Protocol: Novel Interventions for Gulf War Veterans' Illnesses

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Specific Aims

Over 40,000 Veterans who served in the Gulf War (GW) have a persistent form of chronic multisymptom illness that defines Gulf War Veterans Illness (GWVI) (Kang, Li, & Mahan, 2009; Research Advisory Committee (RAC) on Gulf War Veterans' Illnesses, 2008; Institute of Medicine (IOM), 2010). With no existing proven treatments to provide relief to these sufferers, it is critical to find efficacious and acceptable treatments for GWVI.

Our *long-term goal* is to develop a safe, readily available, mind-body treatment to reduce pain and other chronic symptoms and enhance wellness in Veterans with GWVI. Tai Chi is a traditional Chinese mind-body therapy that has been practiced for centuries. In the last decade, we have demonstrated that Tai Chi can improve both *physical health* and *psychological wellbeing* in patients with a variety of chronic conditions (Wang, Collet, & Lau, 2004; Wang et al., 2010b). Furthermore, our team has recently accomplished a successful pilot study that included 17 Veterans who completed a four-session Tai Chi group and reported great enthusiasm for the intervention (See Preliminary Studies for details). This preliminary work provides us with both the experience and the justification to conduct the first full-length trial **in Veterans with GWVI.**

HYPOTHESIS: Tai Chi will be an efficacious mind-body treatment for chronic pain in Veterans with GWVI.

The proposed randomized trial will establish the effectiveness of a Tai Chi mind-body treatment in Veterans with GWVI. One hundred and twenty participants meeting criteria for GWVI will be randomly assigned to either a Tai Chi exercise or a wellness education group for 12 weeks (60 minute groups 2x/week). A post treatment assessment and follow-up assessments 3 and 9 months following treatment will also be conducted.

Specific Aim 1: Evaluate whether the Tai Chi intervention will reduce symptoms of pain in Veterans with GWVI more than the Wellness intervention. We hypothesize that participants randomized to the Tai Chi intervention will show a greater reduction in pain symptoms than those in the Wellness intervention and will maintain changes over a 9-month follow-up period.

Specific Aim 2: Evaluate whether the Tai Chi intervention improves fatigue, cognition, quality of life, and physical functioning in GW Veterans with GWVI, as compared to the Wellness intervention. We hypothesize that participants randomized to the Tai Chi intervention will evidence more improvement in fatigue, cognitive functioning, quality of life, and physical functioning than those randomized to the Wellness intervention and will maintain changes over a 9-month follow-up period.

The proposed trial, informed by our prior investigations, with a robust study design and strong research team, will produce valuable results that can have a direct and immediate impact on healthcare practices for GWVI. If proven as an effective treatment for the symptoms of GWVI, this non-pharmaceutical treatment could easily be implemented in VA facilities and Veterans could be taught how to continue to practice independently within their own homes. Providing GW Veterans even moderate relief from chronic and debilitating symptoms of GWVI could have a profound impact on improving their overall sense of wellbeing and quality of life, the ultimate measure of treatment efficacy.

Background and Significance

Following their deployment to the 1991 Gulf War (GW), many Veterans reported a constellation of unexplained health symptoms including widespread chronic musculoskeletal pain, fatigue, headaches, memory and attention difficulties, gastrointestinal complaints, and mood and sleep problems. The symptom complex persists for many Veterans despite the passage of time. Indeed, it is estimated that at least 25 percent of GW Veterans (170,000 Veterans) have a persistent form of chronic multisymptom illness (CMI) (Kang et. al., 2009; RAC, 2008; IOM, 2010). Chronic musculoskeletal pain and fatigue are some of the most debilitating symptoms of CMI. To date, no treatments have been shown to substantially improve pain and fatigue without significant undesirable side effects, including exacerbating concurrent cognitive symptoms. Identifying effective, safe, and tolerable treatments for the symptoms of Gulf War Veterans' Illness (GWVI) is therefore of paramount importance.

Tai Chi, an ancient Chinese exercise that uses an integrated mind-body approach to enhance both physical and mental health, may be the key to improving health and well-being in Veterans experiencing GWVI. Tai Chi combines diaphragmatic breathing and relaxation with fundamental postures through slow, gentle, and graceful movements (Lan, Lai, & Chen, 2002) . Tai Chi has been shown to be safe and effective at promoting increased muscle strength, range of motion, cardiovascular fitness, emotional functioning, and quality of life in patients with chronic conditions including fibromyalgia, rheumatoid arthritis, and chronic fatigue syndrome. Importantly, the synergy between the physical and mental components of Tai Chi appears key to its efficacy in benefiting the emotional wellbeing of patients with chronic disorders (Wang et al., 2004; Wang, Bannuru, Ramel, Kupelnick, Scott & Schmid, 2010a). In the last decade, members of our team have conducted a series of Tai Chi clinical trials. A recent trial published in the *New England Journal of Medicine* (Wang et al., 2010b) demonstrated that Tai Chi is a useful treatment for the chronic pain associated with fibromyalgia. Given the improvement noted in these prior treatment trials, we believe that Tai Chi will be especially suited to the treatment of chronic pain symptoms associated with GWVI.

These recent studies have reported abnormal central processing of sensory and painful stimuli in subgroups of Veterans with GWVI. Compared to healthy GW Veterans, GW Veterans with chronic musculoskeletal pain report exercise as more painful, and they experience increased pain sensitivity following acute exercise at similar rates as individuals with fibromyalgia (Gopinath et al., 2012; Cook, Stegner, & Ellingson, 2010). These results suggest that fibromyalgia and GWVI may contain similar abnormalities in CNS processing of pain-related information and therapies found to be helpful in fibromyalgia may also be helpful to Veterans with GWVI.

Preliminary Studies

The multidisciplinary team in place for the proposed research has a strong track record of research in Tai Chi and other mind-body interventions, exercise and physical activity promotion, GWVI, and clinical trials of nonpharmacologic interventions for post-deployment symptoms in Veterans.

Health Promotion Intervention Trials for Veterans (Drs. Niles and Mori).

In a study conducted by Dr. Niles and funded by the Samueli Institute, 33 male combat Veterans were randomly assigned to one of two telehealth treatment conditions: Mindfulness or Psychoeducation (Niles, Klunk-Gillis, Ryngala, Silberbogen, Paysnick, & Wolf, 2012). In both conditions, participants completed eight weeks of telehealth treatment (two sessions in person followed by six sessions over the telephone). Results for the 27 participants who completed treatment indicate that Veterans with PTSD are able to tolerate and report high satisfaction with a brief mindfulness intervention and that participation in the mindfulness intervention is associated with a post-treatment reduction in PTSD symptoms. These findings support the proposed study and demonstrate that it is feasible to recruit and retain Veterans for Complementary and Alternative Medicine studies at VABHS (Niles et al., 2012). *This study shows that Veterans with post-deployment distress symptoms can tolerate and report high satisfaction with mindfulness, an important component of Tai Chi.*

Drs. Mori and Niles examined the efficacy of an automated telehealth intervention to promote physical activity and wellness in a population of overweight and sedentary Veterans with type 2 diabetes. Veteran interest in participating in this physical activity intervention study was very strong, facilitating our recruitment efforts. Of the 428 potential participants who were contacted by phone for the study, only 71 (17%) reported that they were not interested in participating. Furthermore, the results exhibited a remarkably high rate of compliance with the intervention. Sixty-six participants were randomized in this study, and of the 32 who were randomized to receive the automated phone calls, only 2 participants dropped out of the intervention (Seligowski, Johnson, Niles & Mori, 2011). *This physical activity intervention study provides strong support for the feasibility to recruit and retain Veteran participants with chronic medical illness in physical activity studies.*

