

Veteran Affairs/ Department of Defense Gulf War Illness Common Data Elements Project Draft Version 1.0

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 Biomedical Laboratory Research and Development (BLR&D) funded a field-based meeting including internal- and external- federal partners and subject matter 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 developed 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 critical for principal investigators to collect for 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 are available for public comment.

The following definitions of the types of CDEs correspond directly to the NINDS 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 National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) working groups in 11 domains. The clinical manifestations of diseases experienced by veterans with GWI (i.e. gastrointestinal, dermatological, and respiratory diseases) are incorporated in these modules. The GWI working groups are in the process of developing CDEs specific to GWI by adding a 12th domain relating to occupational military exposure and military experience.

Despite overlap, the working groups worked in 12 domains:

Symptoms Assessment

- Baseline/Covariate
- Fatigue
- Post-Exertional Malaise
- Sleep
- Pain
- QOL/Functional Status/Exercise Challenge Tests/Activity

Systems Assessment

- Neurologic/Cognitive/CNS Imaging
- Autonomic
- Endocrine/Neuroendocrine
- Immune
- Biomarkers

Military Experience/Environmental Exposure

- Under Development

All GWI CDE modules are 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 and Devra Cohen, MPH, based at the Miami VA Healthcare System and Nova Southeastern University. Please direct any comments to GWICDE@nova.edu.

VA/DoD GWI CDE Project Gulf War Illness (GWI) Baseline/Covariate Subgroup

The baseline/covariate module recommends the use of two case definitions of Gulf War Illness, the Kansas case definition and the CDC case definition as Core instruments, to be employed in studies of veterans diagnosed with GWI, according to the protocol's specifications. Any revisions to the GWI case definition will be addressed and agreed upon in a separate initiative where common inclusion and exclusion criteria will be agreed upon in order to increase consistency and replicability across studies. As changes are implemented, this section will be updated by the GWI CDE subgroup.

This module is comprised of checklists and forms for use in clinical research that are designated as "supplemental—highly recommended." The forms are adaptations of forms that initially were designed by the ME/CFS Common Data Element workgroup. These forms include: demographic information, adult employment and education history, past and current illnesses, family health history, questions from the DePaul Symptom Questionnaire, the symptom checklist, physical examination, laboratory test results and medication/other treatments forms.

Summary Recommendations

GWI Common Data Elements Module: Baseline/Covariate

Instrument Name	Classification (Core, Supplemental-----Highly Recommended, Supplemental, or Exploratory)
General Core	Supplemental—Highly Recommended
Demographic Information for Baseline GWI	Supplemental—Highly Recommended
Adult Employment and Education History	Supplemental—Highly Recommended
Past and Current Illnesses	Supplemental—Highly Recommended
Family Health History	Supplemental—Highly Recommended
Questions from DePaul Symptom Questionnaire	Supplemental—Highly Recommended
Symptom Checklist	Supplemental—Highly Recommended
Physical Examination Form	Supplemental—Highly Recommended
Laboratory Test Results	Supplemental—Highly Recommended
Medication/Other Treatments	Supplemental—Highly Recommended
Kansas Case Definition of Gulf War Illness	Core
CDC Case Definition of Gulf War Illness	Core

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements Draft Version 1.0, 12/1/18

Link to Description of GWI Research Measures

The GWI CDE workgroups created the summary table of recommended data standards for GWI research and classified each instrument as Core, Supplemental - Highly Recommended, Supplemental, or Exploratory. The following table provides the link to a description of the specific instruments, case report forms, or guidelines that are listed in the summary table for this module. These descriptions and forms were developed by the NINDS ME/CFS common data elements workgroups and are linked directly to their website.

GWI Common Data Elements Module: Baseline/Covariate Instrument and Link

Instrument
General Core https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards
Demographic Information for Baseline GWI https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards
Adult Employment and Education History https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards
Past and Current Illnesses https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards
Family Health History https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards
Questions from DePaul Symptom Questionnaire https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/ni
Symptom Checklist
Physical Examination Form https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards
Laboratory Test Results https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards
Medication/Other Treatments https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards
Kansas Case Definition of Gulf War Illness
CDC Case Definition of Gulf War Illness

VA/DoD GWI CDE Project Gulf War Illness (GWI) Post-Exertional Malaise Subgroup

Post exertional malaise (PEM) can generally be characterized as an exacerbation of symptom severity following an exertional stimulus, although the exact definition of the term and what constitutes an exertional stimulus can vary. The two primary objectives of the PEM subgroup are: 1) to determine whether a psychometric instrument could be recommended as a core data element for establishing PEM presence or absence in all Gulf War Illness (GWI) studies, and 2) to recommend common data elements in PEM-focused studies that should be standardized or reported in detail for replication. In terms of judging the degree to which these data elements met the needs of the GWI research community, the recommendations of the PEM subgroup should be interpreted in the context of several gaps in the literature that, if addressed, may improve the ability to make empirically guided recommendations for measuring PEM in GWI research. These gaps include the following:

1. The lack of consensus in the literature for an operational definition of PEM.¹⁻³
2. A dearth of studies that have measured PEM in Veterans with GWI. Most PEM research has been conducted in civilians with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Thus, although ME/CFS and GWI patients have overlapping characteristics, questionnaires that are specifically designed to measure PEM have not been validated in GWI samples.
3. For determining the presence or absence of PEM, it has been argued that question item wording influences the rates at which PEM is reported, and that many research participants do not endorse the presence of PEM because they actively avoid activities that would trigger the response.⁴ For measuring the PEM response, variability issues include symptom type (e.g., pain, fatigue, cognitive dysfunction, mood), exertional stimulus type (e.g., physical, cognitive, emotional, orthostatic), cardio-respiratory fitness and physical activity behavior, and changes in potential biological mediators (e.g., brain function, immune responses, autonomic function).
4. Empirical evidence of an instrument that not only establishes presence or absence of PEM, but also possesses sensitivity to change to detect day-to-day fluctuations in GWI symptom severity is needed to understand the time-course of PEM (i.e., how long does PEM last?). Determining the magnitude and time-course of PEM may also facilitate interpretation of studies aimed toward treating GWI by clarifying the extent to which changes in symptoms are due to the natural history of PEM or the actual treatment, especially in trials for which placebo-control groups are not possible (e.g., cognitive behavioral therapy, mindfulness based exercise, exercise training).

The PEM subgroup includes Jacob Lindheimer, Dane Cook, Matthew Reinhard, Peter Rumm, Lea Steele, and Patricia Janulewicz Lloyd.

Summary Recommendations

GWIC Common Data Elements Module: Post-Exertional Malaise Table 1.

Instrument Name	Classification (Core, Supplemental-Highly Recommended, Supplemental, or Exploratory)
DePaul Symptom Questionnaire 5-item Post Exertional Malaise sub-scale	Supplemental

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements Draft Version 1.0, 12/1/18

[Link to Description of GWI Research Measures](#)

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GWIC Common Data Elements Module: Post-Exertional Malaise Instrument Description and Link

Instrument
DePaul Symptom Questionnaire https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2768

References

1. Clayton, E. W. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: an IOM report on redefining an illness. *JAMA* 313, 1101–1102 (2015).
2. Fukuda, K. *et al.* The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Ann. Intern. Med.* 121, 953–959 (1994).
3. Carruthers, B. M. *et al.* Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. *J. Chronic Fatigue Syndr.* 11, 7–115 (2003).
4. Cotler, J., Holtzman, C., Dudun, C. & Jason, L. A Brief Questionnaire to Assess Post-Exertional Malaise. *Diagnostics* 8, 66 (2018).
5. Jason, L. A. *et al.* The development of a revised Canadian myalgic encephalomyelitis chronic fatigue syndrome case definition. *Am. J. Biochem. Biotechnol.* 6, 120–135 (2010).
6. Jason, L. A., McManimen, S. L., Sunnquist, M. & Holtzman, C. S. Patient perceptions of post exertional malaise. *Fatigue Biomed. Health Behav.* 6, 92–105 (2018).
7. Jason, L. A., So, S., Brown, A. A., Sunnquist, M. & Evans, M. Test–retest reliability of the DePaul Symptom Questionnaire. *Fatigue Biomed. Health Behav.* 3, 16–32 (2015).

GWI Common Data Elements Module: Post-Exertional Malaise Table 2.

Instrument Name	Classification
<p>Study baseline Type of exertional stimulus (e.g., physical exercise, cognitive, emotional, orthostatic) and detailed methodological description of steps that were taken to keep the stimulus as standardized as possible across study participants.</p>	Supplemental—Highly Recommended
<p>Study baseline 5-item post-exertion malaise sub-scale of the DePaul Symptom Questionnaire.</p>	Supplemental
<p>Study baseline Physical activity behavior of participants via self-report or accelerometry (especially when physical exercise is used as the exertional stimulus).</p>	Supplemental
<p>Study baseline Characterization of chronic symptoms using the questionnaires receiving the highest recommendation from each symptom module (e.g., fatigue, pain, sleep, quality of life, etc.).</p>	Supplemental
<p>Study baseline Characterization of health using the measures receiving the highest recommendation from each system module (e.g., neuroimaging, autonomic, immune).</p>	Supplemental
<p>Prior to and following the exertional stimulus Administration of questionnaire(s) with instructions and item phrasing that are designed to capture immediate (e.g., immediately before and after the exertional stimulus) and/or day-to-day changes (i.e., before and 24hr, 48hr, 72hr, etc. after the exertional stimulus), but that are also representative of GWI symptoms. For instance, the Profile of Mood States is a good example because it uses instructional language that is appropriate for capturing immediate and day-to-day changes (e.g., circle the number that best describes how you feel RIGHT NOW?), but also provides data on a symptom that is representative of GWI (i.e., mood disturbance).</p>	Supplemental
<p>Prior to and following the exertional stimulus Functional measures of physiology (e.g., central nervous system, autonomic, immune) and behavior (e.g., physical activity, cognitive performance, pain sensitivity) that may be correlated with symptom changes.</p>	Supplemental

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements Draft Version 1.0, 12/1/18

VA/DoD GWI CDE Project Gulf War Illness (GWI) Fatigue Subgroup

Chronic, often debilitating fatigue is a symptom of Gulf War Illness. The fatigue subgroup began by evaluating the list of instruments to measure fatigue that was recommended by the ME/CFS CDE fatigue subgroup. The use of the instruments are often used to diagnose and treat fatigue as well as to assess the level of severity and level of functioning. The fatigue subgroup agreed with the ME/CFS CDE subgroup in defining the subdomains of fatigue as general fatigue, physical fatigue, mental fatigue (cognitive difficulties), post-exertional fatigue, and fluctuating fatigue.

