The Impact of Modifiable Psychosocial Factors on Veterans' Long-term Trajectories of Functioning and Quality of Life: Promoting Recovery by Targeting Mindfulness and Psychological Flexibility (Study Evaluating Returning Veterans Experienced: Post-Deployment Functioning (Project SERVE))

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RESEARCH PROTOCOL FOR
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SPECIFIC AIMS

Understanding the process of functional recovery among returning Operation Enduring (OEF) and Iraqi (OIF) Freedom and New Dawn (OND) Veterans is of the utmost importance, both to VA and to the national economy. Although most returning OEF/OIF/OND soldiers are resilient, concerning rates of PTSD (12-20%) and depression (14-15%) have been found, and as many as 24-35% report drinking more alcohol than they intended (Hoge et al., 2004). Notably, these figures are likely underestimates due to stigma associated with mental health services in military culture (Wright et al., 2009). Certainly, the course and impact of mental health conditions among returning OEF/OIF/OND Veterans are not well established, with most studies being cross-sectional and retrospective in nature. It is critical to understand the long-term trajectories and functional impact of exposure to war zone stressors and associated mental health disorders, particularly in the context of the current economic environment, which differs considerably from past eras of war zone service.

The purpose of the proposed longitudinal project is to better understand the functional impairment and recovery of returning OEF/OIF/OND Veterans and to identify potentially-malleable risk and resilience factors that predict level of functioning over time. Up to 600 OEF/OIF/OND Veterans will be evaluated over a two-year period in Phase III of this project, including as many participants from Phase I and Phase II as possible. Veterans will complete a detailed baseline assessment, as well as follow-up assessments. The most recently funded continuation Phase (Phase III) will continue and extend the longitudinal assessment study examining predictors of post-deployment functioning, referred to as Project SERVE. The specific aims of Phase III are to 1) identify treatment targets that may predict functional disability and self-directed violence 2) identify gender differences in the sample.

STUDY METHODS

Overview of Study Methods. This study will investigate the course of functioning over time among returning OEF/OIF/OND Veterans enrolled at CTVHCS. The primary outcome measures will assess multiple domains of functioning, including: 1) occupational functioning; 2) social relationships; 3) family functioning; 4) physical functioning; and 5) quality of life. Hypothesized predictors of functioning include: 1) level of exposure to deployment-related stressors, including potentially traumatic events (PTEs) and head injuries/traumatic brain injury (TBI); 2) level of pre-deployment stress and trauma exposure; 3) level of exposure to post-deployment stress and trauma, including "everyday" stressors; 4) modifiable psychological factors including coping, emotion regulation, self-compassion, attributional style, psychological flexibility, and mindfulness; 5) perceived social support; 6) psychopathology including PTSD and depression; 7) substance misuse; 8) physical health symptoms including chronic pain; and 9) exposure to morally injurious events. Saliva/blood samples will also be collected (on an optional basis) to examine genetic contributions.

The proposed longitudinal design will include a baseline assessment and follow-up assessments in order to examine predictors of functioning during post-warzone readjustment. This design enables us to examine mechanisms of action in the development of functional impairment over time.

Participants. In Phase III, we propose to continue following as many of the Phase I and Phase II participants as volunteer and to recruit additional participants until we reach the target sample size of 500 eligible OEF/OIF/OND Veterans. This will increase the total sample size across study phases to approximately 1,000 depending on how many existing participants transfer into the next Phase versus enrolling more new participants. Every effort will be made to represent women and men of all racial and ethnic backgrounds. Several of our main hypotheses focus on the influence of psychopathology and other predictors on functioning over time as well as gender differences. In addition Veterans experiencing mental health problems require higher levels of healthcare service utilization and are at increased risk for maladaptive functional outcomes. Therefore, our recruitment strategy will involve over-sampling for participants experiencing mental health difficulties and women veterans.

