Gulf War Illness Common Data Elements Project Introduction

In an effort to enhance data quality and to facilitate data sharing across research studies focusing on veterans diagnosed with Gulf War Illness (GWI), VA Clinical Science Research and Development (CSR&D) funded a field based meeting of clinical and laboratory research experts in the GWI community. The goal of this meeting was to spearhead an effort to develop Common Data Elements (CDEs) that will promote systematic data collection for GWI research. With the understanding that information that is consistently captured and recorded across research studies will facilitate the comparison of results, the GWI CDE working group members are developing common definitions, terminology, and standardized data sets tailored to GWI research.

This document represents the progress accomplished to date by the working groups in developing the initial draft of a resource that will standardize the collection of GWI research data. The GWI CDEs will provide a core set of data elements and definitions and will not include all data elements, outcome variables, or innovative data elements that will be critical for clinical investigators to collect in a specific funded study. Recognizing that extensive data collection in clinical research presents a significant burden for investigators and study participants, the data elements in each module are designated with the terms Core, Exploratory, Supplemental, or Supplemental-Highly Recommended. All GWI CDE modules will be available for public comment.

The following definitions of the types of CDEs correspond directly to the NIMDS ME/CFS Project.

Data Element: A logical unit of data, pertaining to information of one kind. A data element has a name, precise definition, and clear enumerated values (codes) if applicable. A data element is not necessarily the smallest unit of data; it can be a unique combination of one or more smaller units. A data element occupies the space provided by field(s) on a paper/electronic case report form (CRF) or field(s) in a database record.

Core CDE: A data element that collects essential information applicable to any study, including either those, which span across all disease and therapeutic areas, or those that are specific to one disease area. The working group assign the “Core” classification based on the current clinical research best practices. It is anticipated that investigators will need to collect the Core CDEs for any type of study.

Exploratory CDE: A data element that requires further validation, but may fill current gaps in the CDEs and/or substitute for an existing CDE once validation is complete. Such data elements show great promise, but require further validation before they are ready for prime-time use in clinical research studies. They are reasonable to use with the understanding that limited study has been done for veterans with GWI.

Supplemental CDE: A data element which is commonly collected in clinical research studies but whose relevance depends upon the study design (i.e., clinical trial, cohort study, etc.) or type of research involved

Supplemental-Highly Recommended CDE: A data element which is essential based on certain conditions or study types in clinical research studies. In most cases, these have been used and validated in GWI. These data elements are strongly recommended for GWI research, study type or design.

To develop the GWI CDEs, the GWI working groups first focused on the data elements developed by the NIMDS Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) working groups which are divided into 11 subgroups:in the domains of: Baseline/Covariate, Fatigue, Post-Exertional Malaise, Sleep, Pain, Neurologic/Cognitive/CNS Imaging, Autonomic, Neuroendocrine, Immune, Quality of Life/Functional Status/CPET/Activity, Biomarkers. CDEs specific to GWI will be suggested in other domains relating to occupational military exposure and military experience as well as to clinical manifestations of diseases experienced by veterans with GWI (i.e. gastrointestinal, dermatological, and respiratory diseases).

All GWI CDE modules will be available for public comment. The final draft will include references corresponding to all instruments in all domains. These GWI Common Data Elements are developed by clinical research experts from the community, with administrative support from Nancy Klimas, MD, Devra Cohen, MPH, Kim Sullivan, PhD, and Becky McNeil, PhD. Please direct any questions to Nancy Klimas at nklimas@nova.edu or Devra Cohen at dcohen1@nova.edu.

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Draft Module Recommendations (version 1.0)

Module: Fatigue (Preliminary draft) **Instrument name**	**Recommendation**
Fatigue Severity Scale	Supplemental
Checklist for Individual Strength-Fatigue	Supplemental
PROMIS Fatigue short form	Supplemental
Neuro-QoL fatigue	Supplemental
Modified Fatigue Impact Scale	Supplemental
Multidimensional Fatigue Inventory	Core
POMS fatigue	Undecided

General comments: There are many instruments to measure fatigue. There is redundancy between some instruments and the commonly used symptom assessments (Kansas and the DePaul Symptom Questionnaire). Specific instruments may be more relevant to dimensions examined in a given study and should be considered on a per-study basis.