The measures of fatigue overlaps with instruments in other CDE domains. A redundancy also exists between some instruments in this domain and the commonly used symptom assessments, specifically the fatigue items in the Kansas Case Definition and the DePaul Symptom Questionnaire. GWI researchers use the Multidimensional Fatigue Inventory (MFI); however, the measure is not rated yet in terms of reliability and validity in GWI research. The consensus of the subgroup is that a core instrument is needed to assess fatigue. Additional research with Gulf War veterans with GWI is required before a recommendation can be made. Specific fatigue instruments may be more relevant to dimensions examined in a given study and should be considered on a per-study basis.

Summary Recommendations

GWI Common Data Elements Module: Fatigue

Instrument Name	Classification
Fatigue Severity Scale	Supplemental
Checklist of Individual Strength – Fatigue (CIS)	Supplemental
Multidimensional Fatigue Inventory (MFI)	Supplemental—Highly Recommended
PROMIS Fatigue Short Form	Supplemental
Quality of Life in Neurological Disorders (Neuro QoL)	Supplemental
Modified Fatigue Impact Scale	Supplemental
POMS Fatigue	Supplemental

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements Draft Version 1.0, 12/1/18

Link to Description of GWI Research Measures

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GWIC Common Data Elements Module: Fatigue Instrument Description and Link

Instrument
<p>Fatigue Severity Scale https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2714</p>
<p>Checklist of Individual Strength – Fatigue (CIS) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2715</p>
<p>Multidimensional Fatigue Inventory (MFI) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2720</p>
<p>PROMIS Fatigue Short Form https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F1321</p>
<p>Quality of Life in Neurological Disorders (Neuro QoL) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2724</p>
<p>Modified Fatigue Impact Scale https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F1026</p>
<p>POMS Fatigue https://onlinelibrary.wiley.com/doi/epdf/10.1002/tsm2.65</p>

VA/DoD GWI CDE Project Gulf War Illness (GWI) Sleep Subgroup

Sleep disturbances are a common concern of veterans diagnosed with GWI. For GWI researchers, it is important not only to identify co-morbid sleep disorder, but also to rule out sleep problems as a primary disorder that could potentially explain other conditions (such as fatigue). Clinically, Gulf War veterans with GWI report feeling unrefreshed upon waking, even with an adequate amount of uninterrupted sleep. Difficulties may involve falling asleep, staying asleep, sleeping for too long or too short periods of time, and daytime sleepiness or nighttime wakefulness.

The GWI sleep subgroup identified a redundancy between sleep instruments and the commonly used symptom assessments (Kansas Case Definition and the DePaul Symptom Questionnaire). For many GWI studies, the sleep-related symptoms included in the symptom assessment tools are sufficient to address the needs of studies for which sleep is not a primary outcome. The subgroup recommends 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.

Summary Recommendations

GWI Common Data Elements Module: Sleep

Instrument Name	Classification
Sleep Questions for All Studies---Case Report Form	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

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements Draft Version 1.0, 12/1/18

Link to Description of GWI Research Measures

The GWI CDE workgroups created the summary table of recommended data standards for GWI research and classified each instrument as Core, Supplemental - Highly Recommended, Supplemental, or Exploratory. The following table provides the link to a description of the specific instruments, case report forms, or guidelines that are listed in the summary table for this module. These descriptions and forms were developed by the NINDS ME/CFS common data elements workgroups and are linked directly to their website.

GWJ Common Data Elements Module: Sleep Instrument Description and Link

Instrument
<p>Sleep Questions for All Studies---Case Report Form https://www.commondataelements.ninds.nih.gov/MECFs.aspx#tab=Data_Standards</p>
<p>Sleep Assessment Questionnaire-Moldofsky https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2732</p>
<p>Pittsburgh Sleep Quality Index https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2123</p>
<p>Stanford Sleepiness Scale https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F0798</p>
<p>Sleep Disorders Screening Checklist https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2733</p>
<p>Holland Sleep Disorders Questionnaire https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Comm</p>
<p>Epworth Sleepiness Scale https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F1576</p>
<p>Nonrestorative Sleep Scale https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2735</p>
<p>Global Sleep Assessment Questionnaire https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2736</p>
<p>Restorative Sleep Questionnaire https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2737</p>

VA/DoD GWI CDE Project

Gulf War Illness (GWI) Pain Subgroup

Gulf War veterans diagnosed with GWI reveal that the presence, type, nature, and severity of pain varies. The pain may be constant, intermittent, focused, or widespread. Musculoskeletal pain for these veterans commonly involves joint pain or stiffness, muscle pain, or back pain. Pain also may present across the entire pain spectrum as inflammatory, neuropathic, or central sensitivity responses. Based on cognitive or physical effort, pain symptoms may be minor or debilitating and may come and go. Regardless of the pain location and the level of severity, veterans report its impact on their quality of life and interference with general functioning.

The pain subgroup considered the instruments suggested by the ME/CFS CDE subgroup, evaluated their applicability to GWI research, and recognized the lack of validation in GWI research settings. Based on use in GWI studies, the GWI pain subgroup highly rated the McGill Pain Questionnaire as the only instrument in the Supplemental – Highly Recommended category. Three other instruments, the Brief Pain Inventory (BPI), Visual Analog Scale, and the Widespread Pain Index (ACR) are Supplemental measures, to be chosen if the GWI research requires additional measures of the pain domain.

The consensus is that a core instrument is needed to assess pain; however, additional research with veterans with GWI is required before a recommendation can be made. The subgroup concluded that specific pain instruments may be more relevant to dimensions examined in a given study and should be considered on a per-study basis.

Summary Recommendations

GWI Common Data Elements Module: Pain

Instrument Name	Classification
Brief Pain Inventory (BPI)	Supplemental
Fibromyalgia Impact Questionnaire - revised	Exploratory
McGill Pain Questionnaire SFv2	Supplemental – Highly Recommended
Faces Pain Scale - revised	Exploratory
Pain Frequency - Severity - Duration	Exploratory
Neuropathic Pain Symptom Inventory	Exploratory
PROMIS Pain Behavior Short Form	Exploratory
PROMIS Pain Interference Short Form	Exploratory
Visual Analog Scale	Supplemental
Widespread Pain Index (ACR)	Supplemental

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements Draft Version 1.0, 12/1/18

Link to Description of GWI Research Measures

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GWI Common Data Elements Module: Pain Instrument Description and Link

Instrument
Brief Pain Inventory (BPI) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2727
Fibromyalgia Impact Questionnaire – revised https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2728
McGill Pain Questionnaire SFv2 https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F1315
Faces Pain Scale – revised https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2114
Pain Frequency - Severity – Duration https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2729
Neuropathic Pain Symptom Inventory https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F1773
PROMIS Pain Behavior Short Form https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2790
PROMIS Pain Interference Short Form https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F1322
Visual Analog Scale http://img.medscape.com/article/742/580/VAS.pdf
Widespread Pain Index (ACR) https://www.fmmgmt.com/sites/default/files/pdfs/ACR.pdf

A/DoD GWICDE Project Gulf War Illness (GWI) Quality of Life/Functional Status/Activity/ Exercise Challenge Testing Subgroup

The entire subgroup discussed Quality of Life, Functional Status, and Activity measures relevant to GWI, while a separate group tackled the Exercise Challenge testing recommendations.

Although not a direct measure of quality of life, many studies of veterans diagnosed with GWI employ the Short Form 36 item Health Survey (SF-36) or the Veterans Short Form 36 item Health Survey (VR-36). The physical and vitality subscales are often used as functional measures in GWI research, and some users use alternate item weightings to (de)emphasize the contributions of selected domains. The Department of Veteran Affairs War Related Illness and Injury Study Center assesses health using the VR-36 in the intake package in clinical settings. The VR-36 is adapted for use with veterans from the RAND Corporation's SF-36 survey and the Medical Outcomes Study. The subgroup noted that while SF-36 and VR-36 have been widely used in research, the SF-36 is no longer available free of charge from RAND and is offered for a fee-basis from OPTUM.

The subgroup noted that when capturing quality of life indicators it is also important to capture emotional well-being and not to 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, the VR-36 is recommended as the core instrument.

Common measures of functional status include the Karnofsky scale (adaptation for chronic disease), WHODAS, and the physical and vitality subscores of the VR-36 or 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, the GWI Subgroup recommends the VR-36 physical and vitality subscales as core functional status instruments, with the Karnofsky scale and Bell CFIDS disability scale as Highly Recommended Supplemental instruments. No measures related to activity were selected by the subgroup, in favor of instruments focusing on functional status

Similar to the conclusions of the ME/CFS CDE subgroup, it is recognized that the most severely affected patients are likely not represented in the testing and use of the currently available instruments. The subgroup identified the need for additional valid, reliable instruments and presented the best available instruments in the summary table.

Exercise Challenge Testing

The GWI subgroup recognizes that this section of the module should be referred to as Exercise Challenge Testing, rather than Cardiopulmonary Exercise Testing (CPET). For researchers, the term "CPET" only pertains to studies that pair an exercise test with the use of indirect calorimetry (i.e., metabolic carts). Since it is also possible to have participants perform exercise without the use of a metabolic cart, "exercise challenge" can be used as an umbrella term.

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 GWV⁵⁻¹⁵. Regardless of how or why these protocols are employed, there are important data element considerations that can improve their validity, reliability, and comparability. The subgroup provides a bulleted list of data elements that are recommended to collect in order to improve comparability/ interpretability between exercise challenge studies.