Inclusion Criteria. In keeping with the nature of a longitudinal assessment study, this project has relatively few exclusionary criteria. Potential participants include male and female, English-speaking OEF/OIF/OND Veterans, 18 years of age or older, enrolled at CTVHCS or willing to be enrolled for the purpose of participation in this study. To be eligible, participants must be: 1) able to comprehend and sign the informed consent form; 2) able to complete the structured interviews and self-report assessments; 3) willing to be contacted for follow-up assessments; 4) (for newly enrolled participants), given that we have already recruited a large sample of veterans who are reporting relatively little functional impairment, we will require newly enrolled participants to self-report global functional impairment on the WHODAS 2.0 12-item self-report version equivalent to a mean item score of 0.89, reflecting current research findings. Although we anticipate being able to meet our recruitment goals, should recruitment prove more challenging than expected, we will remove this inclusion criterion; 5) deemed stable on psychotropic medications (defined as ≥3 months on a selective serotonin reuptake inhibitor or monoamine oxidase inhibitor; >1 month on an anxiolytic or beta-blocker; >1 month medication discontinuation or "wash out" for all medications) at the time of the BL assessment; and 6) deemed stable in psychotherapy (≥3 months stabilization for psychotherapy and 1-month psychotherapy wash-out) at the time of the BL assessment. These latter two criteria are instated to ensure that symptoms assessed during the baseline assessment are due to any underlying psychiatric condition and not due to the effects of starting or stopping medications and/or psychotherapy. Changes in treatment will be permissible during the current study, as this reflects real-world practice. All changes in medications will be monitored over time, and appropriately covaried, as treatment can have important effects on functioning over time. Individuals with current and lifetime psychiatric diagnoses, with the exception of schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, unspecified schizophrenia spectrum/other psychotic disorder, and bipolar disorder, will be eligible to participate.

Exclusion Criteria. Veterans will be excluded if they: 1) plan to relocate out of the CTVHCS system within four months of protocol initiation; 2) meet criteria for a diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, or a manic/hypomanic episode; 3) report current suicidal or homicidal risk warranting crisis intervention; 4) report symptoms consistent with severe traumatic brain injury (TBI) that interfere with their ability to complete the consent process or assessment (i.e., due to ethical concerns about obtaining informed consent and difficulties with completing the structured assessment); or 5) report current non-military related hallucinations or delusions that cause significant distress and/or impairment.

Procedures. In Phase III, assessments occur at 0, 8-, 16-, and 24-month time points. Veterans will complete a baseline assessment, lasting approximately 2-3 hours, and a two-year follow-up assessment lasting approximately 1-2 hours. Please note that these times are approximated, and could be shorter or longer depending on the nature of the interview (e.g., diagnostic complexity, taking breaks, talkative Veteran). The baseline and annual assessments include clinical assessments and self-report questionnaires. In addition, follow-up questionnaire assessments (~45 minutes) are administered to track functional impairment and recovery over time. For those who opt to participate in the genetic component of the study, saliva/blood samples will be collected at the baseline and two-year follow-up assessments. Participation in the genetic/biomarker component of the study is completely optional and does not affect participation in the study as a whole. Self-report data at in-person assessments will be collected either using pencil and paper surveys or on VA-issued iPads. These iPads are FIPS-140-2 compliant and will only be used on the VA network behind the VA firewall. Interviews will be conducted by trained masters or doctoral-level assessors and research assistants, and supervised by licensed clinical psychologists. Participants in the Project SERVE pilot, FX Phase I, and FX Phase II studies have tolerated the assessment length well. Those for whom the assessment length poses a problem (e.g. due to work, childcare, etc.) will be offered to split the assessment into two days (preferably consecutive). We will also make efforts to conveniently schedule the assessment around other medical appointments at CTVHCS, which could result in needing to complete two appointments. As needed and appropriate, Veterans may also be given the option to complete assessments by VA approved video communication technology, telephone or online. Veterans who are scheduled for a video appointment, may be sent an encrypted email from study staff with the details of their appointment (i.e., date, time, associated links). We will examine outpatient medical records for the SERVE participants to investigate the association between

PTSD and other mental health symptoms a range of health-related outcomes, including incident heart failure.

