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Gulf War Illness Clinical Trials and Interventions Consortium (GWICTIC): A collaborative research infrastructure for intervention and implementation

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ABSTRACT

Aims: There is an inadequate portfolio of treatments for Gulf War Illness (GWI), a complex disease involving multiple organ systems, and early-phase clinical trials are hampered by many logistical problems. To address these challenges, the Gulf War Illness Clinical Trials and Interventions Consortium (GWICTIC) was formed with the aims of (i) creating a collaborative consortium of clinical and scientific researchers that will rapidly implement rigorous and innovative phase I and II clinical trials for GWI, (ii) perform at least four phase I or II clinical trials, (iii) provide a foundation of scalable infrastructure and management in support of the efficient and successful operation of the GWICTIC, and (iv) partner with the Boston Biorepository, Recruitment & Integrated Network for GWI and other GWI investigators to develop a common data element platform for core assessments and outcomes.

Main methods: The GWICTIC brings together a multidisciplinary team of researchers at several institutions to provide scientific innovation, statistical and computational rigor, and logistical efficiency in the development and implementation of early-phase low-risk clinical trials for GWI. The GWICTIC core trials adhere to a Veteran-centered philosophy and focus on interventions with multiple mechanistic targets to maximize the likelihood of efficacy. To support rapid and efficient study startup and implementation across the GWI research community, the GWICTIC will share infrastructure with investigator-initiated research studies funded under separate mechanisms.

Abbreviations: CDE, Common Data Element; CDMRP, Congressionally Directed Medical Research Programs; DoD, Department of Defense; GW, Gulf War; GWI, Gulf War Illness; GWICTIC, Gulf War Illness Clinical Trials and Interventions Consortium; NIH, National Institutes of Health; WRIISC, War Related Illness and Injury Study Center.

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Significance: The GWICTIC will leverage the efficiencies of centralized research support and innovative trial designs to address several longstanding needs in the GWI interventions research community.

1. Introduction

Patients suffering with Gulf War Illness (GWI) experience a myriad of symptoms that vary and affect multiple organ systems. These commonly include musculoskeletal pain, chronic fatigue, gastrointestinal disturbances, respiratory issues, dermatologic conditions, cardiovascular dysfunction, cognitive dysfunction, and central nervous system problems [1,2]. Other symptoms include muscle pain, joint pain, headaches, and dermatologic conditions. These symptoms may be of sufficient severity that they impact activities of daily living, patients' ability to maintain employment and care for themselves, and may disrupt patients' quality of life. The GWI terminology refers to the specific nature of an illness, inextricably linked to deployment in the Persian Gulf, and distinct from other chronic multi-symptom illnesses. Despite advances in understanding the potential mechanisms of GWI through epidemiologic, clinical, and basic science studies, treatment has remained focused on ameliorating symptoms, as the underlying pathophysiology of this chronic condition has yet to be fully elucidated. In addition, the process of advancing this knowledge into early-phase clinical trials has been limited by a variety of scientific and logistical factors. These include lack of a commonly accepted case definition for GWI, inconsistent methods and instruments of assessment, inefficient trial design, and difficulty in recruiting participants [3].

The Gulf War Illness Clinical Trials and Interventions Consortium (GWICTIC) was established under Department of Defense (DoD) Congressionally Directed Medical Research Programs (CDMRP) funding to strategically address the factors that have limited the success of many early-phase clinical trials of GWI treatment approaches [4]. The GWICTIC builds on extensive investments in pathogenesis and preclinical studies of GWI funded by the CDMRP and Veterans Health Administration (VHA) GWI programs that have yielded a deeper understanding of mediators, biologic subgroups, and the utility of illness modeling to focus therapeutic strategies [5–8]. The overarching goals of the GWICTIC are to: (i) create a collaborative consortium of clinical and scientific researchers that will rapidly implement rigorous and innovative phase I and II clinical trials for GWI, (ii) perform at least four phase I or II clinical trials, (iii) provide a foundation of scalable infrastructure and management in support of the efficient and successful operation of the GWICTIC, and (iv) partner with the Boston Brain, Recruitment & Integrated Network for GWI and other GWI investigators, hosting a common data element working group to develop a platform for core assessment and outcomes with broad consensus, for use in these studies and the wider field in support of our shared research mission. This manuscript describes the Consortium structure, resources, and strategic approach to carrying out low-risk clinical trials in an efficient and rapid manner to help an ailing patient population.