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, the subgroup categorize the recommendations as either “Supplemental - Highly Recommended” or “Supplemental” in the Summary Recommendations. Therefore, these recommendations apply specifically to studies of GWV that include an exercise challenge.

Please note that 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} These recommendations apply to studies that use maximal or sub-maximal exercise protocols.

The Exercise Challenge Testing subgroup includes Jacob Lindheimer, Jeffrey Cournoyer, Rebecca McNeil, Nancy Klimas, and Dane Cook. Jacquelyn Klein-Adams and Michael Falvo are affiliated with the War Related Illness and Injury Study Center, NJ Health Care System, Department of Veterans Affairs, East Orange, NJ, and assisted in the development of this module. Michael Falvo is also affiliated with the New Jersey Medical School, Rutgers Biomedical and Health Sciences, Newark, NJ.

Supplemental Table 1. Exercise challenge studies involving Gulf War Veterans using a Cross-sectional design.

First author (Year)	Sample	Maximal sub-maximal or protocol	Mode	Primary measure	outcome
Medinger (1998) ⁵	29 GWV with exertional dyspnea following deployment	Maximal	Cycle	Cardio-respiratory	
Reference: VA/DoD Gulf War Illness Common Data Elements: Exercise Challenge Testing Draft Version 1.0, 12/1/18					

Supplemental Table 2. Exercise challenge studies involving Gulf War Veterans using a Case-control design.

First author (Year)	Sample	Maximal sub-maximal or protocol	Mode	Primary measure	outcome
Nagelkirk (2003) ^{6A}	15 GWV with ME/CFS; 19 GWV without ME/CFS	Maximal	Cycle	Cardio-respiratory	
Cook (2003) ^{7A}	15 GWV with ME/CFS; 19 GWV without ME/CFS	Maximal	Cycle	Self-report (RPE)	
Whistler (2009) ⁸	9 GWI; 11 non-deployed sedentary control Veterans	Maximal	Cycle	Immune cell function	
Cook (2010) ⁹	15 GWV with CMP; 17 GWV without CMP	Both	Cycle	Pain sensitivity	

Supplemental Table 2 Continued. Exercise challenge studies involving Gulf War Veterans using a Case-control design

First author (Year)	Sample	Max or sub-max protocol	Mode	Primary measure	outcome
Broderick (2011) ¹⁰	9 GWI; 11 non-deployed sedentary control Veterans	Maximal	Cycle	Immune cell function	
Rayhan (2013) ^{11B}	28 GWI; 10 healthy civilian controls	Both	Cycle	MRI	
Rayhan (2013b) ^{12B}	15 GWI; 11 sedentary Veteran and civilian controls	Both	Cycle	MRS	
Broderick (2013) ^{13C}	20 GWI; 22 sedentary Gulf War Era Veterans; 7 ME/CFS patients	Maximal	Cycle	Immune cell function	
Smylie (2013) ^{14C}	30 GWI; 30 sedentary Gulf War Era Veterans; 22 ME/CFS patients	Maximal	Cycle	Immune cell function	
Baraniuk (2017) ¹⁵			Cycle	CSF MicroRNAs	

Reference: VA/DoD Gulf War Illness Common Data Elements: Exercise Challenge Testing Draft Version 1.0, 12/1/18

Note: **CMP** = Chronic Musculoskeletal Pain; **CSF= GWI** = Gulf War Illness; **GWV** = Gulf War Veteran; **ME/CFS** = Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; **MRI** = Magnetic Resonance Imaging; **MRS** = Magnetic Resonance Spectroscopy; **RPE** = Rating of Perceived Exertion.

^AThese publications are from the same participant sample/study.

^BThese publications are from the same participant sample/study.

^CThese publications are from the same participant sample/study.

References

1. Albouaini, K., Egred, M., Alahmar, A. & Wright, D. J. Cardiopulmonary exercise testing and its application. *Postgrad. Med. J.* 83, 675–682 (2007).
2. ATS/ACCP Statement on Cardiopulmonary Exercise Testing. *Am. J. Respir. Crit. Care Med.* 167, 211–277 (2003).
3. Balady, G. J. *et al.* Clinician’s Guide to Cardiopulmonary Exercise Testing in Adults: A Scientific Statement From the American Heart Association. *Circulation* 122, 191–225 (2010).
4. Guazzi, M. *et al.* 2016 Focused Update: Clinical Recommendations for Cardiopulmonary Exercise Testing Data Assessment in Specific Patient Populations. *Circulation* 133, e694–e711 (2016).
5. Medinger, A. E., Chan, T. W., Arabian, A. & Rohatgi, P. K. Interpretive Algorithms for the Symptom-Limited Exercise Test. *Chest* 113, 612–618 (1998).

6. Nagelkirk, P. R. *et al.* Aerobic capacity of Gulf War Veterans with Chronic Fatigue Syndrome. *Mil. Med.* 168, 750–55 (2003).
7. Cook, D. B. *et al.* Perceived exertion in fatiguing illness: Gulf War Veterans with Chronic Fatigue Syndrome: *Med. Sci. Sports Exerc.* 35, 569–574 (2003).
8. Whistler, T. *et al.* Impaired immune function in Gulf War Illness. *BMC Med. Genomics* 2, 12 (2009).
9. Cook, D. B., Stegner, A. J. & Ellingson, L. D. Exercise Alters Pain Sensitivity in Gulf War Veterans With Chronic Musculoskeletal Pain. *J. Pain* 11, 764–772 (2010).
10. Broderick, G. *et al.* A pilot study of immune network remodeling under challenge in Gulf War Illness. *Brain. Behav. Immun.* 25, 302–313 (2011).
11. Rayhan, R. U. *et al.* Exercise Challenge in Gulf War Illness Reveals Two Subgroups with Altered Brain Structure and Function. *PLoS ONE* 8, e63903 (2013).
12. Rayhan, R. U. *et al.* Prefrontal lactate predicts exercise-induced cognitive dysfunction in Gulf War Illness. *Am J Transl Res* 5, 212–23 (2013).
13. Broderick, G. *et al.* Altered immune pathway activity under exercise challenge in Gulf War Illness: an exploratory analysis. *Brain. Behav. Immun.* 28, 159–169 (2013).
14. Smylie, A. L. *et al.* A comparison of sex-specific immune signatures in Gulf War Illness and Chronic Fatigue Syndrome. *BMC Immunol.* 14, 1–14 (2013).
15. Baraniuk, J. N. & Shivapurkar, N. Exercise – induced changes in cerebrospinal fluid miRNAs in Gulf War Illness, Chronic Fatigue Syndrome and sedentary control subjects. *Sci. Rep.* 7, (2017).
16. Riebe, D. *et al.* Updating ACSM’s Recommendations for Exercise Preparticipation Health Screening: *Med. Sci. Sports Exerc.* 47, 2473–2479 (2015).
17. Troiano, R. P. *et al.* Physical Activity in the United States Measured by Accelerometer: *Med. Sci. Sports Exerc.* 40, 181–188 (2008).
18. Ward, D. S., Evenson, K. R., Vaughn, A., Rodgers, A. B. & Troiano, R. P. Accelerometer Use in Physical Activity: Best Practices and Research Recommendations: *Med. Sci. Sports Exerc.* 37, S582–S588 (2005).
19. *ACSM’s guidelines for exercise testing and prescription. 9th Edition.* (Wolters Kluwer/Lippincott Williams & Wilkins Health, 2014).
20. Beedie, C. *et al.* Consensus statement on placebo effects in sports & exercise: The need for conceptual clarity, methodological rigour, and the elucidation of neurobiological mechanisms. *Eur. J. Sport Sci.* (2018). doi:10.1080/17461391.2018.1496144.
21. Cook, D. B., O’Connor, P. J., Eubanks, S. A., Smith, J. C. & Lee, M. Naturally occurring muscle pain during exercise: assessment and experimental evidence. *Med. Sci. Sports Exerc.* 29, 999–1012 (1997).

Summary Recommendations

GWI Common Data Elements Module: Quality of Life

Instrument Name	Classification
Short-Form 36 item Veteran Health Survey (VR-36) Physical Component Summary (PCS) Score Mental Component Summary (MCS) Score	Core
Short-Form 12 item Veteran Health Survey (VR-12)	Supplemental
Short-Form 8 item Veteran Health Survey (VR-8)	Supplemental
NIH Neuro-QoL (PROMIS)	Exploratory
World Health Organization (WHO) Well-Being Index (5)	Exploratory
World Health Organization (WHO) Well-Being Index (10)	Exploratory
EuroQoL	Exploratory
Health Related Quality of Life (HRQoL)	Exploratory

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements Draft Version 1.0, 12/1/18

Summary Recommendations

GWI Common Data Elements Module: Functional Status

Instrument Name	Classification
Karnofsky Scale	Supplemental—Highly Recommended
World Health Organization Disability Assessment Schedule (WHODAS)	Exploratory
Short-Form 36 item Veteran Health Survey (VR-36) or Short-Form 36 item Health Survey (SF-36) Vitality Subscale Disability Subscale	Core
Bell CFIDS Disability Scale	Supplemental—Highly Recommended

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements Draft Version 1.0, 12/1/18

[Link to Description of GWI Research Measures](#)

The GWI CDE workgroups created the summary table of recommended data standards for GWI research and classified each instrument as Core, Supplemental - Highly Recommended, Supplemental, or Exploratory. The following table provides the link to a description of the specific instruments, case report forms, or guidelines that are listed in the summary table for this module. These descriptions and forms were developed by the NINDS ME/CFS common data elements workgroups and are linked directly to their website.