Recruitment. Multiple strategies will be used to recruit new participants for Phase III, which are in keeping with previous procedures. Participants in Phase I and Phase II will be invited to participate in Phase III (i.e., "transfers"). Newly enrolled participants will participate in Phase III only. Participants will be recruited through advertisement at enrollment sites, vet centers, Veteran's networks and service organizations, through in-service presentations to primary care staff, mental health staff, and other relevant VA staff (e.g., OEF/OIF/OND coordinators, etc.), and through the community (e.g. grocery stores, churches, shopping centers, and so forth). In-person recruiting will also be conducted at enrollment and community sites. In these cases, one or more research team members will sit at a table/booth in a high visibility area (e.g., a main VA lobby or outside of a grocery store) with a sign indicating that OEF/OIF/OND Veterans are being recruited to participate in a research study. Staff members will provide interested Veterans with a flyer (see attached flyer and brochure) about the study. In addition, Veterans interested in participating in the study will be given the option of providing staff members with their contact information so that they can be contacted by phone at a later point in time to complete a telephone screen interview. If a private office is available, as a convenience, participants may be given the option to complete the screening interview in person. We will also place advertisements in local newspapers, local community-based advertisement sources, on local Craigslist pages, and in other locally-based media platforms, on relevant VA and other Veteran-oriented websites, and social media outlets, pending required approvals from VA public relations office (see attached ad).

We also request permission to conduct periodic queries to recruit new participants using VISTA, VINCI, the corporate data warehouse, or other approved VA methods for accessing Veteran mailing list information (frequency approximately 1x/year, to be determined based on the number of names generated; i.e. if there are too few or too many names we will adjust the frequency correspondent with staffing so potential participants would not need to wait too long for a research assessment appointment; as the list is exhausted, we will update the list more frequently; maximum number of names generated = 100,000). We will use these VA approved methods to identify OEF/OIF/OND Veterans who meet some of our inclusion criteria (e.g. OEF/OIF/OND Veteran status) so that we can reach out to returning Veterans to let them know that the study is being conducted. Up to two letters per study phase will be sent to participants (see attached). The second letter will be mailed approximately 2 weeks after the first letter, depending on response to the first letter. Depending on recruitment flow from these letters, we retain the option to attempt to contact potential participants by telephone after the second letter (allowing at least 4 days for them to receive the second letter). In the first letter, unique veteran (i.e., those who have not participated in a prior phase) will receive a post-card or form with a potage paid envelope to opt-out. If a Veteran returns this opt-out card or says he/she is not interested at any point in this process (e.g., after the first letter, second letter, or during the follow-up call), their name will be marked on the list and they will not be contacted again during this study phase. We will also send a text message to Veterans to let them know that they are invited to participate (see attached for wording of text messages). Interested Veterans will complete a telephone screen to determine their eligibility (see below). This recruitment procedure requires a waiver of consent and waiver of HIPAA authorization (attached). The retrieval of names and addresses to recruit study participants involves no more than minimal risk to subjects, and will not adversely affect the rights and welfare of subjects. This research could not practically be carried out without the waiver, which enables us to reach out to as many Veterans as possible to make participation in the study available to them. The mailing list of contact information generated by the methods detailed above will be stored electronically on the secure VA Research drive and/or VINCI project folder for this study, depending on the required data storage location associated with the approved method of requesting and storing this information. After a Veteran contacts the CoE (or we contact the Veteran per above), a brief screening will be conducted by telephone (see below). Every effort will be made to schedule eligible participants for the baseline assessment appointment at the enrollment site (CTVHCS campuses and CBOCs) of their choice, pending availability of staffing resources and research space at that time.

