GWI Common Data Elements Project

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What are the goals of the CDE Project?

- Develop **common definitions** and **standardize** case report forms (CRF) and other instruments

- Help investigators conduct clinical research through the development of these uniform formats by which clinical data can be **systematically collected, analyzed** and **shared** across the research community

CDE Working group

- Subcommittee chairs Kim Sullivan, Rebecca McNeil and coordinator Devra Cohen.

- GWI investigators involved in the ME/CFS CDE working groups,

- Clinical and laboratory investigators who are providing materials and data to the laboratory scientists,

- Representative principal investigators and young investigators of the VA BLR&D GWI program, Department of Defense Congressionally Directed Medical Research program (DoD CDMRP)

- VACO representation: Drs. Karen Block, Peter Rumm and Aaron Schneiderman

- CDMRP representation: Dr. Kristie Lidie

The process of our GWI CDE Project

- Identify CDEs used in clinical research
  - (age, gender, race, etc.)

- Present data elements in a standard format available to all

- Identify common definitions
  - (including permissible values, range checks, etc.)

- Standardize CRFs and other instruments

- Provide information to researchers for clinical data collection and sharing

Challenges in Advancing Understanding of GWI

- Outcome measures of domains of illness vary

- Lack of consensus on measures and utility in this illness

- Case ascertainment is complex
  - No single diagnostic test; diagnosis relies on case definition, case definitions and interpretation vary

- Findings differ depending on
  - How persons are identified (e.g. self-report versus clinical assessment)
  - Site of and method of recruitment (e.g. clinic versus community; systematic versus convenience sampling)

- Lack of clinical understanding contributes to under diagnosis and misdiagnosis
  - Limits utility of record review

Enhance Measurement Methods to Improve Understanding

- **Study GWI by focusing on multiple facets of illness**
  - Refine phenotypic measures of all illness domains
    - Basic agreement on illness domains in most case definitions
    - Same measures can be applied regardless of case definition
    - Stratify on dynamic range of measures
  - Optimize instruments and standardize scoring
  - Correlate with biologic measures
    - Identify subgroups reflecting etiology and response to therapy
- **Develop Common Data Elements (CDEs) for GWI starting from the ME/CFS CDE NINDS project, a joint project of NIH (National Institute of Neurologic Diseases and Stroke) and Centers for Disease Control and Prevention**

NINDS/CDC ME/CFS Common Data Element Project

- **NINDS initiated development of Common Data Elements (CDEs) to develop data standards for funded clinical research in neuroscience**

- **CDEs are content standards that can be applied to various data collection models**
  - **Dynamic and evolve over time**
  - **Not a database**
  - **Uniform format to systematically collect, analyze and share data**

- **CDE Projects develop common definitions and standardize case report forms and other instruments**

- **Goal is to add ME/CFS to disease areas covered by NINDS CDEs**

NINDS CDE Disease Areas – over 13,000 CDEs & 800 Instruments

General CDEs

Cerebral palsy

Chiari I Malformation

Epilepsy*

Headache (newly updated)

Mitochondrial disorders*

Movement disorders

- Parkinson's disease
- Huntington's disease

Multiple sclerosis

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) (new)

Spinal cord injury (SCI)*

Stroke*

−Unruptured Cerebral Aneurysms and Subarachnoid hemorrhage

Neuromuscular disorders*

- – Amyotrophic lateral sclerosis
- – Friedreich's ataxia
- – Muscular dystrophies
- • Congenital, Duchenne/Becker, Facioscapulohumeral, Myotoni
- – Myasthenia gravis
- – Spinal muscular atrophy

Traumatic brain injury*

−Sports-Related Concussion (new)

−Biomechanical Sensors in Traumatic Brain Injury (new)

* Includes pediatric-specific recommendations

PROJECT OVERVIEW   CDE SEARCH   CRF SEARCH   FORM BUILDER   CONTACT

NINDS Common Data Elements
Harmonizing Information. Streamlining Research.

▼ CDEs   ▼ Tools   ▼ Learn

Streamline Your Neuroscience Clinical Research using content standards that enable clinical investigators to systematically collect, analyze, and share data across the research community.