In a large VA Cooperative Study of GW Veterans conducted at 18 VA and 2 Department of Defense medical centers (CSP #470 Study Team, 2001). Dr. Mori served as a site-PI. In this study, 1092 GW Veterans who reported symptoms of GWVI (i.e., fatigue, pain, and concentration and memory problems) were randomized to one of 4 conditions: (1) usual care, (2) 12 week cognitive behavioral therapy protocol that focused on stress management and wellness behaviors plus usual care, (3) 12 week exercise protocol plus usual care, or (4) 12 week cognitive behavioral therapy protocol plus exercise protocol plus usual care. The results showed that Veterans who received the cognitive behavioral therapy that focused on stress management and wellness behaviors exhibited an improvement in physical functioning at one year. Those who received exercise showed improvements in their report of fatigue. Both therapies modestly improved cognitive symptoms (concentration and memory problems) and mental health functioning (CSP #470 Study Team, 2001).Results *support the notion that interventions that reduce arousal and promote healthy behavior can have a positive impact on GWVI symptoms.*

Pilot Study of Tai Chi for Veterans (Drs. Niles, Mori, Pless Kaiser, and Wang)
Drs. Niles, Mori, and Pless Kaiser at VABHS and Dr. Wang at Tufts Medical Center worked together to build cohesive relationships, gather pilot data, and set the stage for future collaboration in clinical trials while carrying out our recent NCCAM funded supplemental pilot study (R01 AT005521AS). Investigators worked with Tufts and VABHS IRB Committees to develop a study protocol meeting all requirements at both institutions. These prior collaborations and development of study procedures will allow investigators to commence the proposed trial

without delay.

For this pilot study, we conducted two 4-session Tai Chi groups to provide an introduction to Tai Chi and solicit feedback from Veterans. Recruitment (using flyers, clinical referrals, and a recruitment database) was extremely successful. Of the 27 Veterans who were screened via telephone, 17 (63%) met initial screening criteria and attended the baseline appointment and all 17 entered the study. While recruiting for the first cohort of Veterans in May 2014, we accrued a list of Veterans large enough that no additional recruitment was needed to fill the second cohort (June, 2014). Two experienced Tai Chi instructors who have worked with Dr. Wang on previous Tai Chi trials received approval to conduct work at VABHS and each led one 4-session introductory group. Seventeen Veterans (11 males, 6 females, mean age = 51.1) were recruited into the study and 5 (29%) were GWV (Niles, Mori, Polizzi, Pless Kaiser, Ledoux, & Wang, 2016).

All participants completed a baseline assessment, up to 4 sessions of Tai Chi, and a feedback interview. One participant moved to a different city and sixteen participants (94%) completed the post-treatment assessment and focus group, and attended an average of 83% of the Tai Chi sessions. General satisfaction with the introduction to Tai Chi was very high: 96% (15/16) of Veterans reported they were very or mostly satisfied. In addition, 87% (14/16) endorsed that Tai Chi is an activity they enjoy doing and that it gives them a sense of personal accomplishment. All participants (100%) endorsed that they would recommend the Tai Chi program to a friend and that they would return for more Tai Chi if the program were offered again. Quotes from the GWV participants illustrate the various benefits they felt they derived:

> "I think it's good. Anything that you can use to just kind of stop your fast pace of life we live in nowadays is a good thing for me…."
>
> "It calms me, definitely….I'm dealing a little better with stress."
>
> "It is very relaxing, very soothing. The meditation was really nice. The meditation part, it helped me release my tension, and—believe me—I got tension."
>
> **"**It's low impact, physically, and I felt it to be more emotionally calming than other types of exercise."
>
> **"**I thought it was excellent. I want to do it again… like next week!"

As this pilot study was designed to give a short introduction to Tai Chi, reductions in symptom reporting on psychometric measures were not anticipated. Surprisingly, we detected a trend in reduction of mean scores on the Beck Depression Inventory from 24.56 (*SD* = 11.87) at baseline to 21.00 (*SD* = 11.71) post Tai Chi that approached statistical significance ($t[15] = 1.83$, $p = .087$). In addition, there was a statistically significant shift in scores on the Credibility Expectancy Questionnaire from 34.75 (*SD* = 11.79) at baseline to 39.62 (*SD* = 10.41) post Tai Chi ($t[15] = -2.26$, $p = .039$), indicating increased confidence in the credibility of Tai Chi to address health and mental health issues.

Relevant to the current proposal, *outcomes from the pilot study indicate that (1) recruitment of GWV for Tai Chi is feasible, (2) Veterans were highly satisfied with the introductory program, and (3) Veterans expressed high interest in returning for more Tai Chi groups.*

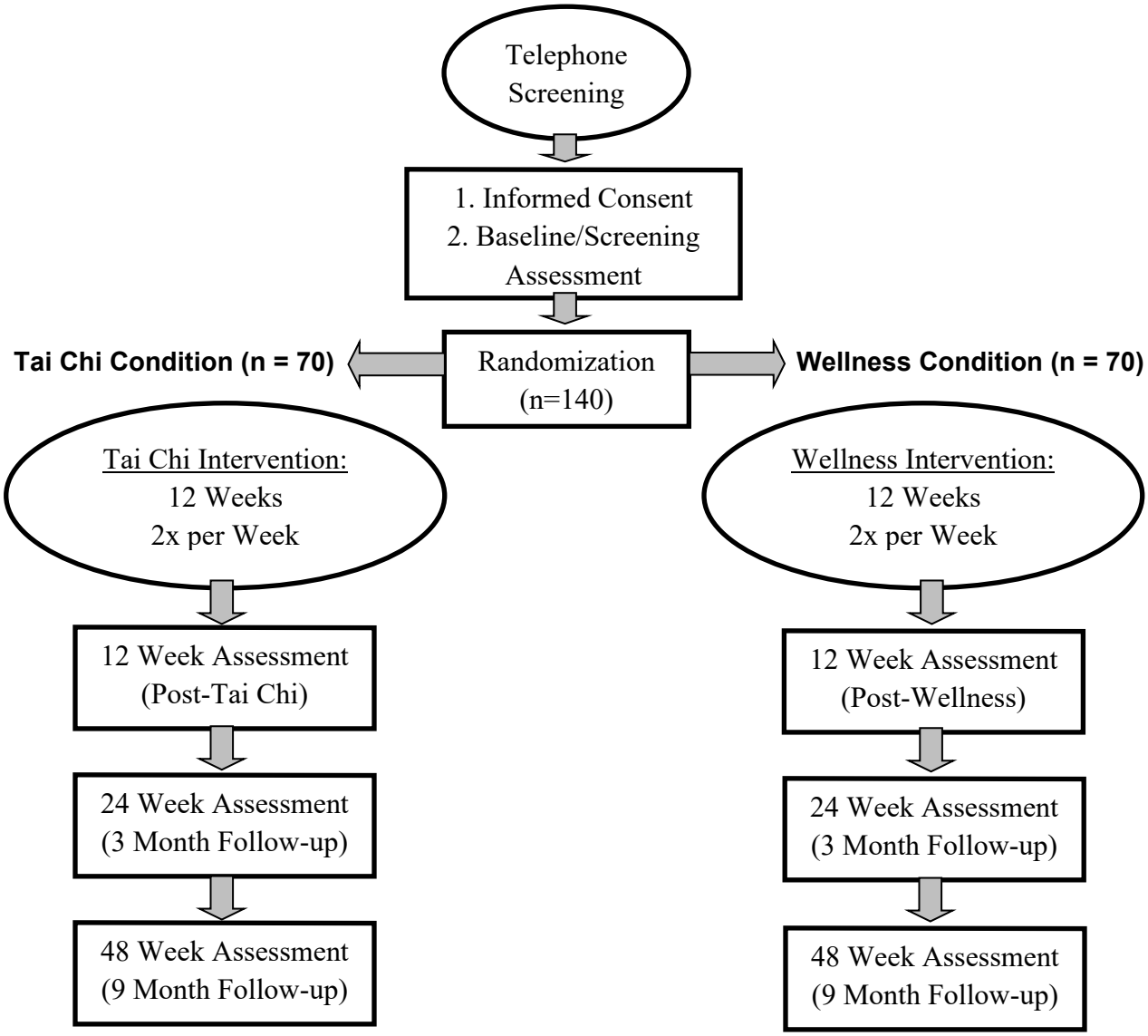
Taken together, findings from previous research by the assembled investigative team provide a strong rationale for a clinical trial to examine Tai Chi as a treatment for GWVI. In addition, these studies demonstrate our ability to accomplish the project as proposed. The proposed study will be pivotal to examine the beneficial effects of Tai Chi on GWVI in Veterans and to establish the efficacy of this mind-body approach to symptom reduction.

