VA grants, publications, clinical trials, and other researcher resources reported by awardees.

Treatment and Alternative Therapy Successes:

- Coenzyme Q10 (CoQ10) pilot study – Found to reduce pain, fatigue, and cognitive symptoms in Veterans with GWI. The VA is currently funding a Phase III study using ubiquinol, the reduced form of CoQ10
- Carnosine pilot study– Found to reduce cognitive symptoms in Veterans with GWI (but not to impact their pain, fatigue, or other outcomes)
- Acupuncture pilot study – Shown to improve GWI symptoms of pain, fatigue, sleep quality, and cognitive symptoms
- Nasal irrigation (saline or Xylitol) pilot – Early results showed improvement of sinus and fatigue symptoms in Veterans with GWI
- Mind-body bridging pilot study – Shown to be an effective intervention in the management of disturbed sleep in Veterans with GWI
- Botanical microglia-modulating agents screening study - Of nine botanical agents tested, four had a significant impact on GWI symptoms over baseline and placebo conditions. These agents were: reserveratrol, stinging nettle, pycnogenol, and CurcumaSorb.
- Methylphenidate plus a GWI-specific nutrient cocktail pilot study - This combination treatment had a significant reduction in overall symptom severity, as well as improved concentration disturbance symptoms, fatigue, sleep, and pain. There was also a significant reduction in serum lipid peroxide levels.
- Neuronavigation-guided rTMS pilot trial – Treatment resulted in significant improvements in muscle pain as well as in concentration and fatigue. Improvements in headache and joint pain also trended toward significance. This pilot provided the foundation to design and conduct larger-scale, multi-center treatment trials of rTMS.

The GWIRP is currently funding numerous pilot clinical trials of investigative treatments (see https://cdmrp.army.mil/gwirp/clinical_trials/GWIRPsct).

Genetics and Genomics: Various research studies either completed or underway have begun to establish associations between GWI and the following genetic features: paraoxonase activity and genotype, abnormalities in mitochondrial and nuclear genetics, varieties of Human Leukocyte Antigen (HLA) genes, genome instability (reflected as elevated frequencies of non-clonal chromosome aberrations), persistently elevated somatic mutations, microRNA regulation, and patterns of gene-environment interaction.

Molecular and Cellular Mechanisms: Objective evidence from various GWIRP-supported studies using clinical samples or preclinical models of GWI have demonstrated the following dysfunctions are associated with GWI: mitochondrial dysfunction, neuro/immune system dysregulation, autonomic imbalance, altered brain structure and function, microvascular injury, evidence of small fiber nerve polyneuropathy, gut microflora dysbiosis, microtubule dysfunction, Na+ and K+ channel dysfunctions, alterations in axonal transport, altered lipid homeostasis, altered calcium homeostasis, toll-like receptor priming, tau pathology, epigenetic alterations, DNA breakage, and single nucleotide polymorphisms.

Systems Biology: The GWIRP has additionally supported research investigating connections between GWI and fatigue, chronic pain, small-fiber polyneuropathy, sleep disorders, chronic rhinosinusitis, chronic bronchiolitis, gut biome alterations, headache, and memory disorders.

Models: Development of the following animal models has been supported by the GWIRP: low dose sarin exposure in mice; rats dermally exposed to DEET (N,N-diethyl-meta-toluamide) and PER (permethrin); PB (pyridostigmine bromide) and PER in mice; diisopropyl fluorophosphate (DFP) treatment preceded by corticosterone in mice and rats; repeated exposure to chlorpyrifos (CPF), DEET, or PER – all with or without PB. Additionally, the GWIRP has supported the development and use in research of Induced pluripotent stem cells (iPSCs) from GWI subjects and controls.

GWI Cohorts: The GWIRP has supported assessments of the following established cohorts: the Fort Devens Cohort, Pest Control Personnel from the Gulf War (GW), the Navy Seabee Cohort, the Kansas Cohort, the Haley Cohort, the Boston Gulf War Illness Consortium (GWIC) Cohort, and a GWI Women's Cohort. GWIRP-supported research has also investigated smaller cohorts with more limited catchment as well as extensive clinical research under the multi-institutional consortia to include the Boston Biorepository, Recruitment, and Integrative Network (BBRAIN) at Boston University and the Gulf War Illness Clinical Trials and Interventions Consortium (GWICTIC) at Nova Southeastern University.