Eligible Veterans who participated in Phase I or Phase II will be contacted to determine their interest in being a part of Phase III (as indicated in original ICF; see attached recruitment letters). As enrollment for Phase I began in 2010 and enrollment for Phase II began in 2014, current SERVE participants will be

contacted to invite them to participate for what would approximately mark their 4-year follow-up if they entered the study in Phase II and their 8-year follow-up if they entered the study in Phase I. They would then be followed for another two-year time-frame, which would culminate with either their 6-year or 10-year follow-up, depending on when they entered the research program. A series of two form letters will be sent to “transfer” participants (attached). The second letter will be mailed approximately 1-4 weeks after the first letter, depending on response to the first letter and to allow flexibility in the recruitment strategy for new vs. transfer participants with whom we have an existing relationship. Recruitment letters may include a small token (e.g., magnet, pen or pin with SERVE logo). We will attempt to contact potential participants by telephone and/or text message at least 4 days after a letter is mailed to allow time for them to receive the letter. Because of the priority to recruit transfers for the scientific mission, and addresses may well change during the interval since their last contact with us, we retain the option of sending up to two additional letters (e.g., personally-written note card) informing them that we have tried unsuccessfully to reach them. In addition, we will utilize the contact information form from Phase I and Phase II to call contact person(s) provided by the Veteran in case we were unable to reach him/her in order to get updated contact information. If a Veteran says he/she is not interested at any point in this process, his/her name will be marked on the list and s/he will not be contacted again. Interested Veterans will complete a telephone screen to confirm their eligibility (i.e., to ensure they are not actively suicidal, etc.; see attached Telephone Screening Form FX3). This recruitment procedure requires a waiver of consent (see attached).

To facilitate recruitment, the study will have a dedicated phone line. After a Veteran calls about the study (or we contact the Veteran), a brief screening assessment will be conducted by telephone or in person. This should help minimize participant burden, as those who are not eligible will be saved time and transportation costs associated with attending a screening appointment in person. If the Veteran is determined to be ineligible based on the telephone eligibility screening procedure, we will not collect any personally identifying information. For veterans determined to be initially eligible, we will collect identifying information for the purpose of scheduling a baseline assessment appointment. This identifying information will be recorded on an electronic telephone screen registry of initially-eligible participants, including Screen ID#, date of screen, salutation, name, contact information, whether or not it is ok to leave telephone messages (e.g., for appointment reminders), the appointment campus/date/time, indication that telephone note entered in CPRS, enrollment date, and reason not enrolled (e.g., unable to schedule, no longer has time to participate). Coded hardcopy eligibility screening documents will be stored in separate files for those deemed initially eligible versus ineligible. Final eligibility will be determined at the baseline assessment (e.g., from the diagnostic evaluation). Telephone screen information will be used in aggregate to report the recruitment process (e.g., number screened, number eligible, number ineligible, percentage/reasons for ineligibility, etc.). The telephone screen asks about mental health problems, and therefore is possible that a veteran who is screened will provide information about a substance use disorder (SUD). The substance data is used to conduct scientific research and will be reported in aggregate such that no individual participant is identified. However, should the participant desire treatment for SUD or mental health services, appropriate clinical referrals will be made.

Following the phone screen, for those deemed initially eligible, a cover letter will be mailed to the Veteran in advance of the baseline assessment appointment with directions and parking instructions. In addition, a copy of the Informed Consent Form (ICF and HIPAA authorization; attached) will be mailed to the Veteran in advance of the appointment (time permitting depending on when appointment is scheduled) for the Veteran to read and consider participation. Mailing the ICF/HIPAA authorization to the Veteran in advance will benefit Veterans in two ways. First, it will provide them with additional information about the study prior to their initial appointment. In the event Veterans read the ICF/HIPAA authorization at home and decide they do not wish to participate, they will be able to cancel the appointment ahead of time, saving them the time and expense of travelling to the appointment unnecessarily. Second, this procedure will reduce participants’ time burden on the day of the assessment, as Veterans will have had the time to read and consider the ICF/HIPAA authorization prior to coming to the initial intake appointment. Upon arrival, the Veteran will be asked if s/he had a chance to read the ICF/HIPAA authorization, and if not, will be asked to read the consent form at that time. It should be noted that, regardless of whether or not participants read the ICF/HIPAA authorization ahead of time, the study staff member will always explain the nature of the study to participants at the time of the baseline assessment,

as well as the potential risks/benefits of participating in the study. In addition, written informed consent will only be obtained prior to the baseline assessment and will not be obtained until the researcher is satisfied that the participant has a good understanding of the risks/benefits of participating in the study. In situations where a Veteran unique to the Project SERVE Phase III study is unable to attend a baseline appointment in person (e.g., due to COVID-19), they may enroll remotely by electronically signing an informed consent form via docusign. Potential participants will be given the opportunity to ask questions and encouraged to contact the PI if they have any additional questions or concerns related to the study.

