The views expressed in this presentation are those of the author and may not reflect the official policy or position of the Department of the Army, Department of Defense, or the U.S. Government.
Outline

◆ Overview of the Congressionally Directed Medical Research Programs (CDMRP)

◆ The CDMRP Gulf War Illness Research Program (GWIRP)
  ❖ Initiation and Funding History
  ❖ Program Objectives
  ❖ Funding Mechanisms and Funded Topics
  ❖ VA and GWIRP coordination
  ❖ Near and Longer Term Priorities
WHO is the CDMRP?

- Department of Defense
- Department of the Army
- Army Medical Command
- U.S. Army Medical Research and Materiel Command (USAMRMC)
- Congressionally Directed Medical Research Programs
Vision
Transform healthcare for Service Members and the American public through innovative and impactful research

Mission
Responsibly manage collaborative research that discovers, develops, and delivers health care solutions for Service Members, Veterans and the American public
About CDMRP

◆ DoD PROGRAMS
  ▶ Provides support to Program Area Directorates (PADs)/Joint Program Committees (JPCs) for managing extramural and intramural research portfolios to advance their missions

◆ CONGRESSIONAL PROGRAMS
  ▶ Manages extramural research programs directed by Congress
  ▶ Started in 1992 with a focus on breast cancer research; currently includes 31 research programs
  ▶ Congress specifies the focus area; the CDMRP determines research strategy and competitively selects the best projects
  ▶ Unique public/private partnership encompasses the military, scientists, disease survivors, consumers, and policy makers
  ▶ Funds high-impact, innovative medical research to find cures, reduce the incidence of disease and injury, improve survival, and enhance the quality of life for those affected

◆ DIRECTOR
  ▶ Col Wanda Salzer

CURRENT PROGRAMS:
- Alcohol and Substance Abuse Disorders
- Amyotrophic Lateral Sclerosis
- Autism
- Bone Marrow Failure
- Breast Cancer
- Breast Cancer Semipostal
- Duchenne Muscular Dystrophy
- Epilepsy
- Gulf War Illness
- Hearing Restoration
- Joint Warfighter Medical
- Kidney Cancer
- Lung Cancer
- Lupus
- Military Burn
- Multiple Sclerosis
- Neurofibromatosis
- Orthotics and Prosthetics
- Outcomes
- Ovarian Cancer
- Parkinson’s
- Peer Reviewed Alzheimer’s
- Peer Reviewed Cancer
- Peer Reviewed Medical
- Peer Reviewed Orthopaedic
- Prostate Cancer
- Reconstructive Transplant
- Spinal Cord Injury
- Tick-Borne Disease
- Tuberous Sclerosis Complex
- Vision

ADDITIONAL SUPPORTED DoD PROGRAMS:
- Defense Medical R&D
- Defense Medical R&D Restoral
- Psychological Health and Traumatic Brain Injury
- Small Business Innovation/Small Business Technology Transfer
- Trauma Clinical
In the early 1990s, grassroots efforts heightened political awareness of breast cancer.

Congress appropriated $210M to the FY93 DoD budget for a new Breast Cancer Research Program (BCRP).

The USAMRMC was directed to manage the BCRP.

The Army sought the advice of the National Academy of Medicine (previously the Institute of Medicine ([IOM]), which resulted in:

- A two-tier review process – scientific and programmatic reviews
- A new research model – incorporating consumers into program policy, investment strategy, and research focus

Since 1996, additional research programs and topics have been added by Congress and administratively managed by the CDMRP.
## Two-Tier Review Process

To **find** scientifically meritorious proposals and **fund those** that best fulfill program goals

<table>
<thead>
<tr>
<th>Peer Review</th>
<th>Partnership</th>
<th>Programmatic Review</th>
</tr>
</thead>
</table>
| - Criterion-based: evaluate each application according to the mechanism-specific peer review criteria  
- Determination of “absolute” scientific merit  
- Outcome: Written critique and scores for individual criteria and overall merit |  | - Comparison-based: comparison among proposals of high scientific merit  
- Determination of program relevance, adherence to intent and portfolio balance (No “pay line”)  
- Outcome: Funding recommendations |

No standing panels  
Peer reviewer panels are recruited *de novo* each year depending on mechanism-specific expertise needs  
Programmatic panel member terms are typically set for 1-3 years  
CDMRP may retain expertise for the benefit of the program
Consumers

The voices and experiences of consumers continue to play a pivotal role in the establishment and growth of CDMRP research programs.