Module: Sleep **Instrument name**	**Recommendation**
Sleep Questions for All Studies	Exploratory
Sleep Focused Study Questionnaire	Exploratory
Sleep Assessment Questionnaire-Moldofsky	Exploratory
Pittsburgh Sleep Quality Index	Supplemental - Highly recommended
Stanford Sleepiness Scale	Exploratory
Sleep Disorders Screening Checklist	Exploratory
Holland Sleep Disorders Questionnaire	Exploratory
Epworth Sleepiness Scale	Supplemental - Highly recommended
Nonrestorative Sleep Scale	Exploratory
Global Sleep Assessment Questionnaire	Exploratory
Restorative Sleep Questionnaire	Exploratory

General comments: There is redundancy between sleep instruments and the commonly used symptom assessments (Kansas and the DePaul Symptom Questionnaire). For many studies, the sleep-related symptoms included in the symptom assessment are sufficient to address the needs of studies for which sleep is not a primary outcome. We thus recommend that sleep instruments be considered supplemental, so as to not increase participant burden. Sleep instruments should be selected with respect to specific study goals. For example, studies focused on daytime aspects of sleepiness might prefer the Epworth Sleepiness Scale, while those focused on night-time aspects may choose the Pittsburgh Sleep Quality Index.

Module: Pain (Preliminary draft) **Instrument name**	**Recommendation**
Brief Pain Index	Supplemental
Fibromyalgia Impact Questionnaire - revised	Exploratory
McGill Pain Questionnaire SFv2	Supplemental
Faces Pain Scale - revised	Exploratory
Visual Analogue Scale	Exploratory
Pain Frequency - Severity - Duration	Exploratory
Neuropathic Pain Symptom Inventory	Exploratory
PROMIS pain interference short form	Exploratory
PROMIS pain behavior short form	Exploratory
Widespread Pain Index (ACR)	Supplemental
General comments: The domain of pain is central to the experience of Gulf War Illness. There are a number of pain assessment instruments suggested for ME/CFS, many of which lack validation in GWI settings. These also have different areas of focus, e.g., pain location, severity, hip/knee pain, and interference with common activities.	

Module: Quality of Life **Instrument name**	**Recommendation**
VR-36 + PCS and MCS	Core
VR-12	Supplemental
VR-8	Supplemental
NIH Neuro-QoL (PROMIS)	Exploratory
WHO Well-Being Index (5)	Exploratory
WHO Well-Being Index (10)	Exploratory
EuroQoL	Exploratory
HRQoL	Exploratory
General comments: The VR-36 is currently the most widely used QoL instrument in ME/CFS and GWI. It is included in the WRIISC intake package. The physical and vitality subscales are often used as functional measures, and some users use alternate item weightings to (de)emphasize the contributions of selected domains. It is also important, when capturing QoL, to be sure that we capture emotional well-being and do not focus entirely on physical aspects of health. Alternate measures include the VR-12, VR-8, NIH Neuro-QoL (PROMIS), the WHO 5- and 10-question Well-Being Indices, EuroQoL, and HRQoL. There is a need for empirical evidence regarding sensitivity to change within the GWI population for many of these measures. In the absence of additional data, we recommend the VR-36 as the core instrument.	

Module: Functional Status	
Instrument name	**Recommendation**
Karnofsky Scale	Supplemental - HIghly Recommended
WHODAS	Exploratory
SF-36 physical component subscale	Core
SF-36 vitality subscale	Core
Bell CFIDS disability scale	Supplemental - Highly Recommended
Functional Disability Index - child	N/A
Functional Disability Index - parent	N/A
General comments: Common measures of functional status include the Karnofsky scale (adaptation for chronic disease), WHODAS, and the physical (PCS) and vitality subscores of the SF-36. The Karnofsky scale is likely redundant to other functional scales as a self-report scale, but may stand alone when considered as an objective clinician-report scale. At this time, we recommend the SF-36 physical and vitality subscales as core functional status instruments, with the Karnofsky scale and Bell CFIDS disability scale as highly recommended supplemental instruments.	