The NINDS strongly encourages researchers who receive funding from the Institute to ensure their data collection is compatible with these common data elements (CDEs). Learn more about the CDE Project.

CDEs Now Available	CDEs Under Review	CDEs in Development

General (CDEs that cross diseases)

Amyotrophic Lateral Sclerosis

Epilepsy

Friedreich's Ataxia

Headache

Huntington's Disease

Mitochondrial Disease NEW!

Multiple Sclerosis

Neuromuscular Diseases

Launch Your Own Studies Faster
- Case report form modules
- Standardized data element definitions
- Instrument recommendations

Incorporate CDEs Into Systems
- Search for current CDEs
- Download CDE metadata
- Download Case Report Forms

Learn About the CDE Project
- Project overview and background
- Meetings and Presentations
- Collaboration with developers around the world

Privacy Statement | NeuroQOL | NIH Toolbox | PROMIS

NINDS Common Data Elements

NIH National Institute of Neurological Disorders and Stroke

NIH National Institutes of Health Turning Discovery Into Health

USA.gov

Page last updated on August 27, 2015

CDE Details Include (but not limited to):

- Metadata name (CDE name)
- Definition
- Example Question Text
- Permissible Values/Permissible Value descriptions
- Data Type
- Instructions
- References
- Population
- Classification
- Input Restriction
- Size
- Min Value and Max Value
- Measurement type

Classification of CDE Terminology
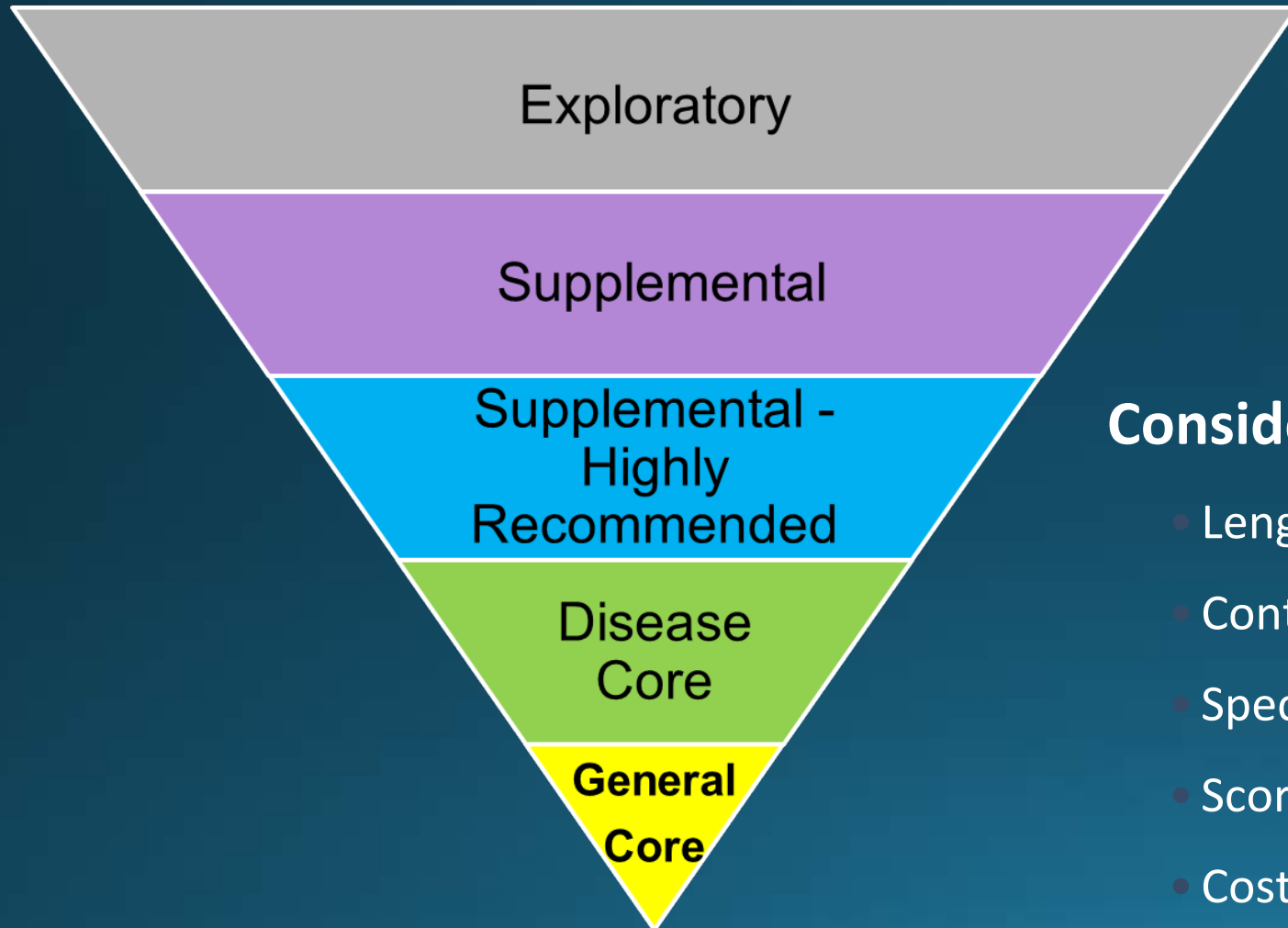
- **Case Report Form Modules** — Case Report Forms (CRFs) that logically organize CDEs for data collection