In order to recruit as many Phase I and Phase II participants as possible, we will offer the option of signing an informed consent form remotely for transfer participants who have moved out of the area. Following the phone screen, if the Veteran is interested in participation, he/she will be mailed the informed consent form and HIPAA authorization. Participants will be provided clear instructions for signing the forms, and a postage-paid envelope for returning them to the study team. Participants will be informed that study procedures will not begin until the forms have been received by a study team member. Any potential participant who wishes to travel to the VA Medical Center to provide informed consent in person will be allowed to do so, unless it is deemed unsafe for the veteran or study staff (e.g., due to COVID-19). Veterans who enrolled in a prior study phase and who are unable to attend an in-person appointment due to having moved out of the area or some other logistical barrier will have the option of renewing their consent online in order to participate in the current study phase. This requires a waiver of documentation of signed informed consent. The elements of informed consent will be displayed on the screen along with a button indicating “I consent/agree to participate.” The screen displaying the study information will be designed so that the participant is required to take an action to signify their acknowledgment of the information before they can proceed. The instruction tells participants that pressing the button confirms they have read the study information and that they agree to participate. Participants will be informed that they have the option of printing the page for their records, or to request study staff to send them a copy of the summary of the elements of informed consent. In addition, these participants will already have of copy of the full informed consent form, which has been mailed to them. Potential participants will be given the opportunity to ask questions and encouraged to contact the PI if they have any additional questions or concerns related to the study. Because these participants are unable to attend in person, they will not have the opportunity to participate in the biomarkers component of the study. Their participation will be limited to completing an assessment by phone or VA approved video communication technology and completing questionnaires online.

Research Setting. Veterans will be recruited from the three primary campuses of CTVHCS (Waco, Temple, Austin) as well as CBOCs in order to represent Veterans from different geographic regions within CTVHCS. Research interviews will be conducted in Waco, Temple and Austin. In Waco, private offices are available in the Center of Excellence Building. In Temple, Research Service Space is available in the Domiciliary, Building 146 and Building 205. In addition, interviews will be conducted in private offices available on the Temple campus (e.g., swing space through Mental Health/Behavioral Medicine, OEF/OIF program, library, etc.). In Austin, only swing space is available at this time, however, we will continue working on other available space. As needed, we will also use the CoE’s Mobile Support Vehicle, which includes two sound-proofed offices and can be relocated as needed (e.g., Waco, Temple, Austin, CBOCs, Vet Centers). The Mobile Support Vehicle is VA/CoE-owned and includes two offices. Laptops that are used for the study will not be locked up in the Mobile Support vehicle, and will stay with the VA employee as assigned/issued by VA IT. The laptops have locking cables and are password protected.

Every effort will be made to conduct assessments at the site of the Veterans’ choice, pending availability of staffing resources and research space at that time. Due to research space limitations, the need may arise to invite participants to come to another campus to complete the interviews (i.e., different campus from where they usually receive their care). When space is not readily available (and budget dependent), we will offer the option to participants to travel to another campus to complete the assessment. In such instances, participants will be provided with supplementary compensation to account for extra time and travel expenses. Calculations will be made using VA mileage rates at the time (currently: 41.5 cents/mile). For example, based on current rates, participants would be paid the following (rounded to nearest 5 or 10): 1) Austin/Temple (142 miles