Module: Cardiopulmonary Exercise Test (CPET)	
GWI Exercise Challenge Studies Prior to instrumentation and testing • Exercise pre-participation health screening,[16] including assessment of physical activity behavior via questionnaire, accelerometry[17,18] or both. • Participant height, body weight, and age • 24 hour recall of drug or supplement use • Whether or not participant arrived to the laboratory in a fasted state • Atmospheric conditions in the testing environment (i.e., barometric pressure, mmHg, humidity, %, and temperature, C°)	Supplemental - Highly Recommended

• Heart rate and blood pressure • Gulf War Illness symptom severity questionnaires During testing	Supplemental - Highly Recommended
• Oxygen consumption, carbon dioxide production, ventilation via indirect calorimetry (resting and during exercise) • Heart rate • Rating of perceived exertion (6-20 scale) • Blood pressure • Exercise intensity (% of estimated maximum) • Workload (rpm and watts for cycling studies, speed/% grade for treadmill studies) Immediately after testing	Supplemental - Highly Recommended
• Reason why exercise was stopped by participant (e.g., target testing duration complete, breathlessness, muscle pain, fatigue, other) or test administrator (e.g., contraindications to exercise)[19] • Blood lactate	
Prior to instrumentation and testing • Participant expectations for effects of exercise on psychological and physical health outcomes[20]	Supplemental-Recommended

During testing	Supplemental-Recommended
• Muscle pain in exercising muscles[21] • Blood lactate (resting and during exercise) • Collection of physiological and perceptual measures during active recovery/cool down	

General comments: **:** In an exercise challenge study, maximal or sub-maximal exercise protocols are used to perturb physiological systems and determine the effects of this perturbation on various other outcomes such as cognitive performance, sensory perception (e.g. pain & fatigue), mood (e.g. depression & anxiety) and others. These changes are often compared between veterans with Gulf War Illness (GWI) and healthy control participants in order to study the patho-physiology of GWI. The term cardio-pulmonary exercise testing (abbreviated as CPET[1,2] or CPX[3,4]) can be applied when indirect calorimetry is used to measure respiratory oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), and ventilation ($\dot{V}E$) during a maximal or sub-maximal exercise challenge protocol.
To date, 11 exercise challenge studies have been published that used maximal or sub-maximal exercise protocols to evaluate a variety of perceptual and physiological outcomes in GWV[5–15] (Supplemental Table 1). Regardless of how or why these protocols are employed, there are important data element considerations that can improve their validity, reliability & comparability. Tables 1 & 2 provide a bulleted list of data elements that we recommend be collected to improve comparability/ interpretability between exercise challenge studies.

Notes:

(i) Because exercise challenge protocols are not considered to be CORE data elements in studies involving Gulf War Veterans, meaning that not all studies are expected to include an exercise component, we categorize these recommendations as either “Supplemental - Highly Recommended” (Table 1) or “Supplemental” (Table 2). Therefore, these recommendations apply specifically to studies of GWV that include an exercise challenge.

(ii) The term “exercise challenge study” can apply to both maximal and sub-maximal exercise protocols. To date, 7 studies involving Gulf War Veterans have reported using maximal exercise[5–8,10,13,14] and 4 have reported using both maximal and sub-maximal exercise[9,11,12,15] (Supplemental Table 1). These recommendations apply to studies that use maximal or sub-maximal exercise protocols.

(iii) We have listed the use of CPET methodology in exercise challenge studies as supplemental-highly recommended because it is regarded as the gold standard method for exercise testing[3] and has demonstrated diagnostic utility in many other clinical populations.[2, 4] However, a majority of the following recommendations also apply to investigators who are conducting exercise challenge studies without the use of indirect calorimetry instruments needed for CPET.

Module: Neurological/Cognitive/Imaging **Neuroimaging** **Instrument name:**	**Recommendation:**
Diffusion Tensor Imaging (DTI)	Supplemental-Highly Recommended
Electroencephalography (EEG)	Supplemental-Highly Recommended
Functional Magnetic Resonance Imaging (fMRI)	Supplemental-Highly Recommended
Low-resolution electromagnetic tomography (LORETA)	Supplemental-Highly Recommended
Magnetic Resonance Imaging (MRI)	Supplemental-Highly Recommended
Magnetic Resonance Spectroscopy (MRS)	Supplemental-Highly Recommended
Magnetoencephalography (MEG)	Supplemental-Highly Recommended
Positron Emission Tomography (PET)	Supplemental-Highly Recommended
Quantitative Electroencephalography (qEEG)	Supplemental-Highly Recommended
General Comments: PET and MRS CRF forms have been updated to reflect neuroinflammatory and oxidative stress markers being studied in GWI. All CRFs have been recommended as supplemental-highly recommended for use if the study is using that imaging modality (i.e. MRS CRF if doing MRS study). In addition, FreeSurfer post-processing software and quantitative susceptibility mapping for iron markers were also recommended in the summary form.	