2. GWICTIC structure

2.1. Leadership

The GWICTIC is a collaborative partnership of respected investigators across nine institutions to support participant recruitment, administrative and outreach activities, clinical trial research activities, data management and biostatistics, biorepository and biomarker evaluation, and computational modeling. Fig. 1 provides a diagram of the organizational structure of the GWICTIC. The six clinical recruitment sites are nationally distributed to facilitate widespread GW Veteran engagement and represent leading GWI research centers in the United States. Reflecting its scientific and operational goals, the GWICTIC is co-led by an established GWI clinical researcher and a biostatistician with GWI research experience. The GWICTIC's Administrative Director brings

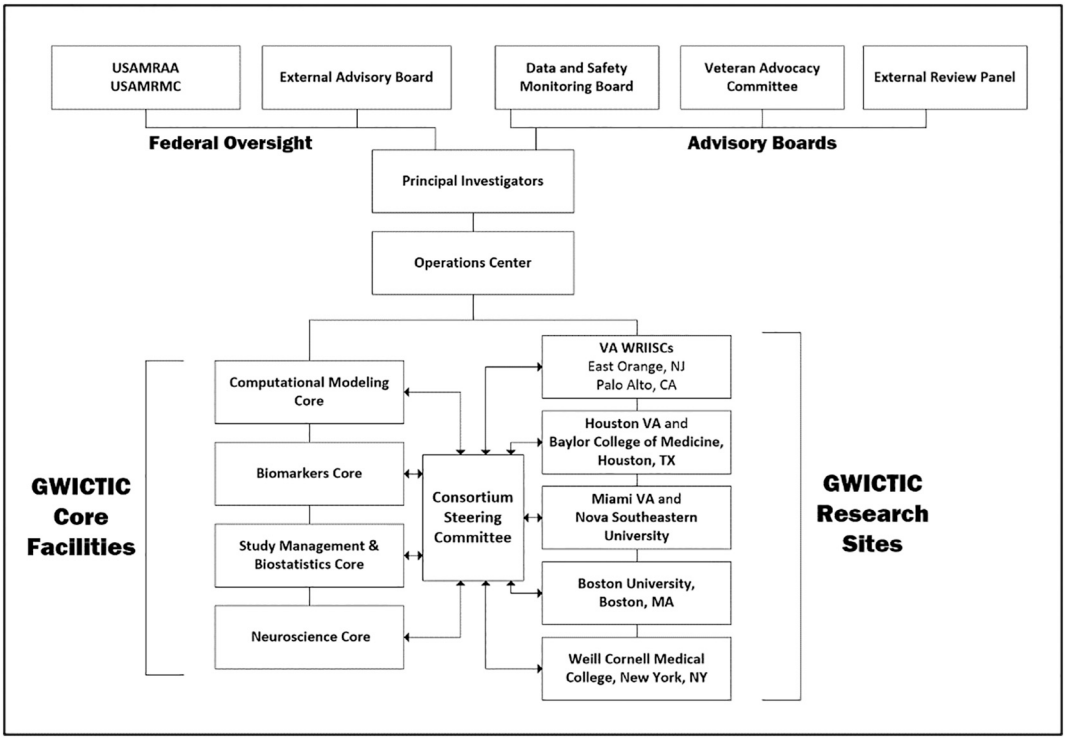

Fig. 1. Organizational structure of the GWICTIC.

additional expertise in biochemistry, nutrition, and complementary therapies. The leadership team's combined scientific, clinical, and operational expertise thus facilitates the research operations of the Central Coordinating Center.