GWI Common Data Elements Module: Quality of Life Instrument Description and Link

Instrument
Short-Form 36 item Veteran Health Survey (VR-36) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2170
Short-Form 12 item Veteran Health Survey (VR-12) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F1323
Short-Form 8 item Veteran Health Survey (VR-8)
NIH Neuro-QoL (PROMIS) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F1462
World Health Organization (WHO) Well-Being Index (5) https://www.psykiatri-regionh.dk/who-5/Documents/WHO5_English.pdf
World Health Organization (WHO) Well-Being Index (10) https://www.psykiatri-regionh.dk/who-5/Documents/WHO5_English.pdf
EuroQoL https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2731
Health Related Quality of Life (HRQoL) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F1408

GWI Common Data Elements Module: Functional Status Instrument Description and Link

Instrument
Karnofsky Scale https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2740
World Health Organization Disability Assessment Schedule (WHODAS) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F1511
Short-Form 36 item Veteran Health Survey (VR-36) or Short-Form 36 item Health Survey (SF-36) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2170
Bell CFIDS Disability Scale https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F2741

Summary Recommendations

GWIC Common Data Elements Module: Exercise Challenge Studies (formerly Cardiopulmonary Exercise Testing (CPET))

Instrument Name	Classification
<p>GWIC 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.</p>	Supplemental-Highly Recommended
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°)	
Heart rate and blood pressure	
Gulf War Illness symptom severity questionnaires	
<p>During testing Oxygen consumption, carbon dioxide production, ventilation via indirect calorimetry (resting and during exercise)</p>	Supplemental-Highly Recommended
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)	
<p>Immediately after testing 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)</p>	Supplemental-Recommended
Blood lactate	
<p>Prior to instrumentation and testing Participant expectations for effects of exercise on psychological and physical health outcomes</p>	Supplemental-Recommended
Muscle pain in exercising muscles	
Blood lactate (resting and during exercise)	
Collection of physiological and perceptual measures during active recovery/cool down	

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements Draft Version 1.0, 12/1/18

VA/DoD GWI CDE Project Gulf War Illness (GWI) Neurologic/Cognitive/CNS Imaging Subgroup

Gulf War (GW) veterans have shown changes in central nervous system functioning in multiple studies of neurological, neuroimaging and neuropsychological outcomes (White et al., 2016). Adverse neurological outcomes include increased rates of amyotrophic lateral sclerosis (ALS) at twice the rate of nondeployed veterans (Horner et al. 2007; Haley et al. 2003), and brain cancer mortality rates, in GW veterans in the 1991 Khamisiyah chemical weapon depot demolitions, at twice the rate of other veterans in theater (Barth et al. 2008; Bullman et al. 2005). There are questions however, whether these rates are still higher or have more recently plateaued. Studies utilizing various imaging techniques (MRI, MRS, SPECT) have identified abnormalities in basal ganglia, brain stem, hippocampus, white matter volume, and cerebral blood perfusion that distinguish veterans with Gulf War Illness (GWI) from healthy controls (Chao et al. 2018; Chao et al. 2015; Gopinath et al., 2012; Chao et al. 2011, Haley et al. 2006; Spence et al. 2006; Meyerhoff et al. 2001; Haley et al. 2000). MRI studies have also identified reduced white matter volumes and microstructural integrity in relation to the Khamisiyah chemical weapons (sarin/cyclosarin) depot demolitions (Chao et al. 2015; Chao et al. 2011; Heaton et al. 2007).

Differences in neuropsychological function have been observed between GW veterans and healthy controls and have been associated with neurotoxicant exposures during the war. A recent meta-analysis of neuropsychological characteristics of GWI identified significantly decreased performance in the functional domains of executive function, visuospatial skills, and learning and memory across 16 studies (Janulewicz et al. 2017). Neurotoxicant exposure during the war including combined exposures of pesticides and anti-nerve gas pills pyridostigmine bromide has also been associated with significantly slowed information processing, increased attentional errors, poor visual memory functioning, and increased mood complaints in exposed GW veterans (Sullivan et al. 2018). These studies suggest that GWI is associated with adverse neurologic, neuroimaging, and neuropsychological outcomes and thus should be further explored in future studies.

The following items were recommended as “Supplementary-Highly Recommended” by subgroup:

Neurological

- Neurological Case Report Form (CRF)

Neuropsychological

- Word Reading Subtest of the Wide Range Achievement Test (WRAT-4)
- Continuous Performance Test -3 (CPT3)
- Wechsler Adult Intelligence Scale-IV (WAIS-IV)
- Digit Spans, Block Design
- Profile of Mood States (POMS)
- Davidson Trauma Scale (DTS)
- Delis-Kaplan Executive Function System
- Color-Word-Interference Test, Trail Making Test, Verbal Fluency
- California Verbal Learning Test – Second Edition (CVLT-II)
- Rey-Osterrieth Complex Figure Test (ROCF)

Neuroimaging

- Diffusion Tensor Imaging (DTI)
- Electroencephalography (EEG)
- Functional Magnetic Resonance Imaging (fMRI)
- Low-Resolution Electromagnetic Tomography (LORETA)
- Magnetic Resonance Spectroscopy (MRS)
- Magnetoencephalography (MEG)
- Positron Emission Tomography (PET)
- Quantitative Electroencephalography

The neurological CRF is considered appropriate for the studies using a neurological exam in veterans with GWI and is therefore recommended as supplemental-highly recommended. The neuropsychological test battery has been updated for highly recommended tests based on those tests 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. 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 are also recommended in the summary form.

The following items were recommended as “Supplemental” by the subgroup:

- Neuropsychological
- Finger Tap Test
- Grooved Pegboard Test
- Hopkins Verbal Learning Test (HVLTL)
- Brief Visual Memory Test (BVMT)
- PTSD Checklist for DSM-V (PCL-5)
- Center for Epidemiological Studies Depression Scale (CES-D)
- Clinical Administered PTSD Scale (CAPS-5)
- Structured Clinical Interview for DSM-V (SCID-5)

Supplemental tests are chosen based on the fact that they offer multiple test versions suitable for repeated testing sessions in treatment trials and cover relevant cognitive domains in GWI. Below are the Table Summaries of Recommendations for the Neurologic/Cognitive/CNS Imaging subgroup:

Summary Recommendations

GWI Common Data Elements Module: Neurological

Instrument Name	Classification
Neurological—Case Report Form (CRF)	Supplemental - Highly Recommended

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements Draft Version 1.0, 12/1/18

Summary Recommendations

GWI Common Data Elements Module: Neuropsychological

Instrument Name	Classification
Word Reading Subtest of the Wide Range Achievement Test (WRAT-4)	Supplemental - Highly Recommended
Continuous Performance Test -3 (CPT3)	Supplemental - Highly Recommended
Wechsler 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 Clinical Interview for DSM-V (SCID-5)	Supplemental

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements Draft Version 1.0, 12/1/18

Summary Recommendations

GWI Common Data Elements Module: Neuroimaging

Instrument Name	Classification
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 Spectroscopy (MRS)	Supplemental - Highly Recommended
Magnetoencephalography (MEG)	Supplemental - Highly Recommended
Positron Emission Tomography (PET)	Supplemental - Highly Recommended
Quantitative Electroencephalography	Supplemental - Highly Recommended

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements Draft Version 1.0, 12/1/18

Link to Description of GWI Research Measures

The GWI CDE workgroups created the summary table of recommended data standards for GWI research and classified each instrument as Core, Supplemental - Highly Recommended, Supplemental, or Exploratory. The following table provides the link to a description of the specific instruments, case report forms, or guidelines that are listed in the summary table for this module. These descriptions and forms were developed by the NINDS ME/CFS common data elements workgroups and are linked directly to their website.

GWI Common Data Elements Module: Neurological GWI Instrument Description and Link

Instrument
Neurological—Case Report Form (CRF) https://www.commondataelements.ninds.nih.gov/MECFs.aspx#tab=Data_Standards

GWI Common Data Elements Module: Neuropsychological GWI Instrument Description and Link

Instrument
<p>Word Reading Subtest of the Wide Range Achievement Test (WRAT-4) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Comm and=Render&rc:Parameters=false&crfID=F2699</p>
<p>Continuous Performance Test -3 (CPT3) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Comm and=Render&rc:Parameters=false&crfID=F1447</p>
<p>Wechsler Adult Intelligence Scale-IV (WAIS-IV) Recommended tests: Digit Spans, Block Design https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Comm and=Render&rc:Parameters=false&crfID=F1467</p>
<p>Profile of Mood States (POMS)</p>
<p>Davidson Trauma Scale (DTS) – PTSD https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Comm and=Render&rc:Parameters=false&crfID=F1489</p>
<p>Delis-Kaplan Executive Function System (D-KEFS) Recommended modules: Color-Word-Interference Test, Trail Making Test, Verbal Fluency https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Comm and=Render&rc:Parameters=false&crfID=F1450</p>
<p>California Verbal Learning Test - Second Edition (CVLT-II) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Comm and=Render&rc:Parameters=false&crfID=F2723</p>
<p>Rey-Osterrieth Complex Figure Test (ROCF) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Comm and=Render&rc:Parameters=false&crfID=F1471</p>
<p>Finger Tap Test https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Comm and=Render&rc:Parameters=false&crfID=F1253</p>
<p>Grooved Pegboard Test https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Comm and=Render&rc:Parameters=false&crfID=F1339</p>
<p>Hopkins Verbal Learning Test (HVL) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Comm and=Render&rc:Parameters=false&crfID=F1468</p>
<p>Brief Visual Memory Test (BVMT) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Comm and=Render&rc:Parameters=false&crfID=F1443</p>
<p>PTSD Checklist for DSM-V (PCL-5) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Comm and=Render&rc:Parameters=false&crfID=F2567</p>
<p>Center for Epidemiological Studies Depression Scale (CES-D) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Comm and=Render&rc:Parameters=false&crfID=F0372</p>
<p>Clinician Administered PTSD Scale (CAPS-5) https://www.ptsd.va.gov/professional/assessment/adult-int/caps.asp</p>
<p>Structured Clinical Interview for DSM-V (SCID-5) https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Comm and=Render&rc:Parameters=false&crfID=F1377</p>

GWIC Common Data Elements Module: Neuroimaging GWIC Instrument Description and Link

Instrument
Diffusion Tensor Imaging (DTI) https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards
Electroencephalography (EEG) https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards
Functional Magnetic Resonance Imaging (fMRI) https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards
Low-resolution Electromagnetic Tomography (LORETA) https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards
Magnetic Resonance Spectroscopy (MRS) https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards
Magnetoencephalography (MEG) https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards
Positron Emission Tomography (PET) https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards
Quantitative Electroencephalography https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards

References

Barth S. Neurological and all-cause mortality among U.S. veterans of the Persian Gulf War: 13-year follow-up. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Sep 16, 2008; Washington, D.C.