- **Guidelines** — to provide further information about the CDEs

Considerations for Instrument Selection:

- Length (number of items, time to complete)

- Content validation/Psychometric properties

- Specific validation

- Scoring algorithm

- Cost

Anticipated Benefits of CDEs

- Encourage standardized approach to phenotyping of those with GWI
  - Allows for future data sharing and searching for subgroups
- Provide guidance on laboratory and research testing
  - Options for sample collection, standards for assay validation and QC
- Expedite study start-up and encourage broader interest in the field
- Plans for incorporation into the VA and CDMRP research programs
  - Potential for broader application
  - Veteran representation in working groups

Start-up Resource Listing

Summary of Core/Supplemental – Highly Recommended Recommendations:
Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) CDEs

NIH Resources: *The NINDS also strongly encourages researchers to use these NIH developed materials for NINDS-sponsored research, when appropriate. Utilization of these resources will enable greater consistency for NINDS-sponsored research studies. Some of these tools are free of charge.*	**NIH Toolbox** **Patient-Reported Outcomes Measurement Information System (PROMIS)** **Quality of Life in Neurological Disorders (Neuro-QOL)**

Core CDEs for all NINDS Studies[1]:

CDE Domain	CDE Name	CDE ID	Classification	Study Type
Demographics	Birth date	C00007	CORE	All studies
Demographics	Ethnicity USA category	C00020	CORE	All studies
Demographics	Race USA category	C00030	CORE	All studies
Demographics	Gender Type	C00035	CORE	All studies
General Health History	Medical history condition text	C00322	CORE	All studies
General Health History	Medical history condition SNOMED CT code	C00313	CORE	All studies

Core CDEs for ME/CFS Studies:

Domain; Sub-Domain	Core Data element	CDE ID
Participant Characteristics; Demographics	Marital or partner status	C00207
Participant History and Family History; General Health History	Condition illness indicator	C58171

[1] Note: Education year count C00015 is no longer a general Core CDE

ME/CFS CDEs – Last Modified 2/13/18   Page 2 of 40

Highlight Summary Document

An overview of all recommendations, grouped by domains and subdomains

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NINDS Common Data Elements
Harmonizing information. Streamlining research.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)
Highlight Summary Document

NIH Resources

The NINDS also strongly encourages researchers to use these NIH developed materials for NINDS-sponsored research, when appropriate. Utilization of these resources will enable greater consistency for NINDS-sponsored research studies. Some of these tools are free of charge.

- National Institutes of Health (NIH) Toolbox
- Quality of Life in Neurological Disorders (Neuro-QOL)
- Patient-Reported Outcomes Measurement Information System (PROMIS)

Suicidal Ideation

Investigators should review the FDA's "Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials" for the most up-to-date information about suicidal ideation and behavior. One scale that FDA suggests is the Columbia Suicide Severity Rating Scale (C-SSRS) (available at Columbia Suicide Severity Rating Scale Website).