roundtrip) = $60; 2) Austin/Waco (204 miles roundtrip) = $85; 3) Temple/Waco (68 miles roundtrip) = $30. This strategy will also be used to appropriately compensate Veterans who have relocated out of the CTVHCS area, but are still within reasonable distance to participate at a CTVHCS site (e.g., travel from College Station, Dallas, Houston, San Antonio). Rates for these cities will be similarly calculated. This procedure is **critical** to the research mission in order to continue following as many transfer participants as possible (i.e., the importance of the Phase I/Phase II to Phase III design is to answer scientific questions over longer periods of time). Numerous participants have expressed a preference for driving to the VA to complete the procedures in person rather than remotely. Thus, we are requesting to have flexibility on this front. These rates are based on federal standards and provide appropriate remuneration to participants (i.e., standard payments do not properly compensate Veterans for time and travel when traveling longer distances). Participants will be informed that they cannot receive compensation for travel to other appointments and research simultaneously (i.e., no double dipping).

Enhancing Retention. In a longitudinal study (Aim 1), retention is as important as recruitment. Every effort will be made to establish personal relationships with participants and to help them feel connected to the study and to CTVHCS. Appointment reminders will be used to decrease attrition. Research assistants will mail appointment confirmation letters to participants and call, text, or email participants prior to their appointment. For follow-up assessments, two methods of completing self-report questionnaires will be offered: filling out the questionnaires via paper and pencil and returning them through the mail, or filling out questionnaires online via a secure web-based survey application. Those who chose the online option will be mailed, texted, or emailed instructions, information regarding our procedures for ensuring their confidentiality and privacy, and a web address and unique code that they will enter as indication of their consent to this procedure. Veterans who do not complete the follow-up assessments will be contacted by telephone and/or letter as a friendly reminder; they will be offered to complete the assessment by telephone if they find that to be more convenient than filling out the written forms or completing them online. Alternately, if it is deemed safe to do so, participants will be offered the opportunity to schedule an appointment to complete the questionnaires in-person, if that is more convenient for them (our experience is that some Veterans prefer this option). At each assessment point, Veterans will complete (or update) a contact information form. In addition, research staff will also periodically contact Veterans to inquire if their contact information is current (e.g. in advance of a follow-up appointment or to confirm mailing address for payment purposes). It is possible that some Veterans will relocate between assessment points and our contact information will become outdated. In these instances, the Veteran's medical record and contact information form will be used to retrieve his/her updated telephone/address so s/he can be contacted to continue to participate in the study. Veterans will also be given the option of completing telephone or VA approved video communication technology interviews in the event that they decline or are unable to attend a follow-up assessment or decline or are unable to complete the packets by mail or online. Additionally, if the Veteran declines or is unable to participate in a telephone/video interview, s/he will be offered the option of completing only the self-report measures either via mail, online, or telephone. These procedures give flexibility to the Veteran to choose to continue participating in a manner that is feasible given life circumstances.

Several incentive strategies will also be used to decrease attrition and optimize retention. Participants will be compensated $75 each for the baseline and annual assessment and $25 for mailed follow-up assessments. That is, a Veteran would be compensated a total of $200 for completing all study procedures. The Veteran will have the option being compensated at any time-point with either the standard payment or with a gift card from a national chain store (e.g. Walmart) should that option become approved for use in VA research. These incentives should reduce participant burden related to their time spent, travel costs, and other expenses (e.g. childcare coverage). To demonstrate our appreciation for their participation, other incentive strategies will also be used. At the baseline and annual assessment, participants will be given small appreciation gifts that make them feel part of the study (e.g. water bottle with study logo; Veteran-oriented magnetic poetry, candy with logo, baseball cap with study logo). Incentives will be used to encourage participants to mail back their self-report questionnaires. Specifically, a raffle will be held every 4-6 months (prize ranging from $50-200; e.g. gift certificate to canteen, amazon.com, Best Buy, cash/check/direct deposit, etc.). Every participant who mails back his/her questionnaires will be entered into the raffle. Raffle tickets will be entered into a drawing and a

winner will be randomly selected. The raffle will be announced in a newsletter. Winners will be announced by participant number only and we will the participant to notify them that they have won.