Additional Observations: Research on animal models of GW exposure support the occurrence of multisystem health complaints, including both persistent and delayed effects, including from low-level Gulf War-relevant chemical exposures. Research suggests the trajectory of symptoms appears to be different for women than for men. Preliminary results published in 2016 also indicate mild traumatic brain injury (mTBI), both during deployment and post-deployment, may be important in the chronicity of health symptoms in GW Veterans.

GWIRP-SUPPORTED COMMUNITY RESOURCES

The GWIRP publishes a GWI Landscape overview of what is currently known about topics related to the mission of the program. This document is publicly available on the GWIRP website (cdmrp.army.mil/gwirp/pdfs/GWIRP_Landscape_2020.pdf) and is a broad overview of what is known about GWI, GWI research gaps, and GWI community needs. The intent is to provide the GWI community with concise information about the state of GWI research. Prospective applicants for program funding are strongly encouraged to read The GWI Landscape before preparing their applications.

The GWIRP compiles a list of Research Resources are products of GWIRP funding, including published biomarkers, molecular profiles, exposure-relevant animal models, established GW Veteran cohorts, completed and ongoing evaluations of clinical interventions, and clinical sample biorepositories. This publicly available list describes the resources and gives a direct point of contact for more information and potential collaboration. This is intended to facilitate collaborations, speed GWI research, and serve as an information hub for the GWI community. The resources list can be accessed from the main GWIRP webpage. (https://cdmrp.army.mil/gwirp/default)

Researchers must perform adequate and realistic planning in order to achieve successful GW Veteran research subject recruitment. In order for GWIRP-funded investigators to establish an effective and sustainable outreach and recruitment plan, the GWIRP, in collaboration with GW Veterans who served in the 1990-1991 Persian Gulf War, developed a document titled, General Guidance for Gulf War Veteran Outreach and Recruitment. This guidance is posted on the main GWIRP webpage, http://cdmrp.army.mil/gwirp/pdfs/General%20_Guidance_for_Gulf_War_Veteran_Outreach_and_Recruitment.pdf.

RESEARCH AND FUNDING ENVIRONMENT

As noted previously, the GWIRP was fully assigned to the CDMRP in response to Congressional directives in FY08. Those directives called for a divergence in focus from past VA, DoD, and Department of Health and Human Services (HHS) efforts and centered around studies of treatments for the complex of symptoms known as GWI, prohibited studies based on psychiatric illness and psychological stress as the central cause of GWI, and recommended competitive selection and peer review to identify research with the highest technical merit and military value. The overall goal of the GWIRP is to fund scientifically meritorious research in accordance with the original and any new directives received from Congress. The GWIRP is conducted according to the two-tier review model recommended by the NASEM, which has received high praise from the scientific community, advocacy groups, and Congress. Veterans with GWI participate as full members on all peer review panels and the Programmatic Panel to enrich the scientific review and research focus with personal perspective, passion, and a sense of urgency. Medical technologies and treatments developed as part of the GWIRP can be leveraged to support healthy and fit military forces and their families.

To identify significant research gaps in the GWI research field, it is important to consider which research areas are already actively funded. GWI research funding opportunities for scientists and clinicians are made possible through support from the Federal government. While the VA, DoD, and HHS have funded over 500 distinct projects from FY92 through FY16 related to health problems affecting GW Veterans, the Congressional shift to funding the GWIRP and its narrow treatment focus represents a focused divergence from other research not similarly focused on treatment development and improving the health and lives of Veterans with GWI. The CDMRP GWIRP is funded through the DoD, via annual Congressional legislation known as the Department of Defense Appropriations Act. Funding for the GWIRP does not appear as part of the DoD core funding in the President's budget request; instead, Congress, on an annual basis in consultation with the advocacy community, directs funding within DoD's appropriations for "peer-reviewed Gulf War illness" research. Unlike other Federally funded programs that receive funding recommendations in the President's budget every fiscal year, each CDMRP program has a separate, one-year, congressionally-directed appropriation and develops an investment strategy based on that appropriation. Full project funding is obligated at the start from the single fiscal year appropriation, ensuring multiyear research projects are not at funding risk. This method is in contrast to other agencies, including the VA and HHS, which fund projects in budget years.