The GWICTIC Steering Committee, made up of the co-Principal Investigators (PIs), Administrative Director, Core facility directors, and research site PIs, is responsible for making decisions regarding GWICTIC activities. The Steering Committee meets monthly by videoconference and annually in person (or by videoconference if circumstances do not permit in-person meetings). Additional Committees and Working Groups include the Veterans' Advisory Committee, a group of Veterans and caregivers who advise on study design, recruitment strategies and outreach, and provide guidance in other areas as needed; and the Publications Working Group, which administers the publications policy for the GWICTIC. Subcommittees have been convening on an *ad hoc* basis to address specific needs. A patient advocate is designated to each Committee and Working Group and will have a defined role during meetings. In this way, the perspectives of the GW advocates will be integrated in every aspect of the GWICTIC's planning and implementation.

2.2. Participating institutions

The GWICTIC includes six clinical recruitment sites and an imaging site (Fig. 2): three at academic medical centers (Nova Southeastern University, Boston University, and Weill Cornell Medical Center), and four at Veterans Affairs medical centers (Houston VA and Baylor College of Medicine, Miami VA, and the War Related Illness and Injury Study Centers (WRIISCs) at East Orange, NJ, and Palo Alto, CA) [9,10]. Non-clinical research sites at RTI International and Rochester General Hospital contribute additional expertise and operational support. This multidisciplinary partnership builds on longstanding collaborations in GWI research to focus efforts at institutions with a demonstrated record of successful recruitment and retention of Veterans in GWI research studies. Table 1 provides a full list of the GWICTIC sites, their roles, and the primary domains of expertise contributed by each.

Table 1
GWICTIC participating institutions and their locations, roles, and primary domains of expertise.

Institution and location	Role	Domains of expertise
Boston University Boston, MA	Conduct clinical trials Imaging Neuroscience Core	Neuroscience/ neurotoxicology Neuroimaging Neuropsychology GWI biomarkers GWI epidemiology
Weill Cornell Medical Center New York, NY	Imaging	Neuroimaging
Houston VA and Baylor College of Medicine Houston, TX	Conduct clinical trials	GWI clinical care CPET Environmental/ occupational medicine
Miami VA Miami, FL	Conduct clinical trials	GWI clinical care CPET
Nova Southeastern University Davie, FL	Conduct clinical trials Administration Biomarker & Biorepository Core Computational Modeling Core	GWI clinical care Nutritional biochemistry CPET GWI biomarkers Computational modeling of GWI
WRIISC East Orange, NJ	Conduct clinical trials	GWI clinical care
WRIISC Palo Alto, CA	Conduct clinical trials Imaging	GWI clinical care Imaging
Rochester General Hospital Rochester, NY	Computational Modeling Core	Computational modeling of GWI
RTI International Research Triangle Park, NC	Administration Study Management and Biostatistics Core	GWI epidemiology Clinical trial design Study operations Biostatistics

Abbreviations: GWI, Gulf War Illness; VA, Veteran's Affairs; CPET, cardiopulmonary exercise testing, WRIISC, War Related Illness and Injury Study Center.

2.3. Oversight

The GWICTIC receives scientific, operational, and ethical oversight from several entities. The **External Advisory Board (EAB)** is a DoD-appointed and chaired steering committee of DoD representatives that

