



A common language for Gulf War Illness (GWI) research studies: GWI common data elements

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Abbreviations: BU, Boston University; CDE, Common Data Element; CDMRP, Congressionally Directed Medical Research Programs; CNS, central nervous system; DoD, Department of Defense; GW, Gulf War; GWI, Gulf War Illness; MRS, magnetic resonance spectroscopy; ME/CFS, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; NINDS, National Institute of Neurological Disorders and Strokes; NSU, Nova Southeastern University; PET, Positron Electron Tomography; QoL, quality of life; RTI, RTI International; VA, United States Department of Veterans Affairs; WRIISC, War Related Illness and Injury Study Center.

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ABSTRACT

Aims: The Gulf War Illness programs (GWI) of the United States Department of Veteran Affairs and the Department of Defense *Congressionally Directed Medical Research Program* collaborated with experts to develop Common Data Elements (CDEs) to standardize and systematically collect, analyze, and share data across the (GWI) research community.

Main methods: A collective working group of GWI advocates, Veterans, clinicians, and researchers convened to provide consensus on instruments, case report forms, and guidelines for GWI research. A similar initiative, supported by the National Institute of Neurologic Disorders and Stroke (NINDS) was completed for a comparative illness, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), and provided the foundation for this undertaking. The GWI working group divided into two sub-groups (symptoms and systems assessment). Both groups reviewed the applicability of instruments and forms recommended by the NINDS ME/CFS CDE to GWI research within specific domains and selected assessments of deployment exposures. The GWI CDE recommendations were finalized in March 2018 after soliciting public comments.

Key findings: GWI CDE recommendations are organized in 12 domains that include instruments, case report forms, and guidelines. Recommendations were categorized as core (essential), supplemental-highly recommended (essential for specified conditions, study types, or designs), supplemental (commonly collected, but not required), and exploratory (reasonable to use, but require further validation). Recommendations will continually be updated as GWI research progresses.

Significance: The GWI CDEs reflect the consensus recommendations of GWI research community stakeholders and will allow studies to standardize data collection, enhance data quality, and facilitate data sharing.

1. Introduction

The combination of the desire to collect data in clinical trials and research studies that characterize the clinical and biologic symptoms that veterans with Gulf War Illness (GWI) experience and the ability to compare findings from different studies, motivated GWI investigators to develop a common set of assessment tools. GWI is a complex, multi-symptom medical illness of uncertain etiology and limited targeted treatment options. Clinicians and researchers confront the challenge to study this medical condition and to interpret results of independent studies conducted by different research groups at multiple institutions who utilize disparate methodologies and clinical trial designs. This makes cross-study comparisons cumbersome and difficult to replicate. As such, GWI research efforts will benefit from standard data collection methods based on measures that demonstrate evidence for content validation of assessment of veterans with GWI.

For three decades since the 1991 Gulf War, GWI research groups have separately performed epidemiologic, clinical, and basic science studies to gain insight into the underlying mechanisms and heterogeneity of this chronic illness in an effort to discover effective treatments affecting approximately a third of the deployed veterans. [1] The condition negatively affects multiple organ systems and results in a myriad of symptoms that include debilitating fatigue, respiratory issues, musculoskeletal pain, gastrointestinal disturbances, cognitive dysfunction, and dermatologic and neurological complaints. [2,3] Diagnosis of GWI relies on the presence or absence of various criteria that vary by individual and are interpreted differently by clinicians. Treatment is palliative in nature, relying on symptom presentation because the

underlying pathophysiology is elusive. While some progress has been made, the ability to clearly understand these mechanisms has been hindered by the lack of an accepted case definition and the heterogeneity of GWI.

Regardless of the case definition, GWI researchers recognize that applying the same standard measurement methods to research will allow aggregation of research findings. As such, the GWI clinical and research communities sought to identify common definitions employed in clinical research and laboratory studies, to present them in a standard format (instruments, forms, and guidelines), and to provide information for research for clinical and biologic collection.