The scope of the Federal GWI research portfolio is broad, from small pilot studies to large-scale epidemiology studies involving large cohorts. Each year the VA, with input from the GWIRP, prepares an Annual Summary to Congress on Federally sponsored research on Gulf War Veterans' Illnesses. Funding trends, cumulative number of funded projects, and new research projects and initiatives can be found in these reports, available at: https://www.research.va.gov/pubs/pubs_individual.cfm?Category=Gulf War Reports.

Federally sponsored GW research expenditures in millions of dollars is summarized in the table below (note that GWIRP expenditures are less than appropriations for the corresponding year due to various reductions):

Fiscal Year	VA Merit Review	VA Contract	GWIRP	HHS	Total FY06-FY19
2006	$13.00M	-	$4.11M	$0.50M	$17.61M
2007	$7.06M	$15.00M	-	$0.50M	$22.56M
2008	$6.93M	$15.00M	$8.48M	$0.50M	$30.91M
2009	$9.63M	$6.97M	$7.14M	-	$23.74M
2010	$11.57M	$2.29M	$7.07M	-	$20.93M
2011	$5.54M	$0.03M	$5.07M	-	$10.64M
2012	$6.72M	-	$12.13M	-	$18.85M
2013	$7.94M	-	$16.21M	-	$24.15M
2014	$9.73M	-	$18.69M	-	$28.42M
2015	$11.63M	-	$16.99M	-	$28.62M
2016	$12.34M	-	$18.99M	-	$31.33M
2017	$13.55M	-	$18.00M	-	$31.55M
2018	$13.33M	-	$19.32M	-	$32.65M
2019	$14.58M	-	$19.50M*	-	$34.08M
Total 2006-2019	**$143.55M**	**$39.29M**	**$171.65M**	**$1.50M**	**$355.99M**

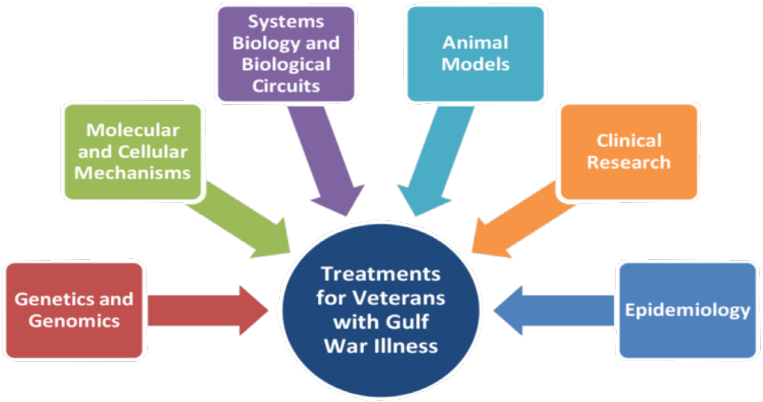
*FY19 funding estimated

Program Announcements and Requests for Applications are issued by the DoD GWIRP and the VA, respectively, each year. Each agency reviews their portfolios of GW research on a regular basis in order to determine research gaps and to expand successful research topic areas. The Federal GW research portfolio is increasingly focused on identifying potential new treatments for ill GW Veterans and identifying new diagnostic markers of disease. The GWIRP and VA Program Managers (PMs) meet regularly to share information regarding funded GW research projects, and a goal of the GWIRP is to coordinate activities in order to maximize combined program impact. Other examples of DoD GWIRP and VA coordination include: VA Gulf War Veterans' Illnesses PM attendance at annual GWIRP Programmatic Review and Vision Setting meetings; contribution of GWIRP funding data and project information to the VA Gulf War Veterans' Illnesses Report to Congress; GWIRP PM attendance at the VA Research Advisory Committee on Gulf War Veterans' Illnesses (RAC-GWVI) meetings; current and past GWIRP Programmatic Panel members serving on the RACGWVI; GWIRP PM and consumer reviewer participation on VA-convened working groups and in VA field-based meetings; and, electronic coordination through the Federal RePORTER website.

STRATEGIC PLAN 2020-2024

STRATEGIC DIRECTION

Nearly three decades after the ceasefire marking the end of hostilities of the 1991 GW, military personnel continue to suffer from lasting repercussions of chronic GWI that, in many if not most cases, remain poorly managed. The development of targeted treatments has not yet clearly elucidated the pathways tied to the disease. However, there have been significant advances in identification of potential mechanisms of action through strong epidemiologic, clinical, and underlying biology investigations. The GWIRP's near-term strategic direction remains focused on prioritizing translational research facilitating expeditious testing of treatments for Veterans with GWI.