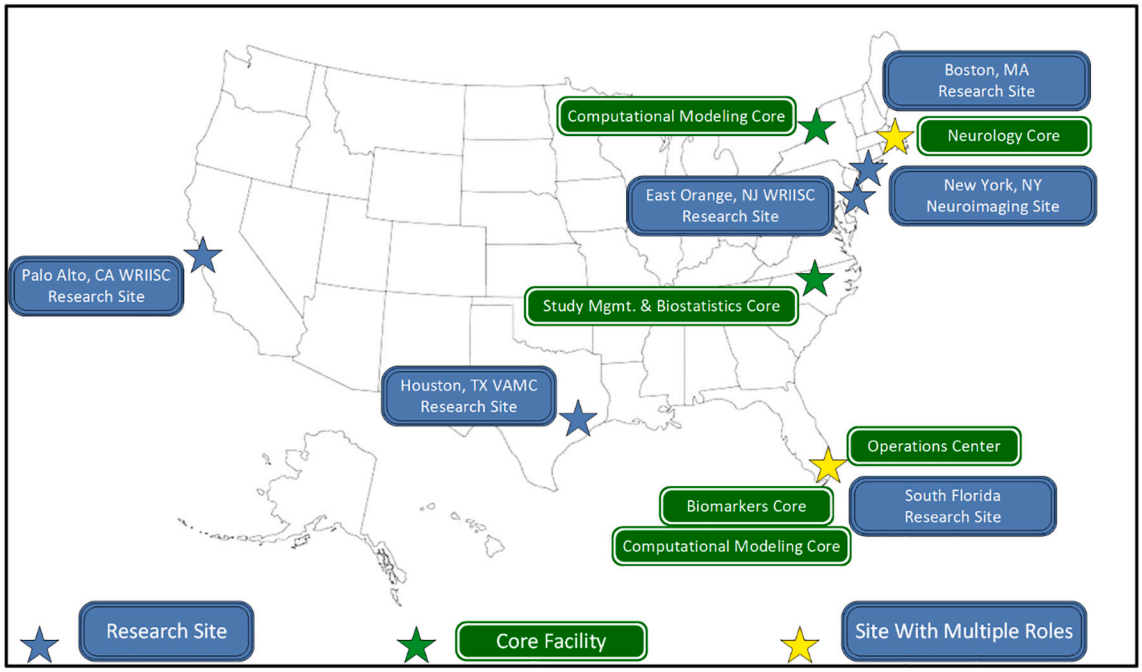

Fig. 2. Map of locations of GWICTIC participating institutions.

serves as the ultimate decisional authority for the GWICTIC. Non-DoD subject matter experts act as advisors to the Board. The **External Review Panel (ERP)**, a GWICTIC-appointed and EAB-approved panel, completes independent peer reviews of the scientific and clinical merits of proposed research studies. The **Data and Safety Monitoring Board** reviews study participant recruitment, retention, and safety data for all active studies on an ongoing basis, and reviews protocols in an advisory capacity. Additional oversight is provided by the DoD Human Research Protections Office (HRPO), local Institutional Review Boards (IRBs), and (for some protocols) the United States Food and Drug Administration. All research protocols undergo review and approval by the DoD HRPO and local IRBs prior to beginning study activities.

2.4. Central Coordinating Center

The GWICTIC's Central Coordinating Center (CCC) provides overall scientific and administrative leadership of the Consortium. This includes supporting the development, review, and implementation of clinical trials, reporting to the External Advisory Board and program officers, and maintaining a high level of compliance with local, governmental, and institutional requirements for human subjects research and data security across the Consortium. The CCC's efficient and cost-effective centralized support for implementation of trials includes the domains of recruitment, site support, outreach and engagement, study management and site monitoring, safety monitoring, Data and Safety Monitoring Board coordination and reporting, regulatory support, clinical informatics and data management, study design, and biostatistical analysis.

Taking into account the unique physical and cognitive challenges that may serve as barriers to participation in clinical trials, the CCC also promotes best practices in the recruitment of patients for GWI trials. These include providing financial support for participant and caregiver travel to research sites, minimizing on-site study visits, prioritizing interventions with a low risk of adverse events, selecting interventions (including nutraceuticals) that will be simple to access if found effective, providing an online platform for completion of study research instruments, and using fully-remote study designs when possible.

2.5. Core facilities

There are four Core facilities in the GWICTIC: Neuroscience, Biomarker and Biorepository, Computational Modeling, and Study Management and Biostatistics.

- Neuroscience Core: The Neuroscience Core provides support across all studies in the objective assessment of neurocognitive domains and provides neuroimaging support to the projects that incorporate imaging in the methods. This core has expertise in evaluation of neurocognitive domains, neuroimaging, and quality control of multisite neurocognitive and imaging assessment platforms.
- Biomarker and Biorepository Core: The Biomarker and Biorepository Core has established and validated the methods needed for functional assays and serologic, flow cytometric, and genomic studies. Additionally, the core follows the established National Institutes of Health (NIH), Clinical Laboratory Improvement Amendments (CLIA), and Food and Drug Administration (FDA) guidelines and has comprehensive measures to assure sample preservation such as full generator back-up and storing cryopreserved specimens.
- Computational Modeling Core: The Computational Modeling Core provides an integrative systems-based computational modeling approach to support endpoint assessment, biologic subgroup identification, and the further the development of novel treatment strategies. The Core supports the management, archiving, and numerical analysis of high-dimensional biomarker data generated from specimens gathered during GWICTIC trials.
- Study Management and Biostatistics Core: The Study Management and Biostatistics Core provides efficient and cost-effective administrative and logistical support for the Cores and study sites, including study management and monitoring, regulatory support, clinical informatics and data management, clinical trial design, and biostatistical analysis.