The ability to identify an effective, safe and non-pharmacological treatment for the pain and fatigue symptoms of GWVI could have a very high impact on the functional well-being and quality of life of many GW Veterans.

Research Design and Methods

Overview and Study Flow. Up to 140 GW Veterans meeting criteria for GWVI[32] will be randomly assigned to either the Tai Chi Condition (12 weeks of Tai Chi intervention twice each week) or the Wellness Condition (12 weeks of Wellness intervention twice each week), half to each condition. Participants in both conditions will receive assessments at baseline, 12 weeks (post-intervention), 24 weeks (approximately 3 months post-intervention) and 48 weeks (approximately 9 months post-intervention). (See Table 1 below.)

Figure 4: Study Flow



GWVI Case Definition. We will utilize the Centers for Disease Control (CDC) definition of GWVI and utilize the health symptom checklist based on the CMI case criteria of Fukuda et al.

(1998)[32]. As described above, CMI is characterized by one or more symptoms of at least 6 months duration from at least two of three symptom categories: 1) musculoskeletal pain (muscle pain, joint pain, or stiffness); 2) fatigue; and 3) mood-cognition. For this treatment trial, musculoskeletal or joint pain or stiffness symptoms of at least 6 months duration (in addition to fatigue or cognitive complaints of the CDC criteria) must be present for study inclusion. For comparison with other clinical trials, we will also determine which study participants meet the Kansas GWI criteria.[33]

Participants. Up to 140 male and female GW Veterans meeting the inclusion and exclusion criteria detailed below.

Table 1: Eligibility Criteria

Inclusion criteria	***Exclusion criteria***
• Served in the 1991 Gulf War. • Meets criteria for chronic multisymptom illness (CMI) based on CDC criteria[32] characterized by one or more symptoms of at least 6 months duration from at least two of three symptom categories: 1) musculoskeletal pain (muscle pain, joint pain, or stiffness); 2) fatigue; and 3) mood-cognition. • One symptom of CMI must be musculoskeletal or joint pain or stiffness of at least 6 months duration (in addition to fatigue or cognitive complaints of the CDC criteria[32]). • English-Speaking: English is the only language to be used during the exercise training program. Our self-reported outcome measures are obtained from validated English-version questionnaires. In addition, using other languages would likely require separate classes, recruitment and instructors which are beyond our current study scope. • Has access to a home computer or tablet device that will allow telehealth delivery of the intervention.	• Lacks the capacity to provide consent. • Major medical, psychiatric, or neurological disorder or has a moderate or severe traumatic brain injury, which could interfere with their ability to safely engage in Tai Chi exercises. • Major medical, psychiatric, or neurological concern that would preclude appropriate participation in the Wellness group • Change in psychotropic or pain medication during the past month. This will minimize amount of symptom change due to medication alterations. (Once enrolled, medication changes are nonetheless expected and will be monitored.) • *Regular* current Tai Chi, formal mindfulness meditation program, or yoga practice, defined as at least three hours per week for more than three months. (Veterans with prior experience who do not currently engage in regular practice at this level *will* be eligible.) • Reports difficulty standing on feet for the majority of a Tai Chi class (approximately 60 minutes). • Participants who are disruptive or disrespectful or engage in behavior that threatens staff and/or participant safety may be terminated from the study. • Participants who demonstrate evidence of falsifying data may be terminated from the study • Participants who are currently involved in another treatment study that might confound our findings (e.g., treatments for GWI, pain).

Participant Recruitment. Up to one hundred and twenty GWV participants will be recruited in the following ways:

1. IRB approved flyers will be posted throughout VABHS and local area Vet Centers.
2. Investigators will inform medical center staff about the study and encourage them to hand

out IRB-approved pamphlets to Gulf War veterans with symptoms of GWI. If veterans express interest in the study to their clinicians, clinicians may obtain verbal permission for study staff to contact veterans. In this case, clinicians will contact study staff via encrypted e-mail to provide contact information for the interested veterans who have provided verbal consent and to document that verbal permission has been obtained. Study staff will then contact participants.

3. IRB approved flyers and brochures and webpage developed on a VA ORD website will be distributed at public events for Veterans and/or at public research affiliated events (e.g., Museum of Science Annual Brain Health Fair) in the Greater Boston Area, or newsletters distributed by the VA. This webpage will be linked to a page currently being developed for Gulf War Veteran studies. (Note: We will seek IRB approval separately to distribute flyers/brochures at individual private events, such as events at Universities or Veteran Service Organizations, after gaining permission from appropriate personnel in those organizations.)
4. We will use IRB-approved "permission to contact" forms to obtain written permission to contact veterans who indicate interested in this study. VABHS clinical or research staff and study staff who attend public or private events described above may use these forms to gain permission from veterans to contact them. For veterans who provide written permission to contact, we will contact them to complete the telephone screening. If we are unable to reach these participants by telephone, we may send them an IRB-approved letter with information regarding the study.
5. IRB approved flyers, brochures and link to the study website may be posted on VA Facebook pages (e.g., Health Promotion Disease Prevention Facebook Page). Information contained in the approved brochure and posted on the approved website may be used by researchers, clinicians, or other interested parties outside VA Boston to inform populations of Gulf War Veterans about this study (e.g. researchers of studies taking place at other VA sites, researchers at non-VA institutions in the greater Boston area, personnel from local or national Veterans organizations).
6. We will utilize the National Center for PTSD's electronic referral database which consists of over 500 potential research participants. Participants are entered into the repository on a voluntary basis, and written permission for future contact has already been established. The IRB of the VABHS has approved this recruitment mechanism (IRB#1293: "Multiproject Subject Recruitment by the National Center For PTSD").
7. We will mail IRB-approved letters to veterans who have received care in the VA Boston Healthcare System, or have an appointment scheduled in relevant clinics (e.g. pain, behavioral medicine, primary care, orthopedics, physical therapy, general mental health, PTSD clinics) as indicated in electronic medical records system, and have been identified as 1) Persian Gulf Veterans and 2) having military service overlapping with 1990-91. A pre-addressed, postage paid postcard will be enclosed in letters to offer potential participants the option to opt out of being contacted to learn more about this study. Participants who do not call or mail back postcards within two weeks of letters being mailed out may be contacted by study staff to complete phone screening as staff time allows. We will obtain phone numbers from the medical record to contact them. We will keep password-protected lists of veterans who have been mailed a letter in order to avoid multiple letters being sent to the same veteran. The list will include: first and last name, last 4, date letter sent, whether they responded, and date of follow-up phone call. In addition, study staff may introduce themselves to veterans while waiting for relevant appointments in VA clinic waiting areas to share information about the study.
8. Following IRB approval of a HIPAA waiver to allow us to access the telephone screening forms for veterans who were previously screened who did not originally meet eligibility criteria, we may re-contact those individuals who may now be eligible to participate given

the change in inclusion criteria.