Bullman TA, Mahan CM, Kang HK, Page WF. Mortality in US Army Gulf War veterans exposed to 1991 Khamisiyah chemical munitions destruction. *Am J Public Health*. 2005;95:1382-1388.

Chao, L. L., Abadjian, L., Hlavin, J., Meyerhoff, D. J., & Weiner, M. W. (2011). Effects of low level sarin and cyclosarin exposure and Gulf War Illness on Brain Structure and Function: A study at 4T. *NeuroToxicology*, 32(6), 814-822. doi:10.1016/j.neuro.2011.06.006.

Chao, L. L., Zhang, Y., & Buckley, S. (2015). Effects of low-level sarin and cyclosarin exposure on white matter integrity in Gulf War Veterans. *NeuroToxicology*, 48, 239-248. doi:10.1016/j.neuro.2015.04.005.

Chao, L. L., & Zhang, Y. (2018). Effects of low-level sarin and cyclosarin exposure on hippocampal microstructure in Gulf War Veterans. *Neurotoxicology and Teratology*, 68, 36-46. doi:10.1016/j.ntt.2018.05.001.

Haley RW. Excess incidence of ALS in young Gulf War veterans. *Neurology*. 2003;61:750-756.

Haley RW, Marshall WW, McDonald GG, Daugherty MA, Petty F, Fleckenstein JL. Brain abnormalities in Gulf War syndrome: evaluation with 1H MR spectroscopy. *Radiology*. 2000 Jun;215(3):807-17.

Haley RW. UT Southwestern Research on Gulf War Syndrome. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; May 15, 2006; Washington, DC.

Heaton, K.J., Palumbo, C.L., Proctor, S.P., Killiany, R.J., Yurgelun-Todd, D.A., & White, R.F. (2007). Quantitative magnetic resonance brain imaging in US army veterans of the 1991 Gulf War potentially exposed to sarin and cyclosarin. *NeuroToxicology*, 28(4), 761-769. Doi:10.1016/j.neuro.2007.03.006.

Horner RD. Reply from the authors: Occurrence of amyotrophic lateral sclerosis among Gulf War veterans. *Neurology*. 2007;68:1083.

Janulewicz, P. A., Kregel, M. H., Maule, A., White, R. F., Cirillo, J., Sisson, E., Sullivan, K.(2017). Neuropsychological characteristics of Gulf War illness: A meta-analysis. *PLOS ONE*, 12(5), e0177121. doi:10.1371/journal.pone.0177121.

Meyerhoff D, Lindgren J, Hardin D, Griffin J, Weiner M. Metabolic abnormalities in the brain of subjects with Gulf War illness [abstract]. *Proc Intl Soc Mag Reson Med*. 2001;9:994.

Spence JS, Carmack PS, Gunst RF, Schucany WR, Woodward WA, Haley RW. Using a white matter reference to remove the dependency of global signal on experimental conditions in SPECT analyses. *Neuroimage*. 2006;32:49-53.

Sullivan, K., Kregel, M., Bradford, W., Stone, C., Thompson, T. A., Heeren, T., & White, R. F. (2018). Neuropsychological functioning in military pesticide applicators from the Gulf War: Effects on information processing speed, attention and visual memory. *Neurotoxicology and Teratology*, 65, 1-13. doi:10.1016/j.ntt.2017.11.002.

White RF, Steele L, O'Callaghan JP, Sullivan K, Binns JH, Golomb BA, Bloom FE, Bunker JA, Crawford F, Graves JC, Hardie A, Klimas N, Knox M, Meggs WJ, Melling J, Philbert MA, Grashow R. Recent research on Gulf War illness and other health problems in veterans of the 1991 Gulf War: Effects of toxicant exposures during deployment. *Cortex*. 2016 Jan;74:449-75. doi: 10.1016/j.cortex.2015.08.022. Epub 2015 Sep 25. Review.

VA/DoD GWICDE Project

Gulf War Illness (GWI) Autonomic Subgroup

The autonomic nervous system (ANS) controls a broad range of functions. ANS pathology includes symptoms of digestive disorders, fatigue, and weakness. Autonomic dysfunction symptoms can manifest in a myriad of ways, thus requiring specific tests to measure distinct systems or functions. There is scientific evidence for autonomic dysfunction in veterans with Gulf War Illness (RAC, 2014; Li et al., 2014; Fox et al., 2018a, Fox et al., 2018b; Rayhan et al., 2013a&b; Haley et al., 2012; Baraniuk et al., 2017; Garner et al., 2018). However, the extent of autonomic dysfunction is not fully evaluated in GWI and needs further assessment. During the process of developing the GWI Autonomic recommendations, the committee discussed the additional needs for studying resting sinus tachycardia and post-exercise reversible postural tachycardia (Rayhan et al., 2013).

Autonomic functions have been primarily assessed in GW veterans via the Exercise Challenge. Such studies have designated postural tachycardia (POTS) as a concern of autonomic dysfunction (Sheldon et al. 2015; Freedman et al. 2011). A recent study revealed one third of GWI subjects developed the symptom after submaximal exercise testing (Baraniuk, 2017). Hypertension is common in GWI and can lead to postural and tachycardia effects. Medication use can complicate adrenergic dysfunction in GWI and medication usage should be assessed in the baseline module.

Because the need for supplemental measures of autonomic function would depend on the specific aims of a given study, the committee only recommended the Compass-31 measure 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. The subgroup recommends the addition of Heart Rate Variability, Tilt Table Test, Romberg Test, Sudomotor Test, and Pupilometry testing because they have been shown to be significantly different in at least one GWI study (RAC, 2014; Fox et al., 2018a, Fox et al., 2018b; Rayhan et al., 2013; Haley et al., 2012; Baraniuk et al., 2017; Garner et al., 2018). It was also recommended that the Passive Standing Test CRF as an objective measurement of heart rate, blood pressure and symptomatic responses to standing be modified to 5 minutes standing rather than 10 minutes (Hyatt et al., 1975). The ME/CFS common data elements committee chose to draft a new version of one of the published questionnaires in an attempt to derive a more appropriate measure of orthostatic intolerance symptom frequency, severity, and impact that the committee chose to keep in the GWI module. However, the modified questionnaire will need to be validated in GWI.

Objective methods listed as exploratory are for focused studies by appropriate laboratories. Heart rate variability (HRV) is listed to assess deficient vagal cholinergic tone that leads to tachycardia. Research has generally had difficulty distinguishing measurements of baseline autonomic dysregulation with veterans vs. control groups. One study did show significantly lower 24-hour heart rate variability (HRV; Haley, 2004 et. al; Stein et. al. 2004). The significant heart rate

variability between Gulf War veterans and controls, however, was seen after exercise or postural challenges. Tilt table testing will provide a means to understand deficient sympathetic adrenergic function and hypotension. Previous studies have demonstrated alterations in blood pressure and heart rate responses in Gulf War veterans using tilt table testing (Clauw, 2001; Davis et al., 2000; Lucas et al., 2005; Sastre and Cook, 2004). Sudomotor testing of postganglionic cholinergic sympathetic neurons in sweating, and total body heating to assess the hypothalamic set point for temperature and sweating have been shown in GWI (Haley et al., 2012). Methods of pupillometry in autonomic dysfunction and blurred vision and loss of accommodation have also been reported.

The following items were recommended as "Supplemental-Highly Recommended" by the subgroup:

- The 'COMPASS - 31' instrument for assessing autonomic symptoms

The following items were recommended as "Exploratory" by the subgroup:

- A Modified Orthostatic Symptom Grading Scale
- Passive Standing Test CRF scale
- Heart Rate Variability
- Tilt Table Test
- Romberg Test
- Sudomotor Testing
- Pupillometry Testing

Summary Recommendations

GWIC Common Data Elements Module: Autonomic

Instrument Name	Classification
Compass - 31	Supplemental—Highly Recommended
Modified Orthostatic Symptom Grading Scale—Case Report Form	Exploratory
Passive Standing Test—Case Report Form	Exploratory
Heart Rate Variability	Exploratory
Tilt Table Test	Exploratory
Romberg Test	Exploratory
Sudomotor Test	Exploratory
Pupillometry Test	Exploratory

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements Draft Version 1.0, 12/1/18

Link to Description of GWI Research Measures

The GWI CDE workgroups created the summary table of recommended data standards for GWI research and classified each instrument as Core, Supplemental - Highly Recommended, Supplemental, or Exploratory. The following table provides the link to a description of the specific instruments, case report forms, or guidelines that are listed in the summary table for this module, when available. These descriptions and forms were developed by the NINDS ME/CFS common data elements workgroups and are linked directly to their website.

GWIC Common Data Elements Module: Autonomic GWI Instrument and Link

Instrument
Compass – 31 https://www.commondataelements.ninds.nih.gov/ReportViewer.aspx?/nindscdereports/rptNOC&rs:Command=Render&rc:Parameters=false&crfID=F1659
Modified Orthostatic Symptom Grading Scale—Case Report Form https://www.commondataelements.ninds.nih.gov/MECFs.aspx#tab=Data_Standards
Passive Standing Test—Case Report Form https://www.commondataelements.ninds.nih.gov/MECFs.aspx#tab=Data_Standards
Heart Rate Variability
Tilt Table Test
Romberg Test
Sudomotor Test
Pupillometry

References

Baraniuk, J. N., & Shivapurkar, N. (2017). Exercise – induced changes in cerebrospinal fluid miRNAs in Gulf War Illness, Chronic Fatigue Syndrome and sedentary control subjects. *Scientific Reports*, 7(1). doi:10.1038/s41598-017-15383-9.

Clauw DJ. Potential mechanisms in chemical intolerance and related conditions. *Annals of the New York Academy of Sciences*. 2001; 933:235–253. [PubMed: 12000024].