Neuropsychological **Instrument name:**	**Recommendation:**
Weschler Adult Intelligence Scale- IV (WAIS-IV) Recommended tests: Digit spans, Block Design	Supplemental-Highly Recommended
Profile of Mood States (POMS)	Supplemental-Highly Recommended
Davidson Trauma Scale (DTS)- PTSD	Supplemental-Highly Recommended
Delis-Kaplan Executive Function System (D-KEFS) Recommended modules: Color-Word-Interference Test, Trail Making Test, Verbal Fluency	Supplemental-Highly Recommended
California Verbal Learning Test- Second Edition (CVLT-II)	Supplemental-Highly Recommended
Rey- Osterrieth Complex Figure Test (ROCF)	Supplemental-Highly Recommended
Finger Tap Test	Supplemental
Grooved Pegboard Test	Supplemental
Hopkins Verbal Learning Test (HVLT)	Supplemental
Brief Visual Memory Test (BVMT)	Supplemental

PTSD Checklist for DSM-V (PCL-5)	Supplemental
Center for Epidemiological Studies Depression Scale (CES-D)	Supplemental
Clinician Administered PTSD Scale (CAPS-5)	Supplemental
Structured Clincal Inteview for DSM-IV (SCID-5)	Supplemental

General Comments: The neuropsychological test battery has been updated for highly recommended tests based on being used in at least 3 GWI studies, covering areas of cognition identified as problematic in GWI in a recent meta-analysis (Janulewicz et al., 2017), and instruments frequently used clinically in these areas were classified as Supplemental-Highly Recommended. Supplemental tests were chosen based on the fact that they offer multiple test versions suitable for multiple testing sessions in treatment trials and cover relevant cognitive domains in GWI.

Neurological	
Instrument name:	**Recommendation:**
Neurological CRF	Supplemental- Highly Recommended

General Comments: The neurological CRF was considered appropriate for the studies using a neurological exam in veterans with GWI and was therefore recommended as supplemental-highly recommended for those studies.

Module: Autonomic	
Instrument name	**Recommendation**
Compass- 31	Supplemental-Highly Recommend
Dolorimetry	Supplemental-Highly Recommend
Passive Standing Test CRF	Exploratory
Modified Orthostatic Symptom Grading Scale CRF	Exploratory
Heart Rate Variability	Exploratory
Tilt Table Test	Exploratory
Romberg Test	Exploratory
Sudomotor Test	Exploratory
Pupilometry	Exploratory
Beighton Score	N/A

General comments: Compass-31 and Dolorimetry measures were considered as Supplemental Highly Recommended for autonomic studies and the additional tasks as Exploratory for GWI. Suggested modifications for the GWI protocol include the removal of the Beighton Score CRF from the CDEs since joint hypermobility is less relevant to veterans with GWI and the addition of Heart Rate Variability, Tilt Table Test, Romberg Test, Sudomotor Test, Pupilometry, and Dolorimetry testing because they have been shown to be significantly different in GWI studies. It was also recommended that the Passive Standing Test CRF be modified to 5 minutes standing rather than 10 minutes.