9. IRB approved flyers, brochures and link to the study website may be posted to Veteran social media platforms such as Gulf War Veterans Facebook groups and pages. Our research team will contact the administrator of each page we wish to post to and inquire if they are willing to post the study flyers, brochures, and link. If yes, the approved recruitment materials will be shared.

We plan to recruit participants in up to 14 cohorts with a goal of approximately 12 Veterans in each cohort. After up to16 Veterans have completed the informed consent process and are eligible for randomization, half will be randomly assigned to each of the two conditions (Tai Chi and Wellness). If we are unable to recruit 12 veterans over a one-month recruitment push, we may randomize a smaller cohort of veterans so that veterans who have agreed to participate will not be kept waiting too long to begin the interventions. If we are successful in recruiting more than 12 Veterans over the recruitment push, we may randomize up to 16 Veterans to help ensure that after attrition we will end up with approximately 12 Veterans who are able to participate in the groups. In the event that we have a small group (e.g., 4-7) of Veterans waiting for randomization for one month or more and we are unable to recruit sufficient numbers to randomize to two groups, we may randomly assign by group. In that case, all Veterans in that cohort would be randomly assigned to one of the two groups (i.e., Tai Chi or Wellness).

An initial screening will take place over the telephone (or in person if the potential participant stops by the research office) to determine if the veteran meets initial inclusion criteria. (Please see Telephone Screening Form.) Telephone screening forms for veterans, including those who do not meet all inclusion criteria, will be completed digitally and kept in a secure data folder on our shared drive (specified below). In the event that we seek and gain IRB approval to amend our inclusion criteria at a future date (e.g. loosen the criteria to include more veterans), we will submit a HIPAA waiver for IRB approval to allow us to access the forms for those who did not originally meet eligibility criteria and to re-contact those individuals who may now be eligible to participate. Additionally, participants who are deemed ineligible after screening will be asked if they would like to be added to the Subject Recruitment Database, in which case they will be mailed the relevant form at a later date.

Informed Consent Process

In the weeks prior to the start of study Wellness or Tai Chi classes, study staff will complete individual baseline assessments. One of the Investigators or a trained, research-credentialed member of the study staff will go through the informed consent process prior to the baseline evaluations for each patient who elects to participate. In order to ensure consistent and thorough administration of the ICF process for this study, study research staff will be trained by the study investigators on the ICF process and will conduct mock ICF sessions with investigators prior to performing the ICF process with participants. The ICF process will take place in a private clinic room or on a private remote video call (e.g. VVC, WebEx). When the ICF process takes place remotely, study staff will send two copies of the ICF and HIPAA forms along with a stamped envelope addressed to Dr. Niles at VA Boston to the veteran's home prior to the Informed Consent discussion.

A study staff member will verbally review each section of the ICF and HIPAA forms with the patient. She/he will explain alternatives to participating in the study, such as treatment available in VABHS clinics. The study staff member will answer any questions about the study the participant might have. Participants will be given as long as they like to consider participation. If they report that they understand the study procedures and are willing to participate in the study, staff will obtain their signature on the ICF and HIPAA forms. When the ICF process takes place remotely, study staff will ask the veteran to hold the signed signature pages of the ICF and

HIPAA forms up to the screen so study staff can capture screen shots of the signed forms to save in secure files. Given the variability in screen-shot quality, study staff will also instruct the veterans to send signed copies of the ICF and HIPAA back to Dr. Niles for VA Boston study records and to keep a signed copy of the forms for their own records. [Note: for participants whose study packets were sent prior to the protocol change to send two copies of the ICF, study staff will ask participants to send back their signed forms and will mail them a copy for their records following the informed consent process.] Following the informed consent process and the signing of the forms, a different study staff member will review all the forms to make sure they were completed accurately. When the ICF process takes place at VA Boston, we will make every effort to complete this second check of the forms while the participant is completing his/her initial evaluation, so that any errors detected can be corrected with the participant on the same day.

Remote Access Trouble Shooting
Study staff may provide some technical assistance via telephone, or via postal mailing or emailing (via encrypted email) instructions to veterans at different points during their involvement in the study. Veterans who meet all telephone screening criteria other than "Has access to a home computer or device that will allow telehealth delivery of the intervention utilize secure audio/video platforms (e.g. VVA, WebEx)" may receive assistance in connecting to secure platforms in order to determine if the home devices are sufficient to meet this criteria. Study staff may assist participants in connecting to complete the Informed Consent process. Study staff may also assist participants prior to and following randomization to ensure that they are able to access the remote systems and utilize devices to participate in the group interventions. This assistance may include provision of telephone numbers and websites for VA technical support, methods to request VA-provided tablets, and trial sessions to work through potential issues (such as where to place cameras, how to maximize audio clarity, how to ensure privacy for the session, etc.). Study staff may provide web-cameras to participants to facilitate their involvement in study groups. These cameras would be connected with participants' computers to generate a better picture so instructors could view them more easily, particularly for those participants assigned to the Tai Chi group. Participants in the Tai Chi group will also be sent a checklist before groups begin and as needed throughout the study to remind them of ways to set up their environment to improve their experience of Tai Chi (e.g., keep a chair nearby, place electronic device high enough for a full body view).

Use of Email. Study staff may use encrypted e-mail to send remote access instructions or previously approved group handouts or measures to participants as needed (e.g. if postal mail is delayed or participants ask for additional copies). Standard VA-approved language indicating that Veterans should not reply to these e-mails will be included in each e-mail.

Tai Chi Treatment. The Tai Chi intervention will be delivered via a secure video platform (e.g. VVC, WebEx) using a standardized Tai Chi protocol that was well tested in Dr. Wang's previous trials (e.g. Wang et al., 2010). Study staff will verify private location and emergency contact of all participants prior to beginning the class. All components of the program derive from the classical Yang Tai Chi 108 postures (China Sports, 1983), which has been shown to be a moderate intensity exercise (Lan et al., 2002). Each Tai Chi session will last 60 minutes, twice a week for 12 weeks. Experienced instructors will follow the Tai Chi protocol and treatment plan. We will also provide the patients with printed materials on the Tai Chi Mind-Body program, including Tai Chi principles, practicing techniques, and safety precautions (Wang et al., 2008). In the first session, the Tai Chi instructors will explain exercise theory and procedures of Tai Chi. In subsequent sessions, subjects will practice Tai Chi under the instruction of one of the Tai Chi instructors. Every session will include the following components: (1) warm up and a review of

Tai Chi principles; (2) meditation with Tai Chi movement; (3) breathing techniques; and (4) relaxation. We will instruct patients to practice at least 30 minutes a day at home throughout the intervention period and will provide them with training materials for home practice, which will be mailed to their home. Home practice exercises are described in the Participant Manual, as well as on a website that will be provided to participants (http://gwistudy.weebly.com/ Password: vaboston). The website includes the same home practice instructions described in the Participant Manual, along with video clips to demonstrate the exercise. Group handouts may be sent to participants via secure email as needed.

Tai Chi Instructor Qualifications. Tai Chi Instructor Brian Muccio has had extensive experience conducting Tai Chi mind-body programs and have successfully completed three trials of Tai Chi for chronic rheumatic conditions at Tufts Medical Center. As part of our joint Tufts-VABHS Tai Chi pilot study Mr. Muccio was credentialed through the VABHS Research Service to provide Tai Chi instruction to Veterans in research projects. He taught one 4-session Tai Chi introductory class as part of the pilot project and has been enthusiastic about continuing to work with Veterans. In addition, Ben Warner has over 15 years of experience as an instructor of Yang style Tai Chi and has worked closely with Mr. Muccio in the past. He will serve as a second Tai Chi instructor. Each instructor will plan to teach all 24 classes in a cohort (5 cohorts each), but they may substitute for each other in cases of illness, travel, or scheduling conflicts. Dr. Wang oversaw the development of the Tai Chi manual and will continue to provide guidance in how the Tai Chi classes will be carried out.