The foundation of this undertaking was supported by the National Institute of Neurologic Disorders and Stroke (NINDS) for a comparator illness, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). [4] ME/CFS is phenotypically similar to GWI and presents with an inability to identify markers of disease activity. [5,6] Both illnesses are currently diagnosed and managed based on presenting symptomatology, necessitating objective measures and valid, reliable tools.

The GWI Common Data Element (CDE) initiative was sponsored by the United States Department of Veteran Affairs (VA) and the Department of Defense (DoD) *Congressionally Directed Medical Research Programs (CDMRP)* and aimed to establish consensus on data collection measures across important illness domains to improve the interpretation and applicability of GWI study results. The CDE GWI initiative developed recommendations across survey instruments, case report forms, and laboratory measures to improve data quality, and to increase the efficiency and effectiveness of clinical and laboratory studies.

2. Materials and methods

2.1. GWI CDE development process

Veterans, advocates, clinicians, laboratory scientists, and GWI investigators convened to develop GWI CDEs to establish the GWI CDE working group. The GWI CDE working group was divided into two sub-groups (symptoms and systems assessment), following the similar NINDS ME/CFS CDE initiative. The GWI working group members were tasked to evaluate the tools recommended by the NINDS ME/CFS CDE within specific domains and to review the applicability of the instruments and forms to GWI research.

Through discussion, the working group provided consensus on assessment tools, instruments, case report forms, and guidelines for GWI research studies.

The symptoms assessment working group reviewed six domains: Baseline/covariate information, fatigue, post-exertional malaise (PEM), sleep, pain, and quality of life/functional status/activity/exercise challenge studies. The systems assessment working group reviewed five domains: Neurologic/neuropsychological/neuroimaging, autonomic, endocrine/neuroendocrine, immune, and biomarkers. The working group members evaluated measures in every domain outlined by the ME/CFS CDE guidelines as a foundation for these GWI CDEs (Table 1). Members of both groups also reviewed a domain specific to GWI research: Deployment exposures and GWI risk factors.

The GWI CDE Working Group began meeting by teleconference in February 2018 and assembled in-person during a field-based meeting in March 2018. The meeting was available via webcast to all interested investigators from the VA and CDMRP research programs. Prior to the March 2018 meeting, all members of the GWI working group were asked to review all of the ME/CFS CDEs and evaluate their applicability to GWI research. During the February 2018 teleconferences, participants were assigned to either the symptoms or systems working groups. Each participant was assigned to review two specific domains in detail and to submit their evaluations via a detailed questionnaire in the Research Electronic Data Capture (REDCap) online database system, prior to the in-person, field-based meeting. The GWI CDE administrative team compiled the responses. For each domain, a primary reviewer was tasked with summarizing all submitted comments for an assigned domain, presenting the key issues, and leading the discussion during the in-person field-based meeting. Regular working group meetings were held via teleconference to review and classify tools within each domain until recommendations for instruments, case report forms, and guideline documents were finalized.

2.2. GWI CDE development classification

The working group classified assessment tools based on their applicability to GWI research. Determinations were made whether to recommend a psychometric instrument as a “Core” data element to establish the presence or absence of a key domain in all GWI studies, and to select specific data elements that should be standardized or reported

Table 1
Gulf War Illness common data elements domains by assigned group.

Symptoms Assessment Working Group	Systems Assessment Working Group
Baseline/covariate Information	Neurologic/neuropsychological/ neuro imaging
Fatigue	Autonomic
Post-Exertional Malaise (PEM)	Endocrine/Neuroendocrine
Sleep	Immune;
Pain	Biomarker
Quality of Life/Functional Status/Activity/ Exercise Challenge Studies	
Deployment Exposures and GWI Risk Factors Questionnaire	

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements, 2/2021.

in detail for replication. The best available tools were selected, despite differences across studies to account for the ceiling and floor effects of self-reported measures of GWI-related symptoms. In many domains, information regarding the reliability and validity of specific measures in GWI studies was limited due to the vast variability of measures employed by the research community. Consistent with the NINDS ME/CFS CDE terminology and approach, each tool was classified as, Core, Supplemental-Highly Recommended, Supplemental, or Exploratory (Table 2).