Davis SD, Kator SF, Wonnett JA, Pappas BL, Sall JL. Neurally mediated hypotension in fatigued Gulf War veterans: a preliminary report. *The American Journal of the Medical Sciences*. 2000; 319(2): 89–95. [PubMed: 10698092].

Falvo, M. J., Lindheimer, J. B., & Serrador, J. M. (2018). Dynamic cerebral autoregulation is impaired in Veterans with Gulf War Illness: A case-control study. *PLOS ONE*, 13(10), e0205393. doi:10.1371/journal.pone.020539.3.

Freeman R. Objective Evidence of Autonomic Dysfunction and the Role of Stress in the Gulf War Syndrome. *JAMA Neurol.* 2013;70(2):158–159. doi:10.1001/jamaneurol.2013.1494.

Freeman, R., Wieling, W., Axelrod, F. B., Benditt, D. G., Benarroch, E., Biaggioni, I Van Dijk, J. G. (2011). Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clinical Autonomic Research*, 21(2), 69-72. doi:10.1007/s10286-011-0119-5.

Fox, A., Helmer, D., Tseng, C., McCarron, K., Satcher, S., & Osinubi, O. (2018a). Autonomic Symptoms in Gulf War Veterans Evaluated at the War Related Illness and Injury Study Center. *Military Medicine*. doi:10.1093/milmed/usy227.

Fox, A., Riska, K., Tseng, C. L., McCarron, K., Satcher, S., Osinubi, O., & Helmer, D. (2018b). Dizziness, Vertigo, and Mental Health Comorbidity in Gulf War Veterans. *J Am Acad Audiol.* 018 Nov 14. doi: 10.3766/jaaa.17122.

Garner RS, Rayhan RU, Baraniuk JN. Verification of exercise-induced transient postural tachycardia phenotype in Gulf War Illness. *Am J Transl Res.* 2018 Oct 15;10(10):3254-3264. eCollection 2018.

Gilfrich, H., Heidelmann, L. M., Grube, F., Frickmann, H., & Jungblut, S. A. (2015). Syncope as a health risk for soldiers - influence of medical history and clinical findings on the sensitivity of head-up tilt table testing. *Military Medical Research*, 2(1). doi:10.1186/s40779-015-0062-1.

Haley RW, Charuvastra E, Shell WE, et al. Cholinergic autonomic dysfunction among veterans with Gulf War syndrome: confirmation in a population-based sample. *JAMA Neurol.* Published online November 21, 2012. doi:10.1001/jamaneurol.2013.596.

Haley RW, Vongpatanasin W, Wolfe GI, Bryan WW, Armitage R, Hoffmann RF, et al. Blunted circadian variation in autonomic regulation of sinus node function in veterans with Gulf War syndrome [Research Support, Non-U.S. Gov't, U.S. Gov't, Non-P.H.S., U.S. Gov't, P.H.S.]. *American Journal of Medicine.* 2004; 117(7):469–478. <http://dx.doi.org/10.1016/j.amjmed.2004.03.041>. [PubMed: 15464703].

Hyatt KH, Jacobson LB, Schneider VS. Comparison of 70°tilt, LBNP, and passive standing as measures of orthostatic tolerance. *Aviat Space Environ Med* 1975;46: 801-808.

Li, M., Xu, C., Yao, W., Mahan, C. M., Kang, H. K., Sandbrink, F., Karasik, P. A. (2014). Self-reported post-exertional fatigue in Gulf War veterans: roles of autonomic testing. *Frontiers in Neuroscience*, 7. doi:10.3389/fnins.2013.00269.

Lucas KE, Armenian HK, Debusk K, Calkins HG, Rowe PC. Characterizing Gulf War illnesses: neurally mediated hypotension and postural tachycardia syndrome [Research Support, N.I.H., Extramural, U.S. Gov't, Non-P.H.S.]. *American Journal of Medicine.* 2005; 118(12):1421–1427. <http://dx.doi.org/10.1016/j.amjmed.2005.06.034>. [PubMed: 16378804].

RACGWI, RACoGWVI. Gulf War illness and the health of Gulf War veterans: Research update and recommendations, 2009–2013. Washington, D.C: U.S. Government Printing Office; 2014.

Rayhan RU, Ravindran MK, Baraniuk JN. Migraine in gulf war illness and chronic fatigue syndrome: prevalence, potential mechanisms, and evaluation. *Frontiers in Physiology*. 2013a;4:181. doi:10.3389/fphys.2013.00181.

Rayhan RU, et al. Exercise challenge in Gulf War Illness reveals two subgroups with altered brain structure and function. *PLoS One*. 2013b;8:e63903. doi: 10.1371/journal.pone.0063903.

Sastre, A., Cook, M. R., Autonomic Dysfunction in Gulf War veterans. In: U. S. A. M. R. a. M. Command, (Ed.), Fort Detrick, MD, 200.

Sheldon, R. S., Grubb, B. P., Olshansky, B., Shen, W., Calkins, H., Brignole, M., Kanjwal, K. (2015). 2015 Heart Rhythm Society Expert Consensus Statement on the Diagnosis and Treatment of Postural Tachycardia Syndrome, Inappropriate Sinus Tachycardia, and Vasovagal Syncope. *Heart Rhythm*, 12(6), e41-e63. doi:10.1016/j.hrthm.2015.03.029.

Stein, P. K., Domitrovich, P. P., Ambrose, K., Lyden, A., Fine, M., Gracely, R. H., & Clauw, D. J. (2004). Sex effects on heart rate variability in fibromyalgia and Gulf War illness. *Arthritis & Rheumatism*, 51(5), 700-708. doi:10.1002/art.20687.

VA/DoD GWI CDE Project Gulf War Illness (GWI) Endocrine/Neuroendocrine Subgroup

Both endocrine and neuroendocrine alterations have been reported in Gulf War veterans. Therefore, the committee changed the name of the module to Endocrine/Neuroendocrine. Specifically, Gulf War Illness (GWI) has been associated with unique hypothalamic-pituitary-adrenal (HPA) axis functions in ill veterans and in those with specific exposures during the war. This was most evident on challenge tasks including dexamethasone challenge which resulted in deployed GW veterans showing greater suppression of cortisol and ACTH (adrenocorticotropic hormone) compared with non-deployed veterans (Golier, Legge, and Yehuda, 2006; Golier, Schmeidler, Legge, and Yehuda, 2006). These patterns of HPA-axis functioning in GW veterans are distinct from those seen in other conditions including depression, PTSD, and CFS (Golier, Caramanica, and Yehuda, 2012; Golier, Schmeidler, Legge, and Yehuda, 2007; Golier, Schmeidler, and Yehuda, 2009). Suppression of these hormones was most pronounced for veterans who reported using pesticides and PB during deployment suggesting an exposure component to these alterations. Whether these exposures are related to reproductive health in GW veterans remains unknown and should be assessed as recommended by the National Academy of Sciences (NAS, 2018).

The following items were recommended as “Supplemental-Highly Recommended” by the subgroup:

- Neuroendocrine Laboratory Tests
- Neuroendocrine/hypothalamic symptoms
- Reproductive and Hormone History

To be more relevant to GWI, the dexamethasone challenge task is added to the Neuroendocrine Labs CRF and the ME/CFS-relevant oral glucose tolerance test, fluid-deprivation test and plasma renin activity are 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.

The following items were recommended as “Supplemental” by the subgroup:

- ASA Dietary Survey
- Dietary Supplements

A separate dietary survey and dietary supplements usage form is recommended. These forms are adopted from the NINDS Mitochondrial and GI disease CDEs.

Summary Recommendations

GWI Common Data Elements Module: Endocrine/Neuroendocrine

Instrument Name	Classification
Neuroendocrine Labs Cortisol Diabetes Thyroid Sex Hormones Other Endocrine	Supplemental—Highly Recommended
Neuroendocrine/Hypothalamic Symptoms	Supplemental—Highly Recommended
Reproductive and Hormonal History	Supplemental—Highly Recommended
ASA Dietary Survey	Supplemental
Dietary Supplements	Supplemental

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements Draft Version 1.0, 12/1/18

Link to Description of GWI Research Measures

The GWI CDE workgroups created the summary table of recommended data standards for GWI research and classified each instrument as Core, Supplemental - Highly Recommended, Supplemental, or Exploratory. The following table provides the link to a description of the specific instruments, case report forms, or guidelines that are listed in the summary table for this module. These descriptions and forms were developed by the NINDS ME/CFS common data elements workgroups and are linked directly to their website.

GWI Common Data Elements Module: Endocrine/Neuroendocrine GWI Instrument and Link

Instrument
Neuroendocrine Labs https://www.commondataelements.ninds.nih.gov/MECFs.aspx#tab=Data_Standards
Neuroendocrine/Hypothalamic Symptoms https://www.commondataelements.ninds.nih.gov/MECFs.aspx#tab=Data_Standards
Reproductive and Hormonal History https://www.commondataelements.ninds.nih.gov/MECFs.aspx#tab=Data_Standards
ASA Dietary Survey http://appliedresearch.cancer.gov/asa24/
Dietary Supplements https://www.commondataelements.ninds.nih.gov/MITO.aspx#tab=Data_Standards

References

- Golier, J. A., Caramanica, K., & Yehuda, R. (2012). Neuroendocrine response to CRF stimulation in veterans with and without PTSD in consideration of war zone era [Research Support, N.I.H., Extramural, U.S. Gov't, Non-P.H.S.] *Psychoneuroendocrinology*, 37(3), 350e357. <http://dx.doi.org/10.1016/j.psyneuen.2011.07.004>.
- Golier, J. A., Legge, J., & Yehuda, R. (2006). The ACTH response to dexamethasone in Persian Gulf War veterans. *Annals of the New York Academy of Science*, 1071, 448e453. <http://dx.doi.org/10.1196/annals.1364.040>.
- Golier, J. A., Schmeidler, J., & Yehuda, R. (2009). Pituitary response to metyrapone in Gulf War veterans: relationship to deployment, PTSD and unexplained health symptoms [Research Support, N.I.H., Extramural, U.S. Gov't, Non-P.H.S.] *Psychoneuroendocrinology*, 34(9), 1338e1345. <http://dx.doi.org/10.1016/j.psyneuen.2009.04.004>.
- Golier, J. A., Schmeidler, J., Legge, J., & Yehuda, R. (2007). Twenty- four hour plasma cortisol and adrenocorticotrophic hormone in Gulf War veterans: relationships to posttraumatic stress disorder and health symptoms [Research Support, N.I.H., Extramural, U.S. Gov't, Non-P.H.S.] *Biological Psychiatry*, 62(10), 1175e1178. <http://dx.doi.org/10.1016/j.biopsych.2007.04.027>.
- Golier, J. A., Schmeidler, J., Legge, J., & Yehuda, R. (2006). Enhanced cortisol suppression to dexamethasone associated with Gulf War deployment [Comparative Study, Research Support, N.I.H., Extramural, U.S. Gov't, Non-P.H.S.] *Psychoneuroendocrinology*, 31(10), 1181e1189. <http://dx.doi.org/10.1016/j.psyneuen.2006.08.005>.
- Research Advisory Committee on Gulf War veterans' Illnesses (RACGWI), (2014). *Gulf War illness and the health of Gulf War veterans: Research update and recommendations, 2009-2013*. Washington, D.C.: U.S. Government Printing Office.
- National Academies of Sciences, Engineering, and Medicine. 2018. *Gulf War and health, Volume 11: Generational health effects of serving in the Gulf War*. Washington, DC: The National Academies Press. doi: <https://doi.org/10.17226/25162>.