Module: Endocrine/Neuroendocrine	
Instrument: Case Report Forms (CRF)	**Recommendation:**
Neuroendocrine Labs	Supplemental-Highly Recommended
(a) Cortisol	
(b) Diabetes	
(c) Thyroid	
(d) Sex hormones	
(e) other endocrine	
Neuroendocrine/ Hypothalamic Symptoms	Supplemental-Highly Recommended
Reproductive and Hormonal History	Supplemental-Highly Recommended
ASA Dietary Survey	Supplemental
Dietary Supplements	Supplemental
General Comments: The module name has been changed to Endocrine/Neuroendocrine. The Neuroendocrine Labs, Neuroendocrine/hypothalamic symptoms and reproductive and hormonal history CRFs were all listed as Supplemental-highly recommended with modifications and the ASA dietary survey and Dietary Supplements CRF were considered supplemental. To be more relevant to GWI, dexamethasone challenge task was added to the Neuroendocrine Labs CRF and oral glucose tolerance test, fluid-deprivation test and plasma renin activity were removed. Other additions to the Neuroendocrine labs CRF include metabolic syndrome measures (cholesterol, triglycerides, BP, glucose) and liver enzymes which have been shown to be associated with GWI in some studies. A separate dietary survey and dietary supplements usage form was recommended and the forms were adopted from the Mitochondrial and GI disease CDEs. Through the quantification of multiple hormones it is possible to generate cross-sectional data that can be used to determine comorbid endocrine conditions in GWI. Prior neuroendocrine differences found in GWI have focused on cortisol and HPA axis function, ACTH and using the dexamethasone challenge test. Differences have also been found to be correlated with neutoxicant exposures. Questions have been added for these areas to the Neuroendocrine Labs form to make it more relevant to GWI.	

Module: Immune	
Instrument name:	**Recommendation:**
(1)Medical History CRF	
a. immune system onset type	Supplemental-Highly Recommended
b. Rome IBS Criteria	Supplemental
(2) Physical Exam CRF	Supplemental-Highly Recommended
(3) Laboratory Tests CRF	Supplemental-Highly Recommended
(a) NK Cell Assay Test	Supplemental
(4) Exposure History CRF	Exploratory (change to GWI specific exposures)

General comments: The four recommended CRFs for Immune function were recommended for GWI with modifications. Modifications were made to the Laboratory Tests CRF to make it more relevant to GWI by removing several sections regarding extensive and costly infectious disease and hypersensitivity testing and adding sections regarding additional proinflammatory cytokine and CNS autoantibody markers shown to be associated with GWI in prior studies. (Table 1 Blood Laboratory Tests, Table 2A Infectious Disease Laboratory Tests- Serum Antibodies, Table 2B Infectious Disease Laboratory Tests- PCR, Other, and Table 3 Autoimmunological and Other Immune Profiling Laboratory Tests, and Table 4 Hypsersensitivity Lab Tests). The exposure CRF was not considered appropriate for GWI and a new exposure form was recommended and classified as exploratory. Rome IBS Criteria was also considered important in GWI research but changed from core to the supplemental category.

Module: Biomarkers	
Instrument name:	**Recommendation:**
Biomarker Categories:	
OMICS:	Exploratory
Microbiome/ Microorganisms	Exploratory
Proteome/ Proteins	Exploratory
Metaolome/ Metabolism	Exploratory
Genome/ Epigenome	Exploratory
Gene expression/ Transcriptome	Exploratory
miRNA profiling	Exploratory
Multiplex vs. SRM assays	Exploratory
Bioinformatics Pathways	Exploratory
Interconnect omic data	Exploratory
NON-OMICS:	
Protein array analysis	Exploratory
Cytokine measurements	Exploratory
Chemokine Measurements	Exploratory
Flow-cytometry measurements of immune cells	Exploratory
Autoantibody analyses	Exploratory
Individual protein quantification	Exploratory
Biomkarkers of autonomic system dysfunction	Exploratory
Blood chemistry	Exploratory
Elements from detoxification pathways	Exploratory
Exosomes	Exploratory
Biomarker Guidelines **Biomarkers- Related Sample and Medication Questions** **Biomarker Reference Table**	Supplemental-Highly recommend

General Comments: The biomarker subcategories were modified by adding eight additional categories relevant to GWI, and they are now divided between omics and non-omics categories. All

tests were considered exploratory, but the Biomarker-Related Sample and Medication Questions form has been listed as supplemental-highly recommended for consistency among biomarker studies. The form has been modified for GWI relevance to now include exposome, CNS autoantibodies, flow cytometry of cell types, Co-Q10, PON1, BChE markers, oxidative stress markers, glutathione and the option for sharing information samples with BBRAIN biorepository. The Biomarker Reference table will be modified for GWI specific references.