3. Results

The completed GWI CDE document was posted for public comment on the DoD CDMRP website in January 2019. Comments received during public review were brought to the GWI CDE working group oversight committee for review. The final version was posted in March 2019 under the GWI research section of the DoD CDMRP website. (https://cdmrp.army.mil/gwirp/research_highlights/19gwi_cde_initiative_highlight.aspx).

These GWI Common Data Elements (CDEs) standardize data collection for clinical assessment, laboratory, and imaging research studies. The GWI CDE initiative recommends the GWI case definitions (Centers of Disease Control and Prevention (CDC) and Kansas GWI case definitions) and the Veteran Short Form 36 item Health survey (VR-36) as “Core” data elements for use in GWI research (Table 3). The case definition of GWI is essential and is recommended to be included as part of the research study’s inclusion criteria.

The general health survey, the Veteran Short Form 36 item Health survey (VR-36), is recommended as a “Core” data element in all GWI human subject investigations. This instrument is relatively short, containing 36-self-report questions. The VR-36 is currently the most widely used instrument to measure quality of life (QoL) in GWI and is used as a clinical assessment in the intake of GWI patients at the Veteran’s Administration (VA) War Related Illness and Injury Study Centers (WRIICs). The physical and vitality subscales are often used as functional measures, and some use alternate item weightings to (de) emphasize the contributions of selected domains. It is also important to use the sub-scales of the VR-36 (physical component summary (PCS) and mental component summary (MCS) scores) to capture emotional well-being and not to focus entirely on physical aspects of health. 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.

The GWI CDE initiative employed expert consensus to select GWI CDEs to recommend tools for future studies involving Veterans diagnosed with GWI. The list of specific instruments, case report forms, and guidelines can be found on the CDMRP website. GWI researchers have a choice of valid, reliable tools that will assist in the comparability of variables across studies and will facilitate meta-data analyses. A

Table 2
GWI common data elements data standards classification [4].

Rating	Definition
Essential	Core CDE: Collects essential information, applicable to any study which span across all disease and therapeutic areas, or that are specific to one disease area. Supplemental-Highly Recommended CDE: Essential to collect, based on certain conditions or study types in GWI clinical research studies, depending upon study type or design.
Additional	Supplemental CDE: Commonly collected in clinical research studies, but relevance depends upon the study design (i.e., clinical trial, cohort study, etc.) or type of research involved. Exploratory CDE: Requires further validation but may fill current gaps in the CDEs and/or substitute for an existing CDE once validation is complete. The instruments are reasonable to use with the understanding that limited study has been done for veterans with GWI.

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements, 2/2021.

Table 3
Classification of GWI Common Data Elements: Core.

GWI Common Data Elements Instrument name	Classification
CDC Case Definition of GWI [7]	Core
Kansas Modified Case Definition of GWI [2]	Core
Veterans RAND Short Form 36 item Health survey (VR-36) [8]	Core
<ul style="list-style-type: none"> Physical Component Summary (PCS) Score Mental Component Summary (MCS) Score 	

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements Version, 2/2021.

summary of the classification of instruments by domain is included in Table 4. For each domain, the number of recommended tools is listed. The baseline/covariate information contains the most measures and forms, which can be selected by GWI researchers to gain an initial understanding of the symptoms experienced by patients or research study participants with GWI. The GWI CDE working group classified tools as “supplemental-highly recommended” when the study focuses on a certain domain and its objectives are to assess the entire spectrum of GWI symptoms experienced by Veterans. In many cases, tools are classified as “supplemental,” when they have not been used extensively in GWI research but demonstrate promising opportunities for future explorations.

4. Discussion

The GWI CDE initiative employed expert consensus to select GWI CDEs to guide instrument recommendations and standardize GWI research efforts, which will be used to guide future studies involving Veterans with GWI and improve study comparisons and replication. These leading experts are sensitive to GWI symptoms and outcomes. In the process of selecting instrument recommendations within specific domains, thoughtful consideration was employed to ensure effective utilization, consideration of instrument advances, and future directions. The working group selected a few “Core” measures, including the GWI case definitions (CDC and Kansas case definitions) and a general health survey (VR- 36).