2.6. Protocol development and approval

All clinical trials conducted using GWICTIC core funding undergo an extensive protocol development process that is coordinated by the Study Management and Biostatistics Core, including full development of the study design, logistical considerations, data collection and management processes, statistical analyses, and reporting requirements. Each protocol then undergoes initial peer review of its scientific merits by the GWICTIC External Review Panel. The review evaluates proposals based on the following domains, consistent with reviews by the National Institutes of Health: rationale, research strategy and feasibility, significance and scientific premise, innovation, investigators, protection of human subjects, statistical and data analysis plans, and future directions / transition plans. At the time of the ERP review, the protocol is also reviewed by the GWICTIC DSMB for matters related to participant safety, appropriate balance of risks and benefits, and design considerations. Feedback from the ERP and DSMB is incorporated into revisions of the protocol and the subsequent version is reviewed by the External Advisory Board, DoD HRPO, and local site IRBs. Upon initial approval by the External Advisory Board, the Study Management and Biostatistics Core begins development of the Electronic Data Capture platform.

2.7. Study monitoring

All active clinical trials are subject to ongoing study monitoring procedures. Safety events are monitored with an established frequency appropriate to the risks of the protocol. Monitoring reports are submitted quarterly to the Data and Safety Monitoring Board to permit review of the risk/benefit balance to participants. Serious Adverse Events are reported in expedited fashion in accordance with IRB requirements.

In addition to routine safety monitoring, each participating site has on-site or remote monitoring visits to ensure that site facilities and record-keeping practices are in accordance with study protocols. These visits include reviews of informed consent forms, data collection forms, research pharmacy records, and other items.

2.8. Features addressing gaps in the field

As previously noted, the creation of the GWICTIC was motived by a number of scientific and logistical factors that have hindered the successful implementation of early-phase clinical trials for GWI. We describe below the specific actions taken to mitigate these factors.

2.8.1. Rationale for using GWI terminology

The lack of a commonly accepted definition is compounded by the inconsistency in language to designate this condition. The recommendation of the term “Gulf War Illness” by the Institute of Medicine 2014 report (now National Academy of Sciences) is preferred by veterans, who have been living with this illness for the last three decades, over other terms of “medically unexplained symptoms” in 2007 or “Chronic Multi-symptoms Illness” in 2013 [11–13]. GWI represents a distinct condition that is linked to deployment and is characterized by widespread symptoms, affecting multiple organ systems. The similarities of GWI to other conditions that are dependent on symptoms to determine diagnosis may offer treatment strategies and collaborative approaches with clinicians and researchers focused on other diseases. Due to its origin in deployment exposures, GWI will remain a separate condition from other chronic illnesses.

2.8.2. Absence of a commonly accepted diagnostic definition for GWI

There have been several case definitions suggested and utilized for research purposes for GWI and the related condition ME/CFS. In research projects, the definition used can impact the success of studies: if a definition is too restrictive, results cannot be generalized to the larger population, and if it is too broad then treatment effect heterogeneity may overwhelm evidence of response among participants. This is the subject of the 2014 Institute of Medicine (IOM) report [11,14] that concluded that the broad Centers for Disease Control (CDC) case definition [15] should be used for clinical "caseness," while the more restrictive Kansas case definition [16] should be used for as a research case definition, with the recommendation that subgrouping strategies be applied as appropriate. The ME/CFS case definition follows broad [12,17] and restrictive [18] approaches for the same reasons. Still, there are ambiguities apparent in the application of both of these symptom-based research case definitions, particularly as they apply to inclusion and exclusion criteria. In light of the current recommendations, the GWICTIC has chosen to use the Kansas case definition with slight modifications to account for age-related conditions for all of its proposed trials to date. However, without a pathophysiological explanation of the disease, the definition remains challenging.