Over 2,100 consumers representing over 1,000 organizations have served on CDMRP Peer Review and Programmatic Review panels.
## FY17 Funding

<table>
<thead>
<tr>
<th>Program</th>
<th>$M</th>
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</thead>
<tbody>
<tr>
<td>Alcohol and Substance Abuse Disorders</td>
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<tr>
<td>Amyotrophic Lateral Sclerosis</td>
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</tr>
<tr>
<td>Autism</td>
<td>$7.5</td>
</tr>
<tr>
<td>Bone Marrow Failure</td>
<td>$3.0</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>$120.0</td>
</tr>
<tr>
<td>Breast Cancer Research Semipostal</td>
<td>$0.6</td>
</tr>
<tr>
<td>Duchenne Muscular Dystrophy</td>
<td>$3.2</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>$7.5</td>
</tr>
<tr>
<td><strong>Gulf War Illness</strong></td>
<td><strong>$20.0</strong></td>
</tr>
<tr>
<td>Hearing Restoration</td>
<td>$10.0</td>
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<tr>
<td>Joint Warfighter Medical</td>
<td>$50.0</td>
</tr>
<tr>
<td>Kidney Cancer</td>
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<tr>
<td>Lung Cancer</td>
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<tr>
<td>Lupus</td>
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<td>Military Burn</td>
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<td>Multiple Sclerosis</td>
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<tr>
<td>Neurofibromatosis</td>
<td>$15.0</td>
</tr>
<tr>
<td>Orthotics and Prosthetics Outcomes</td>
<td>$10.0</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>$20.0</td>
</tr>
<tr>
<td>Parkinson's</td>
<td>$16.0</td>
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<tr>
<td>Peer Reviewed Alzheimer’s</td>
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<tr>
<td>Peer Reviewed Cancer (14 Topics)</td>
<td>$60.0</td>
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<tr>
<td>Peer Reviewed Medical (48 Topics)</td>
<td>$300.0</td>
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<tr>
<td>Peer Reviewed Orthopaedic</td>
<td>$30.0</td>
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<td>Prostate Cancer</td>
<td>$90.0</td>
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<tr>
<td>Reconstructive Transplant</td>
<td>$12.0</td>
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<tr>
<td>Spinal Cord Injury</td>
<td>$30.0</td>
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<td>Tick-Borne Disease</td>
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<td>Trauma Clinical</td>
<td>$10.0</td>
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<tr>
<td>Tuberous Sclerosis Complex</td>
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<tr>
<td>Vision</td>
<td>$15.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$1.1B</strong></td>
</tr>
</tbody>
</table>

**(1) Approximate funding**
Gulf War Illness Research Program
HR 1585 Conferees directed the Secretary of the Army to utilize the authorized funding … to undertake research on Gulf War Illness. Conferees also directed that activities under the Gulf War Illness program include:

- No studies based on psychiatric illness and psychological stress as the central cause
- Studies of treatments for the complex of symptoms known as “Gulf War Illness”
- Competitive selection and peer review to identify research with the highest technical merit and military value
- Coordinate with similar activities in the VA and the NIH
Improved health and lives of Veterans who have Gulf War Illness

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
GWIRP Funding and Awards

- Total Congressional appropriations: $149M
- Total full applications received: 495
- Total awards: 165

(Numbers in parentheses indicate the number of awards for each year.)
Gulf War Illness

Vision - Improved health and lives of Veterans who have Gulf War Illness

The Gulf War Illness Research Program (GWIRP) was initiated in 2006 to provide support for research of exceptional scientific merit to study the health effects of deployment on U.S. Warfighters during the 1990-1991 Persian Gulf War. The GWIRP challenges the scientific community to design high-impact research that will improve the health and lives of Veterans who have Gulf War Illness (GWI).

GWI is characterized by multiple, unresolving symptoms that typically include chronic headache, widespread pain, cognitive difficulties, debilitating fatigue, gastrointestinal problems, respiratory symptoms, sleep problems, and other abnormal lites that could not be explained by established medical diagnoses or standard laboratory tests. The population of Veterans affected by GWI is a subset of the nearly 700,000 U.S. Warfighters who served during the 1990-1991 Gulf War. Studies indicate that approximately 25-32% of Gulf War Veterans continue to experience symptoms associated with their deployment.