Disease/Domain;Sub-domain	Recommendations
Participant Characteristics; Demographics:	**Core:** General Core, Demographics **Supplemental:** Demographics
Participant Characteristics; Social Status:	**Supplemental:** Adult Employment and Education History
Participant History and Family History; General Health History:	**Core:** Past and Current Illnesses, Medical History - Immune Module **Supplemental Highly Recommended:** Medical History - Immune Module, Family Health History **Supplemental:** Reproductive and Hormonal History **Exploratory:** Medical History - Immune Module, Exposure History

Example of an Instrument Recommendation

NINDS CDE Notice of Copyright
DePaul Symptom Questionnaire (DSQ)

Availability	**Please visit this website for more information about the instrument:** The **DePaul Symptom Questionnaire** can be downloaded from the REDCap shared library.
Classification	**Core**: Myalgic encephalomyelitis/Chronic fatigue syndrome (ME/CFS)
Short Description of Instrument	The DePaul Symptom Questionnaire (DSQ) is a comprehensive, 99-item self-report measure of ME/CFS symptomatology based on 3 CFS definitions (Fukuda, et al., 1994). It includes questions on demographics, symptomatology, and occupational, social and medical history. The DSQ has been used in multiple countries including US, Japan, Norway, England, Mexico, Iran and others (and translated in multiple languages). There is a data set of over 1200 patients who have completed the questionnaire. There is now data on it comparing those with MS and post-polio syndrome and patients with ME/CFS. A number of papers have examined the psychometric properties of this instrument.
Comments	Ages: 18–65 Time to complete: 30–50 minutes Psychometic properties: correlates with other similar measures, demonstrates test-retest reliability, correlates with physician diagosis of ME/CFS
Scoring	Scoring algorithms can help support the conclusion that a person meets certain case definitions, including the Fukuda et al., 1994 Canadian Consensus Criteria, ME-ICC, IOM, and others. Participants rate each symptom's frequency over the past six months on a 5-point likert scale: 0=none of the time, 1=a little of the time, 2=about half the time, 3=most of the time, and 4=all of the time. Participants rate each symptom's severity over the past six months on a 5-point likert scale: 0=symptom not present, 1=mild, 2=moderate, 3=severe, 4=very severe. There are different scoring algorithms, each supporting different underlying factor structures and pertinent domains (e.g., autonomic, immune, gastrointestinal). Klimas et al., 2015.

Working Group 1: Symptom Assessment_ 20 VA and CDMRP investigators & veteran advocates chaired by Kim Sullivan, PhD

➤ Symptom Assessment Modules: Baseline/Covariate Information, Fatigue, Post-Exertional Malaise (PEM), Sleep, Pain, Quality of Life (QoL)/Functional Status/CPET/Activity

Working Group 2: Systems Assessment_ : 20 VA and CDMRP investigators &veteran advocates, chaired by Becky McNeil, PhD RTI

➤ Systems Assessment Modules: Neurologic/Cognitive/CNS Imaging, Autonomic, Neuroendocrine, Immune, Biomarkers

Ashford, Wes , Abdullah, Laila, Bunker, James Abreu, Maria, Cheema, Amanapreet Abu Donia, Mohamed, Cohen, Devra, Aenlle, Kristina, Cook, Dan Arocho, Jimmay, Coumoyer, Jeffrey Balbin, Elizabeth, Craddock, Travis Baraniuk, James, Golier, Julia Block, Michelle, Hardie, Anthony DeBeer, Bryann, Helmer, Drew Engdahl, Brian, Kerr, Kathleen Filipov, Nikolay, Krengel, Maxine Fletcher, Mary Ann, Lindheimer, Jake Kokkotou, Efi, Lloyd, Patricia, Janulewicz Lidie, Kristy, McNeil, Becky Little, Deborah M, Paris, Bonnie Loging, William, Reinhard, Matthew Morris, Marianna, Rumm, Peter Nathanson, Lubov, Schneiderman, Aaron Nichols, Denise, Sims, Kellie Pasinetti, Giulio, Steele, Lea Shungu, Dikoma, Turner, Marsha Sullivan, Kim, Gilbert, Beth Van Leeuwen, Jon, Hunt, Stephen Waziry. Paula, Klimas, Nancy Younger, Jarred, Unger, Beth, Whittemore,Vicky