Wellness Comparison (Attention Control Condition). We will utilize a Wellness Education program as the comparison treatment. Participants in the Wellness condition will also attend two 60-minute sessions per week for 12 weeks via a secure video platform (e.g. VVA, WebEx). Study staff will verify private location and emergency contact of all participants prior to beginning the class. The Wellness condition will correspond to the VA Whole Health Program to emphasize wellness across various domains (e.g., physical, emotional, and spiritual lives.) Each session will include a video clip as well as a brief mindfulness exercise that corresponds with the material being presented. Approved session materials (i.e. manual) will be mailed to participants' home. The PIs, project coordinator for this study, other VA Boston Psychologists, and/or VA Boston Psychology Trainees will provide the didactic lessons. (Note: Group leaders that are not on the study staff will be research credentialed and added to this study prior to serving as group leaders.) Group handouts may be sent to participants via secure email as needed (e.g. if postal mail is delayed or participants ask for additional copies).

Following Randomization: After random assignment, participants will begin Tai Chi or Wellness treatment (12 weeks twice each week), half to each condition. Participants may be given a water bottle after attending Tai Chi or Wellness class. The water bottles have a logo that says "Whole Health Study" and display the Operation Desert Storm and Operation Desert Shield ribbon and the circular VA emblem. These water bottles may be mailed to participants with a thank you note from the study team. Participants engaged in the study at the 9-month follow-up assessment may also receive a 25th Anniversary Gulf War Challenge Coin. These coins may be mailed to participants with a thank you note from the study team. Participants in both conditions will receive assessments at baseline, 12 weeks (post-intervention), 24 weeks (approximately 3 months post-intervention) and 48 weeks (approximately 9 months post-intervention). (See Table 1 above.) Weekly measures will be collected by study staff via telephone and entered into a secure database remotely. Weekly measures may be mailed or e-mailed (via encrypted email messages) to participants so they can easily follow along with the weekly measure assessments. At the time of the collection of these weekly measures, feedback regarding preferences and areas for group improvement may be solicited from participants as

needed. This could include topics such as: best ways to maximize telehealth visibility and at-home Tai Chi setup; any feedback to relay to the instructor; preferences for the amount of sitting vs. standing for the class; preferences for the amount of group discussion vs. didactic instruction, etc. In addition, participants will be sent resources (e.g., VA Boston Whole Health handouts, IRB-approved virtual health resources) for continued engagement in health practices outside of group. This information will be recorded in an Excel spreadsheet that will use subject ID identifiers only and will be saved to a previously approved folder in the Drive: "\\r04bhsnas61\resgroups$\PTSD\DATA\RESEARCH\TeleHealth - Niles\Tai Chi Studies\Gulf War Study\Data" . Information will be discussed at weekly lab meetings to help the study team improve the TeleHealth experience for group participants.

Assessments. The primary outcome time point will be the 12-week assessment. (See Figure 1 above for study flow.) Assessments will consist of staff administered interviews and self-report assessment questionnaires. Participants will be remunerated for their time and inconvenience. Assessments are estimated to take 1 to 2 hours. Participants will be remunerated $50 for the baseline assessment, up to $50 for the post-treatment assessment, up to $75 for the 3-month follow-up assessment, and up to $100 for the 9-month (final) assessment. If participants are unable to come into VA Boston for any of the assessments, they will be given the opportunity to complete the assessment at home. Self-report measures will be mailed to participants and a self-addressed stamped envelope will be included with instructions for mailing the forms back to study staff. Assessment measures may also be emailed (via encrypted email messages) to participants as needed (e.g. if postal mailing delays are encountered, participants misplace forms, or if participants prefer email receipt). Participants will be reminded to not put their name on any forms or on the return address label to protect their confidentiality. Only participant ID numbers will be used on self-report measures. Study staff may call participants to check in on any questions participants may have about the assessments or clarify answers on paper and pencil assessment forms returned by participants if answers are ambiguous or have been skipped.

Post-treatment and follow-up assessments will also include a qualitative interview that may be audio-recorded (if the participant agrees to be audio-recorded) to gather information about participants' experiences in and following the group interventions. Given the nature of this instrument, the interviewer will not be blinded to the intervention. If participant interviews are conducted remotely and recorded by staff via telephone, the audio recorder will be stored in a locked box at the interviewer's home. Study staff will bring the recorder in the locked box to the VA at regular intervals to upload the content to a secure location and then delete the contents from the recorder. As an alternative to using an audio recorder, VA WebEx and Teams software may be used to record these sessions. The remuneration is increased for the latter assessments in order to provide incentive to complete these follow-up assessments and to compensate participants for ongoing commitment to the research project. Participants will be remunerated $10 for use of video devices and inconvenience for each intervention session they attend, for a total of up to $240. On occasion, in-person assessments may need to be cancelled with little warning due to staff illness or other unforeseen events. In these cases, participants who cannot be reached prior to the assessment time and who arrive at the study site for the assessments may be compensated $25 for their time and inconvenience.

Measures and Questionnaires.

Primary Outcome Measure

The Brief Pain Inventory – *Short Form* (BPI). The BPI is a self-report measure that examines how pain may interfere with functioning across different areas of life such as general activity, mood, work, walking activity, relationships, enjoyment of life, and sleep across 9 items

(Cleeland & Ryan 1994; Cleeland, 2009). Other questions pertain to pain relief, intensity, quality, and the patient's perception of the cause of the pain.

Secondary Outcome Measures. The following measures will be used to provide a comprehensive description of the sample of Veterans and scores on these measures may be used as covariates in planned analyses.

Demographics. Participants will be asked to report their age, years of education, gender, sex, race, ethnicity, relationship/marital status, employment status, current living situation, number and age of children (if any).

Medications. Study staff will record participants' medication use and assess for any changes in medication throughout the course of the study.

Multi-dimensional Fatigue Inventory (MFI-20) The MFI-20 is a self-report measure that examines symptoms of fatigue. The questions pertain to general, physical, and mental fatigue in addition to reduced motivation and activity (Smets, Garssen, Bonke, & De Haes,1995).

Health Symptom Checklist (HSC). The HSC is a 34-self-report measure that examines health and mental health symptoms over the past 30 days. The symptoms assessed fall under the following categories: cardiac, pulmonary, dermatological, gastrointestinal, genitourinary, musculoskeletal, neurological, and psychological (Proctor et al., 1998). Within this measure there are 5 embedded items that address malingering behaviors (Vanderploeg, & Curtiss, 2001)

The Kansas Gulf War Experiences and Exposures Questionnaire *(The Kansas, Part 1 and 2)* The Kansas Gulf War Experiences and Exposures Questionnaire queries about demographics such as military rank and current military status, GW duty service (active vs. reserve/National Guard), military and deployment history and chronic symptoms and diagnoses required to ascertain Kansas and Chronic Multisymptom Illness (CMI) case status (Steele, 2000). Part 1 contains the questions related to CMI and part 2 contains the questions about exposures and demographics.

The Pain Catastrophizing Scale (PCS) The PCS is a 13-item self-report measure that examines the extent to which participants catastrophize pain in the forms of rumination, magnification, and helplessness (Sullivan, Bishop, & Pivik, 1995).