VA/DoD GWI CDE Project Gulf War Illness (GWI) Immune Subgroup

Immune system functioning involves a complex system of coordinated defense mechanisms that work through innate and adaptive mechanisms. The innate immune system is hardwired to respond to common outside threats such as bacterial infections or other pathogens while the adaptive immune system works through recognizing antigens and building a response through antibodies for future encounters. The innate system responds to common threats through toll-like receptors (TLRs) and other pattern recognition receptors common to bacterial strains and other invaders or pathogens. The innate immune system considers anything that causes tissue stress or destruction to be a 'danger' and reacts to these 'danger' signals by the defensive release of proinflammatory cytokines (IL-1, IL-6, TNF) and chemokines (MCP-1, MIP-1) (Matzinger 2002). Cytokines and chemokines are classic immune signaling molecules. In the short-term, inflammation is helpful and elicits fever and other self-preserving physical responses. However, chronic inflammation can be maladaptive and can result in a complex of symptoms resembling sickness response behaviors (fatigue, joint and muscle aches, attention and concentration difficulties, gastrointestinal distress, headaches) and other problems. It is the chronic inflammatory effects in the *cross-talk pathways* between the brain and the immune system that have spurred the recent interest in neuroinflammation as a potential cause of chronic symptoms in GWI (Parkitny et al., 2015; Alhassan et al., 2017).

Although a clearly defined biological mechanism for GWI has remained elusive, recently defined brain-immune system relationships point to a possible role for neuroinflammation as a prominent factor underlying the symptoms of GWI. Neuroinflammation is a chronic glial activation state resulting in the synthesis and release of proinflammatory cytokines and chemokines. The collection of clinical symptoms reported by GW veterans with GWI includes headache, skin rash, memory and attention impairment, chronic pain, gastrointestinal problems, dyspnea, and fatigue. Multiple studies have identified objective measures that differentiate groups of GWI cases from healthy controls—differences primarily associated with brain structure and function, as well as immune dysregulation including cytokine expression and other inflammatory markers (NK cells, c-reactive protein) and increased circulating CNS autoantibodies in the blood (Abou-Donia et al., 2017; Khaiboullina et al. 2015; Broderick et al., 2013; Smylie et al., 2013; Johnson et al., 2013; Whistler et al., 2009; Brimacombe et al., 2002; Zhang et al., 1999). However, these studies have utilized different measures and methods in assessing GWI cases defined in diverse ways, resulting in a collection of suggestive findings that have not been replicated or further clarified. Thus, studies using the same methods for immune system outcomes are highly needed in GWI research.

The Committee reviewed the ME/CFS forms and tests for relevance to GWI. The four recommended Case Report forms (CRFs) for Immune function were recommended for GWI common data elements (CDEs) 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 (Includes 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 Hypersensitivity Lab Tests). The exposure CRF was not considered to be appropriate for GWI and a new exposure form was recommended and will be classified as exploratory. Rome IBS Criteria, important in GWI research, is in the supplemental category.

Summary Recommendations

GWIC Common Data Elements Module: Immune

Instrument Name	Classification
Medical History—Case Report Form	Supplemental—Highly Recommended
Immune System Onset Type	Supplemental—Highly Recommended
Rome IBS Criteria	Supplemental
Physical Examination—Case Report Form	Supplemental—Highly Recommended
Laboratory Tests—Case Report Form	Supplemental—Highly Recommended
NK Cell Assay Test	Supplemental

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements Draft Version 1.0, 12/1/18

Link to Description of GWI Research Measures

The GWI CDE workgroups created the summary table of recommended data standards for GWI research and classified each instrument as Core, Supplemental - Highly Recommended, Supplemental, or Exploratory. The following table provides the link to a description of the specific instruments, case report forms, or guidelines that are listed in the summary table for this module. These descriptions and forms were developed by the NINDS ME/CFS common data elements workgroups and are linked directly to their website.

GWIC Common Data Elements Module: Immune GWI Instrument and Link

Instrument
Medical History—Case Report Form https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards
Physical Examination—Case Report Form https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards
Laboratory Tests—Case Report Form https://www.commondataelements.ninds.nih.gov/MECFS.aspx#tab=Data_Standards

References

Alhasson F, Das S, Seth R, Dattaroy D, Chandrashekar V, Ryan CN, Chan LS, Testerman T, Burch J, Hofseth LJ, Horner R, Nagarkatti M, Nagarkatti P, Lasley SM, Chatterjee S. Altered gut microbiome in a mouse model of Gulf War Illness causes neuroinflammation and intestinal injury via leaky gut and TLR4 activation. PLoS One. 2017 Mar 22;12(3):e0172914. doi: 10.1371/journal.pone.0172914. eCollection 2017.

Brimacombe M, Zhang Q, Lange G, Natelson B. Immunological variables mediate cognitive

dysfunction in gulf war veterans but not civilians with chronic fatigue syndrome. *Neuroimmunomodulation*. 2002-2003;10(2):93- 100.

Broderick G, Ben-Hamo R, Vashishtha S, Efroni S, Nathanson L, Barnes Z, Fletcher MA, Klimas N. Altered immune pathway activity under exercise challenge in Gulf War Illness: an exploratory analysis. *Brain Behav Immun*. 2013 Feb;28:159-69. doi: 10.1016/j.bbi.2012.11.007. Epub 2012 Nov 29.

Johnson GJ, Leis LA, Slater BC, Bach RR. Elevated platelet count, C-reactive protein and thromboxane analog- induced platelet aggregation in patients with Gulf War veterans' illnesses: evidence of a chronic inflammatory state? *Blood Coagul Fibrinolysis*. 2013 Oct;24(7):736-41. doi: 10.1097/MBC.0b013e328362627f.

Khaiboullina SF, DeMeirleir KL, Rawat S, Berk GS, Gaynor-Berk RS, Mijatovic T, Blatt N, Rizvanov AA, Young SG, Lombardi VC. Cytokine expression provides clues to the pathophysiology of Gulf War illness and myalgic encephalomyelitis. *Cytokine*. 2015 Mar;72(1):1-8. doi: 10.1016/j.cyto.2014.11.019. Epub 2014 Dec 13.

Matzinger P. The danger model: a renewed sense of self. *Science*. 2002 Apr 12;296(5566):301-5.

Parkitny L, Middleton S, Baker K, Younger J. Evidence for abnormal cytokine expression in Gulf War Illness: A preliminary analysis of daily immune monitoring data. *BMC Immunol*. 2015 Sep 30;16:57. doi: 10.1186/s12865- 015-0122-z.

Rook GA, Zumla A. Gulf War syndrome: is it due to a systemic shift in cytokine balance towards a Th2 profile? *Lancet*. 1997 Jun 21;349(9068):1831-3.

Smylie AL, Broderick G, Fernandes H, Razdan S, Barnes Z, Collado F, Sol C, Fletcher MA, Klimas N. A comparison of sex-specific immune signatures in Gulf War illness and chronic fatigue syndrome. *BMC Immunol*. 2013 Jun 25;14:29. doi: 10.1186/1471-2172-14-29.

Whistler T, Fletcher MA, Lonergan W, Zeng XR, Lin JM, Laperriere A, Vernon SD, Klimas NG. Impaired immune function in Gulf War Illness. *BMC Med Genomics*. 2009 Mar 5;2:12. doi: 10.1186/1755-8794-2-12.

Zhang Q, Zhou XD, Denny T, Ottenweller JE, Lange G, LaManca JJ, Lavietes MH, Pollet C, Gause WC, Natelson BH. Changes in immune parameters seen in Gulf War veterans but not in civilians with chronic fatigue syndrome. *Clin Diagn Lab Immunol*. 1999 Jan;6(1):6-13.

VA/DoD GWI CDE Project Gulf War Illness (GWI) Biomarkers Subgroup

Biomarkers are quantitative biological measures that can be used for diagnostic purposes and to monitor a patient's response to treatment. For veterans with GWI, no laboratory testing methods are available to accurately diagnose individual patients, but studies from different research groups have identified objective biological measures that significantly distinguish groups of ill Gulf War veterans from healthy controls. Identified differences relate primarily to brain structure and function, function of the autonomic nervous system (RAC, 2014; Li et al., 2014; Fox et al., 2018a, Fox et al., 2018b; Rayhan et al., 2013a&b; Haley et al., 2012; Baraniuk et al., 2017; Garner et al., 2018), neuroendocrine alterations (Golier et al. 2009; Golier et al. 2006), immune parameters (Broderick et al. 2018; Michalovicz et al 2018), and coagulation indicators (Johnson et al. 2016).