Status Report

Modules Completed	New Modules Completed	Underway
Sleep	Fatigue	Baseline/Covariate Information
Quality of Life (QoL)	Pain	Post-Exertional Malaise (PEM)
Functional Status	CPET/Activity	Military Experience/
Neurologic		Environmental Exposure
- Cognitive		
- CNS Imaging		
Autonomic		
Neuroendocrine/Endocrine		
Immune Biomarkers		

Timeline from here

| Now-November | December | February |

completed modules

- subcommittees

public review

- followed by revision

post for use

- VA RAC site, CDMRP, NINDS CDE
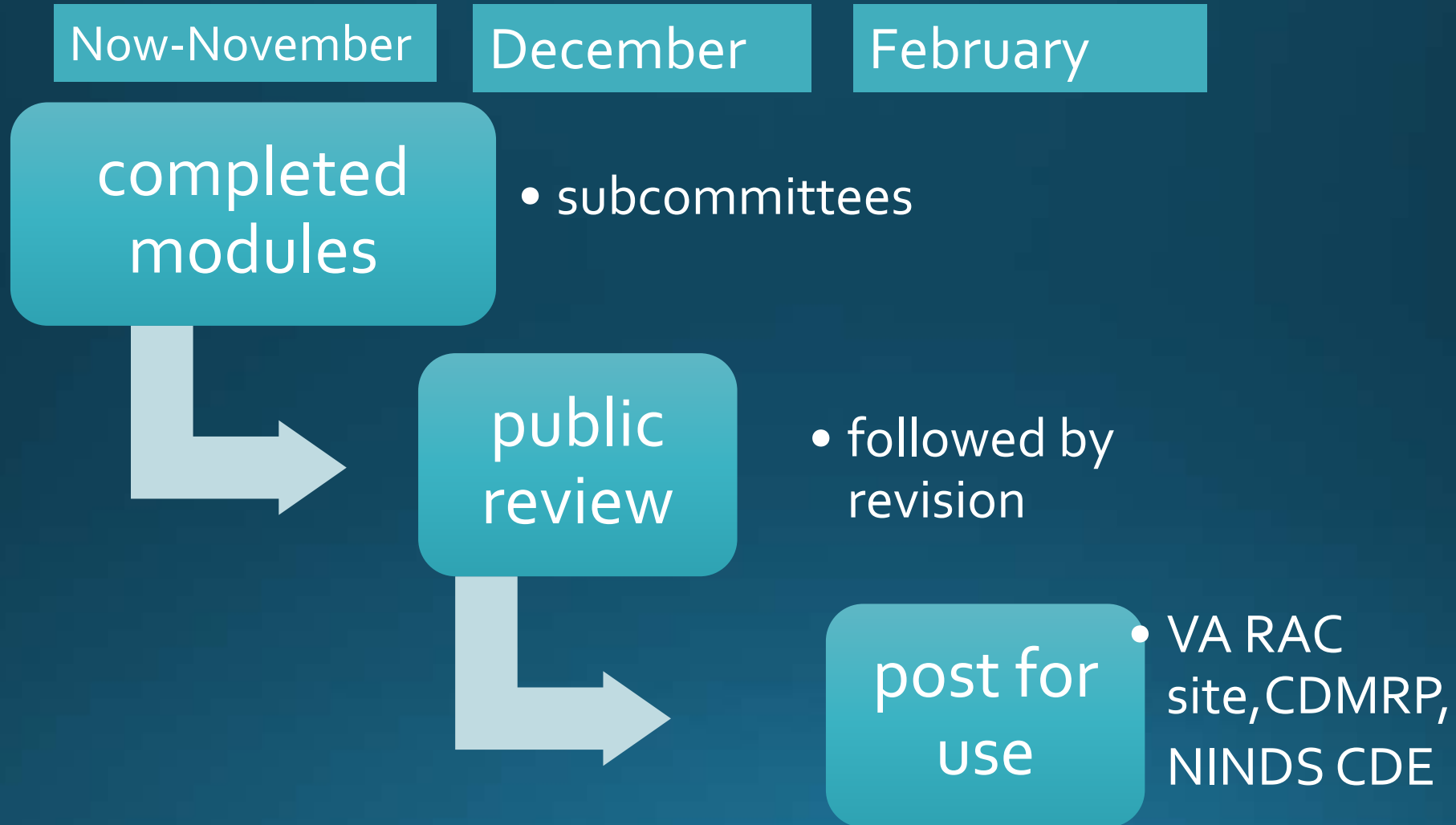
Process from here