The PTSD Checklist for DSM-5 (PCL-5) The PCL-5 is a 20-item self-report measure that examines symptoms of DSM-5 posttraumatic stress disorder criteria over the past month (Weathers et al., 2013; Blevins, Weathers, Davis, Witte, & Domino, 2015).

Group Cohesiveness Scale (GCS) The GCS is a 5-item self-report measure that that examines group cohesion within a therapeutic atmosphere (Wongpakaran, Wongpakaran, Intachote-Sakamoto & Boripuntakul, 2013).

Depression Anxiety Stress Scales (DASS-21) The DASS-21 is a 21-item self-report measure that examines emotional states of depression, anxiety and stress (Lovibond & Lovibond, 1995).

Insomnia Severity Index (ISI) The ISI is a 7-item self-report measure that examines components associated with insomnia that may occur during the daytime and nighttime (Bastien, Vallières, & Morin, 2001).

PROMIS Self Efficacy for Managing Symptoms Short Form 8a (PROMIS Self Efficacy) The PROMIS Self Efficacy for Managing Symptoms is an 8-item self-report measure that examines elements of self-care (Gruber-Baldini, Velozo, Romero& Shulman, 2017). The PROMIS measures are freely available at http://www.healthmeasures.net/explore-measurement-systems/promis.

PROMIS Global Health Scale Short Form 8a (PROMIS Global Health) The PROMIS Global Health Scale is an 8-item self-report measure that examines physical function, fatigue, pain, emotional distress, and social health (Cella et al., 2010).

Chronic Pain Severity Scale (CPSS) The CPSS is a 22-item self-report measure that examines perceived self-efficacy to cope with components chronic pain such as pain management, physical function, and coping with symptoms (Anderson, Dowds, Pelletz, Thomas Edwards, & Peeters-Asdourian, 1995).

West Haven-Yale Multidimensional Pain Inventory (WHYMPI) The WHYMPI is 52-item self-report measure that examines experiences with chronic pain and engagement in everyday activities (Kerns, Turk & Rudy, 1985).

Physical Activity Recall (PAR) The PAR is a measure that will be administered by the study staff in an interview format. The PAR examines participants' physical activity over the past week and time spent sleeping (Sallis et al., 1985).

Mindfulness Attention Awareness Scale (MAAS) The MAAS is a 15-item self-report measure that assesses participants' openness towards, awareness of, and attention to the present. This scale can reveal information about one's self-regulation and well-being (Brown & Ryan, 2003).

Personal Health Inventory (PHI) The PHI is a 12-item self-report measure that assesses participants' relationship with each of the 8 dimensions of the VA Whole Health Circle (model that is frequently referred to throughout the course of the Wellness Intervention) including relationships, sleep, exercise, food and drink, personal development, spirituality, surroundings, and power of the mind. This scale will be administered to participants in the Wellness Intervention to measure potential growth across these 8 domains over the course of the study.

Measures of Satisfaction.

Post-Treatment Intervention Satisfaction Interview This semi-structured interview will be administered after the intervention and will gather qualitative information about the participants' experience in the group. For participants enrolled prior to the move to telehealth, the previous approved interview feedback form will be administered.

Client satisfaction questionnaire (CSQ-8) The CSQ is an 8-item self-report measure that examine participants' satisfaction with services provided (Larsen, Attkisson, Hargreaves & Nguyen, 1979).

Measure of Distress Related to COVID-19 and Social Distancing.

The Epidemic – Pandemic Impacts Inventory (EPII) is a 92-item questionnaire. This recently-developed measure was designed to learn about and describe the impact of the coronavirus disease pandemic on various domains of personal and family life, including employment, education, home life, social life, economic, physical health, infection experiences, and positive changes (Grasso, Briggs-Gowan, Ford, Carter (2020).

Measure/Questionnaire	Pre	Post	3-Month	9-Month	During Tx (specify)	Study Staff	Self-Report
BPI	X	X	X	X	X Weekly		X
MFI-20	X	X	X	X			X
Demographics	X						
Medications	X	X	X	X		X	
HSC	X	X	X	X			X
Kansas Part 1	X	X	X	X			X
Kansas Part 2	X						
PCS	X	X	X	X			X
PCL-5	X	X	X	X			X
GCS					X Weeks 1, 4, 8, 12		X
DASS-21	X	X	X	X			X
ISI	X	X	X	X			X
PROMIS Self-Efficacy	X	X	X	X			X
PROMIS Global Health	X	X	X	X			X
CPSS	X	X	X	X			X
WHYMPI	X	X	X	X			X
PAR	X	X	X	X		X	
MAAS	X	X	X	X			X
Post-Treatment Intervention Satisfaction Interview		X	X	X		X	
CSQ-8		X					X
EPII	X	X	X	X			X
PHI (Wellness only)		X	X	X	X towards beginning & end of intervention		X

Procedures for Randomization and Ensuring Blind Assessment. The Project Coordinator will use a random number generator from Random.org to create 10 tables of up to 16 integers limited to 1 (to denote Tai Chi) and 2 (to denote Wellness). After up to 16 participants are recruited and given consecutive participant numbers, study staff will release a randomization table to un-blinded staff and will assign condition in consecutive order. Un-blinded staff will record participant condition in a tracking excel file, and study staff will call participants to inform them of their condition assignment and schedule the group intervention sessions. Thus, all study staff will be blind to condition throughout the baseline assessment. When assessments are conducted remotely, the study will not maintain a blinded assessor. Blinding of staff is not necessary for remote assessments as participants will complete assessments on their own in their homes.

Statistical Plan and Data Analysis

SPSS, SAS, R, and RedCap will be used for data entry and/or analysis in this study.

Splitting the Study into Two Sub-Studies

The administrative halt on in-person research in 2020 required us to make several important changes to our research protocol. To adapt the Tai Chi intervention for telehealth, components that included sequential stepping and movement across the floor were removed and components done standing in one place were added. To adapt the Wellness intervention for telehealth, the method for reviewing SMART goals each week was altered; participants could not hand in their goal sheets for written feedback and instead group discussion time is devoted to goal setting. For the remote assessments, the physical function and neuropsychological measures could not be administered remotely in a valid and reliable manner and were removed from the assessment battery and a measure that addresses distress and functioning related to the pandemic was added. The protocols for the in-person and telehealth versions of the interventions differ enough that it would not be prudent to combine data from them. Thus, we propose to break up our clinical trial into two sub-studies: Sub-Study I (in-person) and Sub-Study II (telehealth).

Splitting the study into two parts has important implications for data analysis and the interpretation of our results. In March 2020, we had randomized 53 participants (27 to Tai Chi and 26 to Wellness) in Sub-Study I and 43 (81%) completed post-treatment assessments. This number falls substantially short of the original target of enrolling 120 Gulf War veterans and the administrative halt on research precluded us from continuing to enroll to approach the enrollment target. As a result, the power to detect differences between the two intervention groups is low, an unfortunate consequence of low enrollment due to a restricted sample of Boston-area GW Veterans and the premature termination of the study. Analysis of data from Sub-Study I would include examination of the rich qualitative interview and satisfaction data we have collected as well as within-group changes on outcome measures. We expect that this will yield important results that will guide future studies. Dr. Karen Block, the Scientific Program Officer for Gulf War studies, has approved this change to the analytic plan for our study.