The GWIRP focuses on funding innovative, competitively peer-reviewed research to (1) provide a better understanding of the pathobiology underlying GWI; (2) identify objective markers (biomarkers) for improved diagnosis, and (3) to develop treatments for the complex of GWI symptoms and their underlying causes. Our Vision is to make a significant impact on GWI and improve the health and lives of affected Veterans and their families.

The Gulf War Illness Landscape (130kb)  

The GWIRP has prepared the above Landscape overview of what is currently known about topics consistent with the mission of identifying treatments, improving definition and diagnosis, and understanding pathobiology and symptoms. Applicants are strongly encouraged to read and consider the Gulf War Illness Landscape when preparing applications.

<table>
<thead>
<tr>
<th>Congressional Appropriations</th>
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<tbody>
<tr>
<td>$129.8 million PY06, PY08-16</td>
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<tr>
<td>$26.5 million FY17</td>
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</table>

<table>
<thead>
<tr>
<th>Funding Summary</th>
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<tbody>
<tr>
<td>155 Awards in PY06, PY08-16</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Programmatic Panels</th>
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</thead>
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<tr>
<td>FY18 Programmatic Panel</td>
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<table>
<thead>
<tr>
<th>Peer Review Participants</th>
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</thead>
<tbody>
<tr>
<td>PY17 Peer Review Participants</td>
</tr>
</tbody>
</table>

155 Awards (FY06 – FY16)

$149M (FY-06-FY17)

Outcomes and Resources

GWI Landscape

Program Book

News & Project Highlights
The Gulf War Illness Landscape

- Describes the state of the science and current research gaps
- Covers topics consistent with the GWIRP mission
- Provides context for research priorities
- Reference and link to the landscape are included in each GWIRP Funding Opportunity Announcement
- Applicants are strongly encouraged to read and consider when preparing applications
Program Cycle

- Congressional Appropriation (Restart cycle annually)
- Stakeholders Meetings*
- Approval Authority Decision
- Award Negotiations
- Award Management
- Award Closeout
- Research Outcomes
- Research News and Reports

Vision Setting
- Program Announcement Release
- Pre-Application Receipt
- Pre-Application Screening and Invitation to Submit*
- Application Receipt
- Peer Review
- Programmatic Review
- Programmatic Panel

Annual Appropriation, Review, and Award Cycle
- Month 6
- Month 12
- To Month 24
- Month 18
- To Month 84

*As needed
GWIRP Programmatic Panel

- Anthony Hardie, former Staff Sergeant USA (Chair)
  Florida Veterans for Common Sense

- Roberta F. White, Ph.D.
  Boston University School of Public Health

- Fiona Crawford, Ph.D.
  Roskamp Institute

- Elizabeth Hauser, Ph.D.
  Duke University School of Medicine/
  Durham VA Health Care System

- David Jackson, Ph.D.
  U.S. Army Center for Environmental Health Research

- K. Jeffrey Myers, M.D.
  Department of Veterans Affairs

- Marni Silverman, Ph.D.
  Henry M. Jackson Foundation for the
  Uniformed Services University of the Health
  Sciences

- Vicky Whittemore, Ph.D.
  National Institute of Neurological Disorders and
  Stroke, National Institute of Health

- David K. Winnett, Jr., Captain
  USMC Retired
  Veterans for Common Sense
Prioritize treatment and accelerate high-impact research

- Support clinical trials
- Support preclinical screening of therapeutics
- Support mechanistic research that can shed light on optimal treatment
  - Support discovery of therapeutic targets and markers of clinical efficacy
  - Support objective measures to better define GWI and subgroups

Create a structure that allows the best ideas to emerge from all disciplines

- All organizations and independent investigators at all levels are eligible
- Encourage innovation and stimulate creativity
- Facilitate meaningful collaborations
- Bring new investigators into the GWI field
GWIRP Strategy Through the Years