2.8.3. Inconsistent methods and instruments of assessment

The GWI Common Data Elements (CDEs) [19] were selected through joint venture among the NIH, CDC, VA, DoD GWI Research Program, GWI researchers and the Veteran community. The CDEs provide evidence-based recommendations for self-report instruments to measure domains of illness, function, and quality of life, as well as objective measures such as neuroimaging, CPET, neurocognitive assessment and laboratory markers. The GWICTIC has implemented many of the recommended CDEs in its Electronic Data Capture platform. This common assessment platform will be used across the GWICTIC trials to improve the consistency of research measures and allow comparability across clinical trial outcomes. In the future, as more specific pathophysiological mechanisms are understood, methods and instruments can be tailored more specifically.

2.8.4. Inefficient trial design

The challenges to efficient trial design include a limited pool of potential participants in any single location and heterogeneity of clinical presentations. These hurdles require the ability to challenge traditional funding structures and recruitment methods, yet design trials that yield reliable and reproducible results. The GWICTIC addresses this in two ways. First, the GWICTIC's infrastructure and multisite clinical network is available to investigator-initiated studies funded under separate mechanisms, helping to mitigate the effects of budget caps that have historically limited clinical trial expansion to multiple sites. Second, dynamic modeling studies conducted by members of the GWICTIC Computational Modeling Core have allowed the development of study designs based on subgrouping strategies derived from homeostatic models of the illness. The innovative approach of designing studies around targets identified using preclinical and clinical data-based modeling approaches allows the rapid translation of preclinical to phase I-II designs. As additional data accrue during GWICTIC trials, the dynamic models will continue to improve in accuracy, identifying new subgroups and therapeutic targets and suggesting new treatment approaches. This offers a unique opportunity to focus limited resources on trials of interventions that have a higher likelihood of efficacy.

2.8.5. Difficulty in recruiting participants

The successful implementation of a GWI clinical trial requires a multi-pronged approach to support participant recruitment and continued engagement. The GWICTIC approach includes reaching out *via* established connections to GW Veterans and developing new approaches to communicate with them through a variety of social media outlets. Our strategies include but are not limited to: (i) recruit from existing cohorts of GW Veterans; (ii) collaborate with investigators funded by the DoD or VA; (iii) collaborate with clinicians and health professionals who treat Veterans with GWI; (iv) encourage direct referrals from GW Veterans; (v) participate in conferences, events, and health fairs directed to GW Veterans; and (vi) engage patient advocates directly from the geographic locations where clinical studies are recruiting. The GWICTIC investigators have a history of successful engagement and partnership with the patient and advocacy community. Patient advocates hold advisory status on the Consortium's EAB and are tasked to incorporate the consumer voices into study designs and logistics. In addition, the GWICTIC hosts regular research seminars and events to build the bridge between researchers and consumers. In the GWICTIC, we continue to promote respectful partnerships between patients and researchers, engaging the Veterans' Advocacy Committee to advise and assist in all aspects of the mission.

2.9. Resource sharing

The GWICTIC recognizes the critical importance of sharing resources and infrastructure throughout the Gulf War research community. All biospecimens collected during GWICTIC-supported trials will (with participant consent) be shared with the Boston Biorepository, Recruitment & Integrated Network for GWI (BBRAIN) and may be requested using the Network's standard process. Study materials such as protocols, manuals, and training materials will be made available upon Consortium Steering Committee approvals of requests for these materials. Open-source electronic data capture (REDCap) implementations of CDEs in the public domain and other study forms will also be available upon approved request. Information regarding these resources may be requested from the corresponding author of this publication. It is our hope that sharing these resources will support additional innovative research studies, increasing the pace of research into potential treatments for GWI.

3. Conclusion

The GWICTIC, building on a strong history of multidisciplinary collaborations, interweaves the broad experience and resources of government, academic, and nonprofit research institutes to deliver a reliable platform for the efficient and scientifically sound evaluation of potential GWI therapies. Rich in innovation and devoted to a Veteran-centered philosophy, this collaboration represents a critical advance in GWI research, one which will leverage the efficiencies of centralized research support and innovative trial designs across clinical disciplines to address the longstanding need for effective treatments for GWI.

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