More recent potential biomarkers of individuals with GWI include alterations in gut microbiome (Seth et al. 2018; Alhasson et al. 2017), proteome/proteins (Abou-Donia et al. 2017; Johnson et al. 2016; Georgopoulos et al. 2016), metabolome/metabolism (Koslik et al. 2014), lipidome (Emmerich et al. 2017; Abdullah et al. 2016) genome/epigenome (Liu et al. 2018; Ashbrook et al. 2018), and gene transcription/transcriptome (Phillips et al. 2018).

These biological findings are generally considered preliminary, since most have been evaluated in one study, or a limited number of studies, using different measures and methods. Taken together, however, such studies have been useful in providing insights concerning the diverse biological processes that may underlie the causes of GWI and point toward areas of research that can potentially lead to useful biomarkers for diagnostics.

The committee modified the biomarker subcategories 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 exosome, CNS autoantibodies, flow cytometry of cell types, Co-Q10, PON1, BChE markers, oxidative stress markers, glutathione and the option for sharing samples with the Boston Biorepository and Integrative Network (BBRAIN) for GWI. The Biomarker Reference table has been modified for GWI specific references.

The following items were recommended as "Supplemental-Highly Recommended" by the subgroup:

- Biomarker
- Biomarkers Related Sample and Medication
- Biomarker Reference Table

The following items were recommended as "Exploratory" by the subgroup:

Omics

- Microbiome/Microorganisms
- Proteome/Proteins

- Metabolome/Metabolism
- Genome/Epigenome
- Gene expression/Transcriptome
- miRNA profiling
- Multiplex vs. SRM assays
- Bioinformatics Pathways
- Interconnect Omic data

Non-Omics

- Protein array analysis
- Cytokine measurements
- Chemokine measurements
- Flow-cytometry measurements of immune
- Autoantibody analyses
- Individual protein quantification
- Biomarkers of autonomic system dysfunction
- Blood chemistry
- Elements from detoxification pathways
- Exosomes

Summary Recommendations

GWI Common Data Elements Module: Biomarkers

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

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements Draft Version 1.0, 12/1/18

[Link to Description of GWI Research Measures](#)

The GWI CDE workgroups created the summary table of recommended data standards for GWI research and classified each instrument as Core, Supplemental - Highly Recommended, Supplemental, or Exploratory. The following table provides the link to a description of the specific instruments, case report forms, or guidelines that are listed in the summary table for this module. These descriptions and forms were developed by the NINDS ME/CFS common data elements workgroups and are linked directly to their website.

GWIC Common Data Elements Module: Biomarkers GWI Instrument and Link

Instrument

Biomarker Guidelines

https://www.commondataelements.ninds.nih.gov/MECFs.aspx#tab=Data_Standards

Biomarkers- Related Sample and Medication Questions

https://www.commondataelements.ninds.nih.gov/MECFs.aspx#tab=Data_Standards

Biomarker Reference Table

https://www.commondataelements.ninds.nih.gov/MECFs.aspx#tab=Data_Standards

References

Abdullah, L., Evans, J. E., Joshi, U., Crynen, G., Reed, J., Mouzon, B., Crawford, F. (2016). Translational potential of long-term decreases in mitochondrial lipids in a mouse model of Gulf War Illness. *Toxicology*, 372, 22-33. doi:10.1016/j.tox.2016.10.012.

Abou-Donia MB, Conboy LA, Kokkotou E, Jacobson E, Elmasry EM, Elkafrawy P, Neely M, Bass CR, Sullivan K. Screening for novel central nervous system biomarkers in veterans with Gulf War Illness. *Neurotoxicol Teratol*. 2017 May; 61:36-46.

Alhasson, F., Das, S., Seth, R., Dattaroy, D., Chandrashekar, V., Ryan, C. N., Chatterjee, S. (2017). Altered gut microbiome in a mouse model of Gulf War Illness causes neuroinflammation and intestinal injury via leaky gut and TLR4 activation. *PLOS ONE*, 12(3), e0172914. doi:10.1371/journal.pone.0172914.

Ashbrook, D. G., Hing, B., Michalovicz, L. T., Kelly, K. A., Miller, J. V., De Vega, W. C., McGowan, P. O. (2018). Epigenetic impacts of stress priming of the neuroinflammatory response to sarin surrogate in mice: a model of Gulf War illness. *Journal of Neuroinflammation*, 15(1). doi:10.1186/s12974-018-1113-9.

Baraniuk, J. N., & Shivapurkar, N. (2017). Exercise – induced changes in cerebrospinal fluid miRNAs in Gulf War Illness, Chronic Fatigue Syndrome and sedentary control subjects. *Scientific Reports*, 7(1). doi:10.1038/s41598-017-15383-9

Broderick, G., Fletcher, M. A., Gallagher, M., Barnes, Z., Vernon, S. D., & Klimas, N. G. (2018). Exploring the Diagnostic Potential of Immune Biomarker Co-expression in Gulf War Illness. *Methods in Molecular Biology*, 101-120. doi:10.1007/978-1-4939-7828-1_7.

Emmerich, T., Zakirova, Z., Klimas, N., Sullivan, K., Shetty, A. K., Evans, J. E., Crawford, F. (2017). Phospholipid profiling of plasma from GW veterans and rodent models to identify potential biomarkers of Gulf War Illness. *PLOS ONE*, 12(4), e0176634. doi:10.1371/journal.pone.0176634.

Fox, A., Helmer, D., Tseng, C., McCarron, K., Satcher, S., & Osinubi, O. (2018a). Autonomic Symptoms in Gulf War Veterans Evaluated at the War Related Illness and Injury Study Center. *Military Medicine*. doi:10.1093/milmed/usy227.

Fox, A., Riska, K., Tseng, C. L., McCarron, K., Satcher, S., Osinubi, O., & Helmer, D. (2018b). Dizziness, Vertigo, and Mental Health Comorbidity in Gulf War Veterans. *J Am Acad Audiol*, 30(9).

Garner RS, Rayhan RU, Baraniuk JN. Verification of exercise-induced transient postural tachycardia phenotype in Gulf War Illness. *Am J Transl Res*. 2018 Oct 15;10(10):3254- 3264.

Georgopoulos, A. P., James, L. M., Mahan, M. Y., Joseph, J., Georgopoulos, A., & Engdahl, B. E. (2016). Reduced Human Leukocyte Antigen (HLA) Protection in Gulf War Illness (GWI). *EBioMedicine*, 3, 79-85. doi:10.1016/j.ebiom.2015.11.037.

Golier, J. A., Schmeidler, J., & Yehuda, R. (2009). Pituitary response to metyrapone in Gulf War veterans: Relationship to deployment, PTSD and unexplained health symptoms. *Psychoneuroendocrinology*, 34(9), 1338-1345 doi:10.1016/j.psyneuen.2009.04.004.

Golier, J. A., Schmeidler, J., Legge, J., & Yehuda, R. (2006). Enhanced cortisol suppression to dexamethasone associated with Gulf War deployment. *Psychoneuroendocrinology*, 31(10), 1181-1189. doi:10.1016/j.psyneuen.2006.08.005.

Haley RW, Charuvastra E, Shell WE, et al. Cholinergic autonomic dysfunction among veterans with Gulf War syndrome: confirmation in a population-based sample. *JAMA Neurol*. Published online November 21, 2012. doi:10.1001/jamaneurol.2013.596.

Johnson, G. J., Slater, B. C., Leis, L. A., Rector, T. S., & Bach, R. R. (2016). Blood Biomarkers of Chronic Inflammation in Gulf War Illness. *PLOS ONE*, 11(6), e0157855. doi:10.1371/journal.pone.0157855.

Koslik, H. J., Hamilton, G., & Golomb, B. A. (2014). Mitochondrial Dysfunction in Gulf War Illness Revealed by ³¹Phosphorus Magnetic Resonance Spectroscopy: A Case- Control Study. *PLoS ONE*, 9(3), e92887. doi:10.1371/journal.pone.0092887.

Li, M., Xu, C., Yao, W., Mahan, C. M., Kang, H. K., Sandbrink, F., Karasik, P. A. (2014). Self-reported post-exertional fatigue in Gulf War veterans: roles of autonomic testing. *Frontiers in Neuroscience*, 7. doi:10.3389/fnins.2013.00269.

Liu, G., Ye, C. J., Chowdhury, S. K., Abdallah, B. Y., Horne, S. D., Nichols, D., & Heng, H. H. (2018). Detecting Chromosome Condensation Defects in Gulf War Illness Patients. *Current Genomics*, 19(3), 200-206. doi:10.2174/1389202918666170705150819.

Michalovicz, L. T., Locker, A. R., Kelly, K. A., Miller, J. V., Barnes, Z., Fletcher, M. A., O'Callaghan, J. P. (2018). Corticosterone and pyridostigmine/DEET exposure attenuate peripheral cytokine expression: Supporting a dominant role for neuroinflammation in a mouse model of Gulf War Illness. *NeuroToxicology*, 70, 26-32. doi:10.1016/j.neuro.2018.10.006.

Phillips, K. F., & Deshpande, L. S. (2018). Chronic Neurological Morbidities and Elevated Hippocampal Calcium Levels in a DFP-Based Rat Model of Gulf War Illness. *Military Medicine*, 183(suppl_1), 552-555. doi:10.1093/milmed/usx148.

Rayhan RU, Ravindran MK, Baraniuk JN. Migraine in gulf war illness and chronic fatigue syndrome: prevalence, potential mechanisms, and evaluation. *Frontiers in Physiology*. 2013a;4:181. doi:10.3389/fphys.2013.00181.

Rayhan RU, et al. Exercise challenge in Gulf War Illness reveals two subgroups with altered brain structure and function. *PLoS One*. 2013b;8:e63903. doi: 10.1371/journal.pone.0063903.

Seth, R. K., Kimono, D., Alhasson, F., Sarkar, S., Albadrani, M., Lasley, S. K., Chatterjee, S. (2018). Increased butyrate priming in the gut stalls microbiome associated-gastrointestinal inflammation and hepatic metabolic reprogramming in a mouse model of Gulf War Illness. *Toxicology and Applied Pharmacology*, 350, 64-77. doi:10.1016/j.taap.2018.05.006.