As clinical and model system research expand our knowledge into molecular mechanisms, genetics/genomics, and systems biology underlying GWI, the GWIRP enables researchers to build on these research findings and pursue novel approaches to therapeutic discovery and development.

GWIRP Overarching Challenges

- **Treatments:** Eliminate the health consequences associated with GWI and revolutionize treatment
- **Diagnosis:** Better define and diagnose GWI
- **Subtyping:** Distinguish symptom clusters to better target treatments, identify underlying causes, and elucidate differences in severity
- **Determinants:** Validate exposures associated with GWI and impacts on organs and systems
- **Consequences:** Determine whether GWI is associated with greater risk for developing other disease states including neurological diseases, cancers, or other life-threatening and severely debilitating conditions
- **Communication:** Help Veterans, their caregivers, researchers and health care providers communicate effectively about GWI, its symptoms, and potential treatments

The GWIRP seeks to invest in the following priorities/strategic goals. The GWIRP enables investigators to propose their best research ideas that are aligned with these priorities/goals and in the context of the overarching challenges. These priorities and goals will be re-evaluated and updated as necessary during the program's Vision Setting meetings.

1. **Direct resources toward accelerating the identification of effective GWI treatments and their clinical translation.**
    a. Support treatment approaches derived from the current understanding of GWI mechanistic pathways (target-based).
    b. Support investigation of viable treatments based on the current understanding of symptoms of GWI (symptoms-based).
    c. Encourage trial designs that target subgroups of Veterans sharing the same symptoms.
    d. Support research and research protocols to generate resources to facilitate information sharing and collaboration between GWI researchers.
    e. Support research and research protocols to improve education of and outreach to GWI clinicians, patients, and their caregivers.
    f. Support research protocols that enhance the recruitment of ill (i.e., GWI) and healthy 1991 GW Veteran study subjects.
    g. In parallel, support the development of widely accessible research and clinical communication resources.
2. **Inform treatment development by directing resources toward understanding the pathobiology underlying GWI symptoms.**
    a. Support investigation into biological and molecular pathways underlying GWI symptoms, including validation/replication studies, including:
        i. Of molecular signatures (e.g., biomarkers) underlying GWI symptom clusters via genomic, proteomic, metabolic, or epigenetic technologies
        ii. To identify, replicate, and/or validate the causes of dysregulated biological system function in GWI
    b. Support investigation into the relationship and impact of environmental factors on GWI symptoms.
    c. Support the use of models to characterize GWI's pathobiology, multisymptom nature, prognosis, and to identify potentially viable treatment pathways and treatments.

3. **Inform treatment development by directing resources toward improving definition and diagnosis**
    a. Support collaborative research efforts, including outside the GWIRP, to improve or refine GWI's case definition.
    b. Support research related to the connection of GWI pathobiology and core GWI symptoms to comorbid symptom sets, which alone or in combination may have an underlying pathobiology relevant to the definition and diagnosis (and broader pathobiology) of GWI, such as:
        i. Diagnosed/diagnosable sleep disorders and undiagnosed sleep symptoms, such as sleep apnea, insomnia, narcolepsy, undiagnosed non-restorative sleep, undiagnosed sleep disturbances, etc.
        ii. Diagnosed/diagnosable gastrointestinal conditions and undiagnosed G-I symptoms, such as dietary intolerances and dietary impact on GWI symptomatology (e.g., FODMAP's, Glutamate, etc.), Gastroesophageal Reflux Disease/ Functional Gastrointestinal Disorders (GERD/FGID's), etc.
        iii. Diagnosed/diagnosable upper and lower respiratory conditions and undiagnosed symptoms with onset during or highly proximate to GW service, such as Chronic Sinusitis/Rhinosinusitis, Respiratory diseases, currently undiagnosed respiratory symptoms, etc.
        iv. Diagnosed/diagnosable dermatological, neurodermatological, vascular dermatological conditions, undiagnosed dermatological signs/symptoms, etc.
        v. Diagnosed/diagnosable immunological or auto-immune conditions, undiagnosed immunological or auto-immune signs/symptoms, etc.
        vi. Diagnosed/diagnosable cardiovascular conditions, undiagnosed cardiovasular signs/symptoms, etc.
        vii. Diagnosed/diagnosable endocrine or neuroendocrine conditions, undiagnosed endocrine or neuroendocrine signs/ symptoms, etc.
        viii. Diagnosed/diagnosable mitochondrial conditions, undiagnosed mitochondrial dysfunction or disorder signs/ symptoms, etc.
        ix. Diagnosed/diagnosable neurological conditions, undiagnosed neurological dysfunction or disorder signs/symptoms, etc.
        x. Diagnosed/diagnosable hepatorenal conditions, undiagnosed hepatorenal dysfunction or disorder signs/symptoms, etc.
        xi. Diagnosed/diagnosable hematological conditions, undiagnosed hematological signs (e.g. coagulopathy, etc.), etc.
    c. Support for investigations into genetic factors that predispose individuals to GWI, impact the prognosis of GWI, or contribute to future gene-exposure vulnerabilities.
    d. Support the discovery and validation/reproducibility of biomarkers of illness, including markers of disease severity.
    e. Support for epidemiology of comorbidities and mortality, including sex and ethnic differences, and the potential for increased incidence/prevalence of comorbid neurological conditions, cancers, and downstream long-term impacts on other organs and systems.