New funding opportunities developed to fill gaps and address program priorities

<table>
<thead>
<tr>
<th>FY06-11</th>
<th>FY12-14</th>
<th>FY15-16</th>
<th>FY17</th>
</tr>
</thead>
<tbody>
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<td><strong>Gap/Priority</strong></td>
<td><strong>Gap/Priority</strong></td>
<td><strong>Gap/Priority</strong></td>
<td><strong>Gap/Priority</strong></td>
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<td>Treatment Basic Research Disease Models Detection</td>
<td>Treatment Preclinical Research Detection Consortia</td>
<td>Treatment Clinical Translation Focused Topics Diagnosis New Investigators</td>
<td>Treatment Quality of Life Research Resources Focused Topics</td>
</tr>
<tr>
<td><strong>Funding Opportunities Developed</strong></td>
<td><strong>Funding Opportunities Developed</strong></td>
<td><strong>Funding Opportunities Developed</strong></td>
<td><strong>Funding Opportunities Developed</strong></td>
</tr>
<tr>
<td>• Clinical Trial</td>
<td>• Clinical Trial</td>
<td>• Clinical Trial</td>
<td>• Clinical Consortium</td>
</tr>
<tr>
<td>• Innovative Treatment Evaluation</td>
<td>• Innovative Treatment Evaluation</td>
<td>• Treatment Evaluation</td>
<td>• Qualitative Research</td>
</tr>
<tr>
<td>• Investigator-Initiated</td>
<td>• Investigator-Initiated</td>
<td>• Clinical Partnership</td>
<td>• Biorepository</td>
</tr>
<tr>
<td>• Consortium</td>
<td>• Epidemiology</td>
<td>• Focused Investigator-Initiated</td>
<td>• Focused Investigator-Initiated</td>
</tr>
<tr>
<td><strong>Awards</strong></td>
<td><strong>Awards</strong></td>
<td><strong>Awards</strong></td>
<td><strong>Awards</strong></td>
</tr>
<tr>
<td>51 awards</td>
<td>48 awards</td>
<td>56 awards</td>
<td>10 awards</td>
</tr>
</tbody>
</table>
Completed Clinical Interventions

◆ Coenzyme Q10

◆ Mifepristone

◆ Carnosine Therapy

◆ Acupuncture

◆ Mind Body Bridging

◆ Nasal Irrigation

◆ Naltrexone and Dextromethorphan
Ongoing Clinical Interventions

◆ Active Trials
  - Probiotic (VSL#3)
  - Intranasal insulin
  - Botanical Microglia Modulators
  - Yoga*
  - Prednisone
  - Methylphenidate plus a GWI-Specific Nutrient Formula*
  - Flavonoid-rich dietary supplementation
  - Portable vestibular stimulator
  - D-cycloserine
  - Low FODMAP diet
  - Mitochondrial cocktail
  - Liposomal Glutathione and Curcumin
  - Vagus nerve stimulation
  - Repetitive Transcranial Magnetic Stimulation (rTMS)
  - Transcranial Direct Cortical Stimulation (tDCS)

◆ Newly Recommended
  - B-Cell depletion therapy
  - Low-glutamate diet
  - Resveratrol
  - tDCS by targeting the occipital nerve field
  - Entanercept and mifepristone (through phase II)
  - Antioxidant (CoQ10 or glutathione) + intranasal insulin
  - Nutraceutical, Bacopa

*Intervention complete. Final report and publication pending
## Pre-Clinical Treatment Pipeline

<table>
<thead>
<tr>
<th>Therapeutic</th>
<th>Mode of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monosodium Luminol</td>
<td>Antioxidant</td>
</tr>
<tr>
<td>Dantrolene, Levetiracetam</td>
<td>Pharmacological blockade of the calcium plateau</td>
</tr>
<tr>
<td>Oleoylethanolamine</td>
<td>Ethanolamide to inhibit NFkB phosphorylation</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Neurotrophic factor</td>
</tr>
<tr>
<td>Curcumin</td>
<td>Enzyme inhibitor</td>
</tr>
<tr>
<td>LNA-antimiR-124</td>
<td>Inhibition of microRNA-124</td>
</tr>
<tr>
<td>LDN/OSU-0212320</td>
<td>Brain-penetrant small molecule that increases glutamate transport</td>
</tr>
<tr>
<td>Naltrexone, Losmapimod, Minocycline</td>
<td>Inhibitors of neuroinflammatory pathways</td>
</tr>
<tr>
<td>Anatabine</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Antioxidant and sleep inducer</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Antidepressant, reversal of elevated Ca2+ levels</td>
</tr>
<tr>
<td>Growth Hormone-Releasing Hormone (GHRH) Analogs</td>
<td>Inhibit the activation of signaling mediators common to the innate immune system</td>
</tr>
<tr>
<td>Sigma-1 Receptor Agonists</td>
<td>Restore mitochondrial energy metabolism in neurons and enhance neuroplasticity</td>
</tr>
<tr>
<td>Glycan conjugate immunotherapy</td>
<td>Restore the immune system balance</td>
</tr>
<tr>
<td>Glial and cytokine inhibitors (TNFa, IL-1)</td>
<td>Interfere with glial activation, inhibition of two major components of inflammatory signaling</td>
</tr>
</tbody>
</table>
GWIRP-Supported Cell/Animal Models:

- iPSCs
- Low dose sarin
- DEET and permethrin
- PB and permethrin
- DFP preceded by corticosterone
- Repeated exposure to chlorpyrifos
- DEET, permethrin, chlorpyrifos, +/- PB
- Inhalation model

GWIRP-Supported Clinical Sampling:

- CFS
- Blood
- Saliva
- Skin biopsy
- Adipose tissue
- Muscle biopsy
- Stool

Limitations:

- Length of time elapsed
- Lack of earlier data points
- Confounding effects of aging
- Repeated/lifetime exposures matter

GWIRP-Supported Clinical Assessments:

- Cytokine panels
- Mitochondrial assays
- Genetic analysis
- Genomics/Proteomics/Lipodomics
- Genome-wide association
- RNA-Seq
- Neuroimaging
- Neuronal cultures
- Histology
- Physiological testing
- Cognitive testing

- Computational Modeling
### Mechanistic Outcomes

#### Progress

**Evidence of:**
- Mitochondrial dysfunction
- Neuro/Immune system dysregulation
- Autonomic imbalance
- Altered brain structure and function
- Microvascular injury
- Evidence of SFPN
- Alterations in gut microflora
- 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
- Detoxification pathways
- SNPs
- Gender differences

#### Challenges

- Availability of negative or neutral study outcomes to enable prioritization
- Different biological systems rarely evaluated in the same Veteran
- Few individual findings have been replicated/validated by multiple investigators

#### Opportunities

- Greater transparency
- DoD/VA coordination
- Multi-scale investigations
- Replication/validation studies
- Integrated approaches – combining computational modeling with animal models and clinical data

#### Potential Outcomes:

- Targeted and effective treatments
- Objective measures to define GWI and subgroups
- Markers of clinical efficacy
DoD GWIRP / VA Coordination

- VA Gulf War Veterans’ Illnesses Program Manager (PM) attends annual GWIRP Programmatic Review and Vision Setting meetings

- GWIRP contributes funding data and project information to the VA GWVI Report to Congress

- GWIRP PM attends RACGWVI meetings

- GWIRP PM participation on VA convened working groups

- Participation in GWI Workshops and VA field-based meetings

- GWIRP funds many VA Investigators

- VA has funded GWIRP spin-off proposals

- Regular briefings/updates between Gulf War PMs and electronic coordination (FedRePORTER)
Fiscal Year 2018 Priorities

**Clinical Trial Initiatives**
- Clinical trial award to move preclinical candidates into trial; projects may range from small proof-of-concept trials through expansion to large-scale, definitive trials
- Launch of the first set of trials under the newly established Clinical Consortium leveraging existing consortia organizations and collaborations

**Investigator-Initiated Focused Research**
- Backbone of the program for discovery and preclinical development
- Two Tiers:
  1. Discovery and proof of concept; no preliminary data
  2. Validation and development; preliminary data in GWI field required
- Replication/validation of previous observations, including multiple model systems, replicating preliminary data with more time points, additional doses, etc. is encouraged

**Qualitative Research**
- Fills gaps in treatment and care knowledge
- Development of materials aimed at clinicians or for Veterans/caregivers
- Explores not only care and treatment but barriers to knowledge and two-way communication

**Contributions to the Biorepository Resource Network**
- Encourage submission of samples and data to the GWIRP supported Biorepository Resource Network
- Community research resource
- Establish common data elements and sample standardization
Longer Term Strategic Plan

- The GWIRP undertook a planning project in early 2018 to develop a more strategic, longer-term approach for the research under its management.

- 3- to 5- Year Strategic Plan to be posted on the CDMRP Website Spring 2018

Plan Outline:

- Program Overview
- Current GWI Research Landscape
- GWI Funding – GWIRP and VA
- Strategic Objectives for the GWIRP
  - Strategic Direction
  - Strategic Goals
  - Short-Term Investment Strategy
- Measurable Outcomes – Tracking and Informing Future Initiatives
http://cdmrp.army.mil
Thank you