- The final document will be turned into both a paper and a resource "how to use" document for the resources pages of the CDMRP GWRP and VA GWI program

- This is version 1.0, revisions are expected

Using field based meetings to tackle barriers

- Case definition?
  - refining criteria using CDE
  - Clearly defining comorbid conditions and severity
  - Exclusion and entry criteria recommendations
- Primary outcome variables and clinical trials design
- The VA medical record as a research tool – utilizing CDE in the EMR
- ICD 11 or ICD 12 – creating an ICD code

Engaging veterans/recruitment

- Field based meeting specifically to look at ways to improve veteran engagement, recruitment efforts

- CDMRP.army.mil/gwirp resources – recruitment guide

- 91outcomes.com. 1,000,000 visitors

- Gulf war illnesses facebook page , 12,000 members usmc1one@gmail.com

- VSOs, Veterans of Foreign Wars , other veteran organizations

- The other main GWI veterans social media sites

- ExploreVA.gov – consider link research efforts to this new initiative

- Field base meeting to brainstorm and create solutions

Case Definitions for Research

- **Multiple definitions have been used**
  - **Kansas , but with variable modifications** The Kansas definition of GWI requires that cases have moderately severe or multiple chronic symptoms in at least three of six categories: fatigue/sleep problems, pain, neurological/cognitive/mood symptoms, respiratory complaints, gastrointestinal problems or skin symptoms (Steele, 2000). Veterans who have severe psychiatric disorders or other medical conditions that might predict similar symptoms are excluded. The 2014 IOM report on GWI case definitions recommended that this definition be used for research purposes or the CDC case definition of CMI (IOM, 2014).

Case Definitions for Research

- **Multiple definitions have been used**
  - **CMI, often used in epidemiology** must report one or more symptoms that have been ongoing for at least six months in two of three categories, which include musculoskeletal pain (symptom list: joint pain, joint stiffness, muscle pain); mood-cognition (feeling depressed, feeling moody, feeling anxious, trouble sleeping, difficulty remembering or concentrating, trouble with word finding), and fatigue. CMI can be categorized as "severe" if the veteran rates each defining symptom as severe or "mild-moderate" for milder complaints.
- **None have provided methods to standardize (operationalize) their use**
  - **Variation in how illness domains (criteria) are assessed (e.g. questionnaires, laboratory tests, scoring methods)**

Areas of Agreement Among Definitions

- Fatigue, post exertional relapse, pain, cognitive issues and non restorative sleep

- May be accompanied by other co-morbid conditions such as
  - Fibromyalgia, irritable bowel syndrome, temporomandibular joint syndrome, interstitial cystitis, migraines. But Co-morbid PTSD, TBI, major depression tend to be included or excluded based on severity (does it explain symptoms?) but vary by study

  - The case definition working group is formeing to address these issues

  - Survey should be in your email boxes in the next week – please be thoughtful and consider the issues when you reply. Kim Sullivan, Maxine Krengel and Nancy Klimas are leading this project

Conclusion

- Thanks to the full participation of the GWI research community and the advocacy community we are on track to deliver the CDE version 1 on time.

- People applying for grants this round should be aware of the process, and use the language suggested referring to the implementation of the recommendations in the final studies prior to implementation. The CDMRP program announcement requires this compliance and the VA should consider the use of preferred assessment platform when reviewing applications as well.

- We look forward to a robust public comments period and will revise accordingly.

- We plan to provide a similar process addressing the use of the case definition in research

- Thank you