INVESTMENT STRATEGY

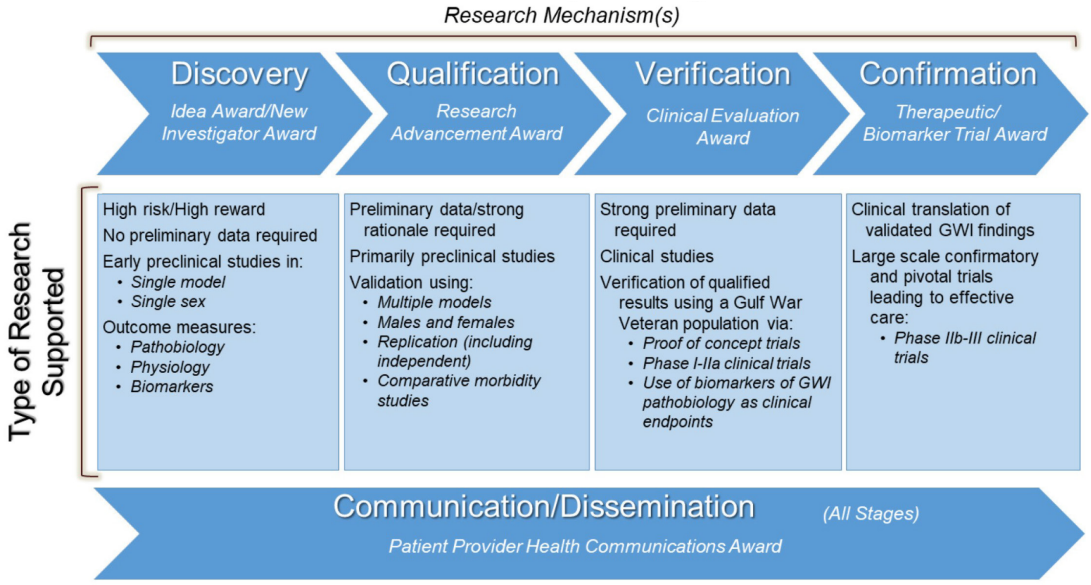
The investment strategy outlined in the figure on the next page represents the GWIRP's approach to soliciting the type of research that will facilitate accomplishment of its strategic goals in the short term. The program sets out to invest in distinct steps along the GWI research pipeline.

The **Discovery** stage represents innovative biomarker or treatment research that is in the earliest stages of development.

The **Qualification** stage represents preclinical research already supported by preliminary or published data in the GWI field that is ready for validation through expansion, replication, or comparative studies.

The **Verification** stage represents clinical translation of concepts previously validated through expansion, replication, or comparative studies. Examples of projects in the Verification phase include large-scale biomarker trials or Phase I through IIa intervention trials.