Participant Attrition and Missing Data

Based on results from previous studies conducted by the PI with medical populations and with Tai Chi and physical activity interventions, it is anticipated that a high rate of participants will complete all assessments. A high rate of completion is also anticipated since participants will be compensated for their assessments and will have established rapport with study personnel. Participants who drop out of treatment will be encouraged to remain in the study and to

complete all assessments. In order to provide incentive to complete the follow-up assessments and to compensate participants for ongoing commitment to the research project, participants will receive additional compensation for the later assessments. Although rigorous attempts will be made to keep participants in the study and to gather complete data at each of the scheduled assessments, we conservatively anticipate up to 20% attrition and other incomplete data at the 12-week assessment due to factors outside our control (e.g. participant unwillingness, time constraints). In addition to planning for dropouts a priori by recruiting a larger sample, we plan to conduct intent-to-treat analyses (see below) to protect against potential bias that may occur when individuals drop out of the study due to their level of disability and their response to treatment and by using imputation methods for missing data as described below.

Data and Power Analysis for Sub-Study II

With 80 participants in the telehealth study (40 in each condition), assuming that 15% would not complete the post-treatment assessment, we would have sufficient (.80) power to show a medium-large between group effect (0.69). Importantly, we would also have .80 power to detect a medium (0.5) within-group effect.

Data Analyses for Specific Aims

The goal of the primary analysis is to determine whether participants in the Tai Chi Condition show more advantageous change in Brief Pain Inventory scores from baseline to 12-week assessment than those in the Wellness Condition. The analysis will follow an intent-to-treat approach (all randomized patients will be included in the analysis). The primary analysis will compare groups on the change from baseline Brief Pain Inventory to 12-week using generalized estimating equation (GEE) analysis of covariance adjusting for baseline score. The GEE analysis model will incorporate change from baseline to all patient visits through 12-week into the analysis, and will include main effects of treatment, visit, and the baseline score, and a treatment-by-time interaction effect. From this model, an assessment of the treatment difference on mean change from baseline to 12 weeks will be carried out on the robust estimates using a two-sided 0.05 level of significance. An unstructured correlation structure will be assumed as the within-patient correlation between time points.

The primary analysis will be based on all available data. However, as supportive analyses, missing Brief Pain Inventory scores will be imputed at each visit in a monotone manner via multiple imputation linear regression approach and the above analysis will be repeated on the imputed data. Specifically, the imputation model will include important covariates such as age, gender, and baseline Brief Pain Inventory score. A total of 10 imputed datasets will be generated, and the above GEE analysis will be carried out on each imputed dataset; the Week 12 score results will be combined across the 10 datasets using the standard techniques for multiply imputed data sets in order to yield on overall Week 12 on the imputed data.

Similar analyses will be used for secondary endpoints. We anticipate that the distribution of the pain scale and scores on secondary outcome measures will be skewed, and that log transformed scores will be used in the analysis.

Human Subjects Research

a. Human Subjects Involvement and Characteristics

The participant population is to be comprised of up to 140 male and female Gulf War Veterans. These individuals will be recruited on a volunteer basis. Only individuals who provide written informed consent may participate. A participant may withdraw his/her consent at any time and without prejudice. A clear and detailed explanation will precede all procedures.

Informed consent will be obtained by the study PI or by another IRB-approved study staff member prior to the initiation of any study procedures. Informed consent will be reviewed with the participant at the beginning of this scheduled appointment, prior to initiating the assessment.

Participants will be interviewed in a private research or clinical office at the VABHS or on a private remote video call (e.g. VVC, WebEx). As the initial step in the consent process, the informed consent document will be provided to the participant. The participant will be given time to read over the informed consent, then the PI or another IRB-approved study staff member will summarize each section and ask if the has any questions. All study staff members will be credentialed at VABHS to conduct research and will have certification of Human Subject Education. Delegate study staff will practice the informed consent process with investigators and one of the investigators will sit in and observe the study staff member for the first few times he or she conducts the process with participants to ensure that the process is conducted appropriately. In addition, we will conduct periodic internal audits of the Informed Consent Forms to ensure that they are completed appropriately. These audits will take place weekly at the outset of the study (i.e. first month), then reduce in frequency as the study continues, but will be at least 2 times per year.

The participant will be fully informed about all aspects of the study and will be given ample time for clarification and to have his or her questions answered. The participant will be able to bring the consent form home and can discuss the study with his or her physician, family members, or others prior to making a decision. At that time, or after further consideration of the study by the patient and his physician and family, the patient will be asked to sign the informed consent document and HIPAA authorization in the presence of authorized study staff either in person or on a private remote video call (e.g. VVC, WebEx)., copies of which will be given to the participant. After the signed informed consent document is obtained, additional screening procedures covered in the informed consent document will be conducted prior to randomization. The investigators consider this consent process to be an ongoing process maintained throughout the study to provide patients with a continued understanding of the protocol, their participation, and their rights as human research subjects.

All discussions concerning consent will emphasize that participation is voluntary and that the Participant's medical care/benefits will be unaffected by his or her decision regarding participation. Participants will be informed that they will be compensated for time and travel at a rate of $50 for the baseline and 12-week assessments, $75 for the 24-week (approximately 3 month post Tai Chi) assessment and $100 for the 48-week (approximately 9 month post Tai Chi) assessment for a total of up to $275 for 4 assessment visits. Participants will also receive $10 for use of video devices and inconvenience for each Tai Chi or Wellness session they attend, for a total of up to $240. This remuneration for time, inconvenience, ongoing commitment, and travel is not so high as to coerce an individual to participate who would otherwise not participate.

b. Potential Risks

While the risks of the Tai Chi and Wellness protocols are minimal, there is some potential for injury from the exercises, including muscle tears, strain, sprains, and joint pain. In addition, participants may feel some stress, frustration, or boredom while completing the questionnaires. There will be a mental health professional available throughout the study for participants to talk with if needed.

The social risks of participating in this protocol are minimal. There may be some embarrassment as participants learn to do Tai Chi in a group with other participants, but the instructors will be trained to be very sensitive to the individual needs of each participant and create an environment that feels safe and nonjudgmental. There is no economic risk associated with participating in this study.

In order to protect participant privacy, all personnel proposed for this project will have the required human subjects and confidentiality training, which includes information about maintaining data integrity and security. Once study team members are no longer a part of the research team, their access to data and research materials will be terminated. Confidentiality will be guarded using established procedures such as storing electronic data in password-protected database files on a password-protected network system, and hard copy data will be stored in locked cabinets within locked offices or locked data rooms. Data will be coded by study identification numbers rather than any personally identifying information to avoid revealing the identity of subjects, and data will be aggregated across participants. As noted above, the codes that link names and their ID numbers will be kept confidential by the PI in a password protected file on a password-protected network system. Only study personnel will have access to the data, and the datasets will be kept on protected servers. Oversight of all aspects of data management will occur with the PI and Co-Is.

Research records and the information within them will not be used for any purpose other than that which is described in the study as approved by the IRB.
In order to ensure that participants are adequately informed about the protocol and any anticipated risks, research staff will carefully review the IRB approved Informed Consent with the participants. A summary of the potential risks to participants will be provided, and study staff will provide participants with an opportunity to ask questions to insure an adequate understanding.

c. Sources of Research Materials

All research material will be obtained specifically for research purposes. The sources of research material obtained from individually identifiable living human subjects in the form of records or data will be obtained specifically for this research project. All information pertaining to this project (e.g., screening forms, questionnaire data, interviews, audio recordings) will be held in the strictest confidence, will be kept in locked files or in password protected digital files on encrypted PCs with secure server and will be available only to individuals directly involved with the project. Under no circumstances will individually identifiable data be released to anyone without written consent of the participant. Results will be published as group findings only. Assessment and treatment results will be discussed with the participant only.

Data will be stored at this secure location:
\\r04bhsnas61\resgroups$\PTSD\DATA\RESEARCH\TeleHealth - Niles\Tai Chi Studies\Gulf War Study\Data

d. Protection Against Risk

The following steps will be taken to minimize risk to participants who participate in the Tai Chi activity:

- Exclusion of individuals with comorbidities and any serious medical conditions that carry a potential risk.
- Warm-up and stretching exercises at the beginning of each Tai Chi session will be an integral part of the training program, because these maneuvers are known to prevent injury.