Table 4
Number of measurement tools and level of classification by CDE domain and area.

GWI CDEs domain and area	Supplemental-highly recommended	Supplemental	Exploratory
Baseline/covariate information	10	–	–
Post Exertional Malaise	1	7	–
Fatigue	1	6	–
Sleep	2	–	8
Pain	1	3	6
Quality of Life	–	2	5
Exercise Challenge	–	2	2
Functional Status	2	–	1
Neurological	1	–	–
Neuropsychological	8	8	–
Neuroimaging	8	–	–
Autonomic	1	–	7
Endocrine/Neuroendocrine	3	2	–
Immune	4	2	–
Biomarkers	3	–	2
Deployment Exposures and GWI Risk Factors	1	–	–

Note: Measurement Tools include survey instruments, case report forms, and guidelines.

Reference: VA/DoD Gulf War Illness (GWI) Common Data Elements Version, 2/2021.

4.1. Selection of additional “Core” CDEs

While some recommended tools have yet to be rated in terms of reliability and validity in GWI research, GWI investigators recognize that certain measures are useful in gauging clinical symptoms, which are significant to GWI Veterans. The consensus of the GWI CDE working group was that “Core” instruments should be identified to assess certain domains significant to GWI, including fatigue and pain. Additional research involving Veterans with GWI is needed before the selection of specific recommendations of additional instruments can be made. However, this is an ongoing process as potential newer and more sensitive measures are tested and established in the field.

4.2. Utilization of CDEs

The GWI CDE working group recommends that GWI researchers use these CDEs to standardize clinical and biologic data tools. These leading experts are sensitive to GWI symptoms and outcomes, as well as the research participant burden. When initially designing the research assessment platform, researchers should review the twelve CDE domains, incorporate the “Core” data elements (Kansas and CDC case definitions and VR 36), and select additional domain measures that match the study’s objectives. Prior to implementation, researchers are encouraged to consider the participant burden with respect to the number tasks, which may affect the participants’ level of fatigue, influence cognition, and, ultimately, affect the completion of all tasks outlined in the research study platform. The focus is on the order the research participant performs the surveys and tests, such that the assessments that are most germane to the study’s objectives are completed early in the research encounter.

4.3. Presence or absence of operational definition of a domain

Discussions by the GWI CDE working group focused on the degree to which a data element met the needs of the GWI research community and if it had been previously published in the literature and found to be sensitive to GWI case status. In addition, they also considered how a measure could be interpreted in the context of several gaps in the literature. For some domains that are important in diagnosing GWI, like post-exertional malaise (PEM), there is a lack of consensus among experts for an operational definition, and few questionnaires have been designed to measure this symptom. This presents challenges and opportunities for GWI clinicians and researchers.

In contrast to PEM, questionnaires are often used to diagnose and treat fatigue and assess the level of severity, and the level of functioning. Even subdomains are well-defined in GWI research in terms of general fatigue, physical fatigue, mental fatigue (cognitive difficulties), post-exertional fatigue, and fluctuating fatigue. Although there is limited evidence for content validation in GWI research, GWI clinicians and researchers often use the Multidimensional Fatigue Inventory (MFI) to gain a better understanding of the debilitating fatigue experienced by veterans with GWI.

4.4. Domains as outcome measures

For many GWI studies, assessment tools represented in the ME/CFS CDEs are commonly sufficient to address the needs of studies when the domain is not a primary outcome variable. Throughout the CDEs, these instruments were deemed to be “supplemental” and recommended for selection depending on the goals of a study. Specific instruments may be more relevant to dimensions examined in a given study and should be considered on a per-study basis. In some cases, a study may focus on the presence or absence of a domain, but other studies may prefer a measure that possesses sensitivity to change to detect day-to-day fluctuations in GWI symptom severity, which is essential to understand the time-course of the domain.