The **Confirmation** stage represents large-scale confirmatory and pivotal trials that will transform and revolutionize the clinical management of GWI. Sufficiently powered Phase IIb through Phase III clinical trials of previously piloted interventions will be supported. Objective biomarkers to measure the biological effect of an intervention or predictive/cohort-selective biomarkers that indicate whether a specific therapy will be effective in an individual Gulf War Veteran or Gulf War Veteran subgroup are required.



The development and maintenance of **strategies to effectively communicate GWI research and clinical recommendations** to Gulf War Veterans, their caregivers and health care providers, with the goal of informing and raising awareness, shall be considered at each phase of the research pipeline.

In addition to investments along the research pipeline, the GWIRP encourages community collaboration with the BBRAIN for GWI for retention and distribution of Gulf War Veteran biospecimens and/or data related to GWI research. Community collaboration with the Gulf War Illness Clinical Trials and Interventions Consortium (GWICTIC), a network of institutions focused on designing and executing Phase I and II clinical trials, is also encouraged to make use of the established infrastructure including recruitment networks, existing protocols, common data elements (CDEs), and data management procedures.

MEASURING PROGRESS

To maintain transparency of GWIRP-supported outcomes, the GWIRP will publish the following on its website: updates to The Gulf War Illness Landscape document, the Gulf War Illness Researcher Resources document, the Gulf War Illness Research Program booklet, and updates to the General Guidance for Gulf War Veteran Outreach and Recruitment document on an as needed basis.

The GWIRP will measure anticipated short-term outcomes based on successful investments in areas that are important to the program strategy. Longer term-outcomes will be evaluated based on contributions to the GWI treatment-development scientific community and by following research linked to GWIRP funded projects.

NEAR-TERM OUTCOMES (1-3 YEARS)

1. **Investments in discovery and development of GWI treatments research in preclinical and clinical stages of development**
    a. Support for discovery of new treatment approaches in model systems
    b. Support for qualification of promising leads by replication of results – in models, in vivo, and in one or both sexes –with a high degree of statistical validity
    c. Support for verification of treatment concepts in smaller-scale Phase I and IIa clinical trials employing rigorous endpoints
    d. Support for confirmation of treatment concepts in large-scale Phase IIb and III clinical trials anticipated to lead to translation and improvements in Veteran's care
2. **Investment in research leading to improved detection and diagnosis in the clinic**
    a. Support for tests/tools to objectively measure GWI and GWI symptoms
    b. Support for validation of objective GWI biomarkers
    c. Support for research that can inform new and GWI-specific clinical practice guidelines, with consideration of implementation strategies, as well as educational tools for Veterans suffering from GWI or their caregivers

3. **Investment in research defining the pathobiology underlying GWI symptoms**
    a. Support for the use and enhancement of models and in vivo replication to characterize the multisymptom nature of GWI, including etiologic and pathobiologic investigations
    b. Support for further discovery and clinical validation of the biological and molecular pathways underlying GWI symptoms, including genetic predisposition/susceptibility studies
    c. Support for studies of GWI subpopulations, including those based on gender, race, comorbidities, and age-related comorbidity
4. **Investment in research developing and implementing strategies to more effectively communicate GWI research, clinical recommendations, and state of the science knowledge regarding GWI to and between GWI clinical care providers, Veterans with GWI, and their caregivers and loved ones**
5. **Investment retaining and further developing a widely accessible repository for GWI research samples and data that incorporates standardization of CDEs, methods, and samples to improve, enhance, and facilitate effective GWI research and provide opportunities for comparison and combination of data from multiple studies and/or with health records.**

LONG-TERM OUTCOMES (3-5+ YEARS)

6. **Contributions to the scientific community, including publications and patents, that provide tangible contributions to the understanding of GWI, identify or validate GWI diagnostic markers, GWI treatment targets, and evidence-based treatments for GWI from pilot- or replication-level studies**
7. **Availability of surrogate markers of GWI that are viable as a monitor of GWI's progression and to serve as readouts of the efficacy of GWI treatment testing**
8. **Completed GWI treatment trials (Phase I/II) and publication of outcomes, including their mechanistic/biopathological rationale**
9. **Publicly accessible health communications materials, guidelines, and/or tools related to GWI for clinicians providing healthcare to Veterans suffering from GWI, the Veterans themselves, and/or their caregivers or loved ones**
10. **Widespread use by GWI researchers of a physical repository for research data and samples**
11. **Widespread use by GWI researchers of CDEs and/or other standardization**