- The research team and Tai Chi instructors will provide participants with opportunities to report any potential negative effects they may be experiencing during the 12 weeks of Tai Chi. The research team and Tai Chi instructors will specifically ask patients if they have experienced any adverse events that may be associated with exercise (i.e. falling down, joint swelling, muscle aches) as part of this study.
- A research staff member (PI, Study Coordinator, or Research Assistant) will be present at all Tai Chi intervention classes. Research staff will be CPR certified before the initiation of the interventions. Research staff will be instructed to obtain immediate emergency care for any participants in case of an emergency.

Participants will be informed that if suicidal or homicidal intentions are disclosed, confidentiality may be broken in order for protective measures to be taken. Although there will be no questions asked in the assessments regarding care of children or geriatric persons, if a participant were to disclose child or elder abuse, appropriate agencies would be contacted, and participants will be so informed in the consent form.

All personnel involved in this proposed project will have the required ethics, human subjects, and confidentiality training, which include information about maintaining data integrity and security. Careful monitoring of participants during all phases of study participation will be conducted by the project staff. Each participant will see the same clinicians for each of their treatment visits. Participants will be instructed to contact study personnel at any time (including during the follow-up interval) in the event of worsening of symptoms. Participants who begin treatment and experience adverse outcomes sufficient to require removal from the study will receive appropriate clinical care.

As in any type of treatment or clinical research program, participants' confidentiality must be carefully guarded and respected. All data with identifying information will be stored in locked files or password-protected computer files. Data being analyzed will be identified by subject codes, and identifying information will be removed. The identity of participants will not be revealed in the presentation or publication of any results from the project. All project staff working on the project will be educated about the importance of strictly respecting participants' rights to confidentiality and will have completed several training courses including proper practice in accordance with HIPAA regulations, protection of human subjects, and computer security.

The VABHS will provide care to participants during their enrollment in this study for any study related adverse events or injuries. In the event that emergency care is needed during the Tai Chi classes, participants will either be escorted to the Urgent Care Clinic located within VABHS, or a code will be initiated for the VABHS emergency response team to come to the patient. Participants will not be required to pay for any services they receive as a subject in an approved VA research study. However, some Veterans are required to pay co-payments for medical care and services provided by the VA. These co-payment requirements will continue to apply to medical care and services (including, but not limited to, dental services, supplies, medicines, orthopedic and prosthetic appliances, and domiciliary or nursing home care) provided by the VA that are not part of this research study.

e. Potential Benefits of the Proposed Research to the Subjects and to Others.
The current research shows that Wellness and Tai Chi programs appear to have both physical and mental benefits and appears to be safe and effective. Tai Chi has been shown to promote balance control, muscle strength, flexibility, and cardiovascular fitness. For Veterans with Gulf

War Illness who have limited therapeutic options, our project will provide a complementary and alternative approaches to the management of the symptoms of Gulf War Illness.

Of note, it is the policy of the VABHS IRB to state on all Informed Consent Forms (ICF) that there are no known benefits to participating in any study. Therefore, although we have provided above what we believe are the potential benefits to this study, we will not delineate these benefits in the ICF.

f. Importance of the Knowledge to be Gained

The current research demonstrates the apparent physical and mental health benefits of Tai Chi and indicates that Tai Chi appears to be safe and effective in improving balance control, muscle strength, flexibility, and cardiovascular fitness. This study will fill important knowledge gaps and generate critical insights into the clinical effectiveness of using Tai Chi to treat Veterans with Gulf War Illness. The successful completion of the proposed study will demonstrate that Tai Chi is a simple, effective, durable treatment for a major disabling disorder.

g. Data Safety Monitoring Plan

Monitoring of safety and data quality in the proposed study will be the responsibility of all personnel on the project, with primary responsibility and supervision by the investigators. The VA Boston Institutional Review Board will approve the Statement of Informed Consent for the study and provide institutional oversight of data and safety issues. The study protocol will be approved prior to recruiting or consenting any participants. Moreover, the study will be reviewed on an annual basis by the IRB committee. Each participant will sign the Informed Consent Form prior to participating in the study. To ensure participant safety, once participants are enrolled in the study, study staff will immediately report all adverse and serious adverse events to one of the PIs. The PI will, per standardized procedures, report them to the IRB for their review. With regard to monitoring of data quality and protected health information, all required personnel proposed for this project will have the required human subjects and confidentiality training, which includes information about maintaining data integrity and security. Confidentiality will be guarded using established procedures such as storing data in locked cabinets within locked offices or locked data rooms, coding by study identification numbers rather than any personally identifying information to avoid revealing the identity of subjects, and aggregating data across participants. The key linking names and study identification numbers will be kept separately from the data sets with limited access by study personnel. Only study personnel will have access to the data sets on protected servers. Data will not be removed from the VA protected environment at any time, except by methods approved through a Data Use Agreement. Data will be securely transmitted using VA approved methods. We will use FIPS 140-2 validated encryption. In order to maintain the highest standard of data entry quality, all data will be double-entered, with discrepancies highlighted so that they can be reviewed by the project coordinator. Oversight of all aspects of data management will occur with the PIs.

Data will be collected using standardized forms and will only be identified using the participant's ID number (no names or identifying information will be on the forms). The codes that link the names of participants and their ID numbers will be kept confidential by the PI in a secure, password protected file in the research drive. Data will be entered in the computer independently by trained data entry staff, and data entry discrepancies will be corrected by the project coordinator, based on source documents. The quality of the data will be monitored on an ongoing basis. Data quality will be monitored by inspection of the completed forms by a research assistant and any problems detected will be discussed with the PIs. Electronic data will be stored in password-protected database files on a password-protected network system. Only the study staff will have access to the data. Suspected information security and privacy

incidents will be reported within one hour to the Information Security and Privacy Officers and Research Administration.

Records will be destroyed in accordance with the VA Record retention schedule (www1.va.gov/VHAPUBLICATIONS/RCS10/rcs10-1.pdf). Records will be destroyed, when applicable, in the following manner: All research data for this study that is maintained on electronic storage and memory devices (e.g., computers, laptops, CDs, audio recordings, etc.) will be destroyed in a manner in which it cannot be retrieved. All paper records will be destroyed by shredding. Research records and the information within them will not be used for any purpose other than that which is described in the study as approved by the IRB.

In the proposed study we will use the FDA definition of adverse events (AE) and serious adverse events (SAE). Any SAE, whether or not related to study intervention, will be reported within the required 10 day reporting period to the IRB and will be followed by an additional letter detailing the nature of the SAE. In the event that a participant either withdraws from the study or the PIs decide to discontinue a participant due to a SAE, the participant will be monitored by the investigators until (a) a resolution is reached (e.g., the problem has resolved or stabilized with no further change expected), (b) the SAE is determined to be clearly unrelated to the study intervention, or (c) the SAE results in death. Outcomes of SAEs will be regularly reported to the IRB. A summary of all AEs and SAEs that occurred during the previous year will be included in the annual IRB renewal. The study will be conducted at VA Boston Healthcare System. Under the arrangement to conduct the study on site at the VA facilities, the VA agrees to provide emergency services to anyone who participates in this project. We will specifically outline in the Informed Consent Forms the availability of emergency services to participants who may seek them during and after normal working hours. In the Informed Consent Form, we will provide specific information about emergency contacts. Participants are instructed to contact Dr. Niles or Mori during working hours. We will also provide a list of crisis hotline numbers and community resources that participants may access as well as making sure the Veterans have access to the Crisis Hotline for Veterans (1-800-273-TALK).

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