4.5. GWI CDE departures from ME/CFS CDE

The GWI CDE working group departed from some decisions recommended by the ME/CFS CDE committee and chose to draft new versions of published questionnaires in an attempt to derive more appropriate measures that will need validation in GWI research efforts. Case report forms that were not considered to be appropriate for GWI were replaced with new forms and classified as exploratory measures. For example, neuroimaging case report forms for positron electron tomography (PET) and magnetic resonance spectroscopy (MRS) scans have been updated to reflect neuroinflammatory and oxidative stress measures, which are important in understanding GWI pathophysiology. [9] [10].

Given that NINDS supported the development of CDEs for multiple diseases, in addition to ME/CFS, the GWI CDE working group modified some domain sub-categories by adding additional categories relevant to GWI and adopted CDEs created by other NINDS CDE working groups. For example, the endocrine/neuroendocrine sub-group recommended a separate dietary survey and dietary supplements use form adopted from the mitochondrial and gastrointestinal (GI) disease CDEs to better address the assessment of GWI. (See supplemental materials).

An additional domain was developed by the GWI CDE working group to assess deployment exposures and GWI risk factors. When assessing this domain, GWI clinicians and researchers are encouraged to survey patients or study participants about their experiences rather than on their direct exposures. This orientation was selected both because of the potential for recall bias on reporting prior exposures and to improve the recall of past events. This survey was designed to assist with future gene-environment and genetic susceptibility biomarker and treatment trial studies.

4.6. Limitations and future directions

The approach taken for choosing common data elements for GWI was to focus on measures which had been used previously in other studies and found to be sensitive to particular aspects of the disorder. However, this approach has clear limitations that should be noted. There may be newer tests or clinical measures that are in fact more sensitive to GWI but have not been included in multiple publications to date and were therefore not chosen for use in the current CDE recommendations. That is the reason that the GWI Common Data Elements platform is considered to be a dynamic resource that will evolve based on the results of evidenced-based GWI investigations that employ and validate these measures, allowing comparability across research studies. All updates to the GWI CDEs will undergo a thorough review process including approval by the GWI CDE Working Group Oversight Committee prior to implementation. This committee is comprised of up to ten individuals who are clinicians, laboratory researchers, investigators, veterans, and GWI advocates. The committee may include representatives from the U.S. Veterans Affairs Office of Research and Development, and the U.S. Department of Defense CDMRP GWI research programs. The leadership of these two GWI programs continues to participate in every step of the CDE development process and notes the use of CDEs in the study design of future investigations of Veterans with GWI. Benefits of CDEs will advance scientific knowledge in the understanding of the etiology and treatment of GWI to assist Veterans.

Interested researchers and clinicians are welcome to send comments or suggestions for new CDEs to the committee at any time. As two large, funded efforts currently underway involve evidence-based outcome trials, it is anticipated that these Consortia, Gulf War Illness Clinical Trials and Interventions (GWICTIC) and Boston, Biorepository, Recruitment, and Integrated Network for GWI (BBRAIN), will share study results within the next two years. The GWI CDE Working Group Oversight Committee will review the sensitivity and reliability of measures used in these and other GWI investigations to inform the recommended measures presented in the next CDE platform.

5. Conclusion

GWI research data can be systematically collected, analyzed, and shared across research studies by using common data elements that represent the predominant symptoms experienced by Veterans with GWI. Investigators of clinical and laboratory studies are encouraged to incorporate the GWI CDEs Core instruments into their research designs to enhance data quality and promote meta-analyses. By recommending valid and reliable clinical and biologic assessment tools for use in GWI clinical trial designs and laboratory investigations, a better understanding of GWI disease pathology and accompanying targeted treatment approaches may be realized in the future.

Author contributions

DC, NK, KS, and RM contributed to the conception of the article. DC wrote the initial manuscript. DC, NK, KS, and RM contributed to the manuscript revision, read, and approved the submitted version. The GWI CDE Working Group members contributed to the supplementary material. We also acknowledge Beth Gilbert for formal review.

Declaration of competing interest

The authors declare no financial or other conflicts of interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.lfs.2021.119818>.

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