Assessment Procedures. The assessment instruments for Phase III are presented in Table 1 (see attached). Assessment domains were selected based on the empirical literature to capture biopsychosocial variables associated with responses to stressful life events and include: 1) pre-deployment characteristics (demographic variables, pre-deployment psychiatric history; pre-deployment stress and trauma); 2) cognitive functioning; 3) deployment related stress, trauma, exposure to potentially morally injurious events, and TBI (number of deployments, deployment-related PTEs); 4) post-deployment stress and trauma (exposure to PTEs following deployment, exposure to everyday/chronic stressors); 5) psychopathology (PTSD, depression, alcohol and substance use, abuse and dependence); 6) coping methods (acceptance, self-compassion, emotion regulation, attribution style, mindfulness, psychological flexibility, active coping); 7) multi-dimensional functioning; 8) response style/validity; and 9) information from VA electronic health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.

Table 1. Phase III Assessment Instruments.

Measures/ Proposed Indicators	Purpose	Assessment Time Point			Description/Rationale
		BL	8 & 16 mo	24 mo	
Telephone Screen	E				Administered prior to the baseline assessment to determine initial eligibility. Assesses inclusion/exclusion criteria.
Contact Information	Contact	✓	✓	✓	Collected to verify Veteran status in CPRS, scheduling, send appointment confirmation letter, contact for follow-up, etc.
Demographic Questionnaire & Military History Form (DHMQ)	Demographic, PV	✓		✓	Assesses basic demographic and Veterans-specific characteristics (e.g., years of education, years of military service, family history of military service). Re-administered at annual to assess changeable demographics (e.g. marital status, employment).
Mini International Neuropsychiatric Interview (MINI)	E	✓			Modules administered from this widely used screening Interview to assess for exclusionary criteria (manic/hypomanic episode and psychosis).
Full Combat Experiences Scale (FCES)	PV	✓		✓	Self-report measure of exposure to combat situations (Hoge et al., 2004). Re-administered if re-deployed. Items added from the National Vietnam Veterans Readjustment Survey to assess potentially morally injurious combat events.
Nash Moral Injury Events Scale (MIES)	PV	✓		✓	Self-report questionnaire developed as a measure of exposure to potentially morally injurious events (Nash, et al, 2013). Re-administered if re-deployed. The MIES has excellent internal consistency, both the overall scale and the 2 subscales showed temporal stability, and early research found preliminary support for the construct validity (Nash, et al., 2013).
Deployment Risk and Resilience Inventory (DRRI)	PV	✓		✓	The DRRI (King, King, and Vogt, 2003) is a collection of scales assessing pre-deployment, deployment, and post-deployment risk and resilience factors. The DRRI was validated for use with OIF Veterans (Vogt et al., 2008). Scales administered will include the military sexual trauma scale at baseline and the post-deployment social support scale at baseline and 24 months.
Acquired Capability for Suicide Scale	PV	✓		✓	Self-report of perceived ability to tolerate fear and pain associated with suicide. Has adequate internal consistency in a study that built on SERVE (.80).
Interpersonal Needs Questionnaire (INQ)	PV	✓		✓	Self-report measure that assess thwarted belongingness and perceived burdensomeness (Van Orden et al., 2012). The INQ has demonstrated good convergent validity, internal consistency and concurrent validity (Van Orden et al., 2012).
Treatment Involvement Form (TIF)	CV	✓	✓	✓	Form created for the current study that will be used to assess treatment involvement during the prior interval, including medical, psychiatric and psychological treatment, as well as supportive interventions (e.g.

					Alcoholics Anonymous, Narcotics Anonymous).
Columbia Suicide Scale	DV	✓		✓	The Columbia Suicide Scale (Posner et al., 2008) is a state-of-the-art suicide assessment for individuals perceived to be at high risk for suicidality. Internal consistency ranged from .73 to .95 (Posner et al., 2011).
Clinician Administered NSSI Disorder Index (CANDI)	DV	✓		✓	The CANDI is a clinical interview that diagnoses Nonsuicidal Self Injury (NSSI) disorder and type and frequency of NSSI. Demonstrated good reliability and validity in prior research, including in Co-I Kimbrel's VA-funded study of NSSI in veterans. Administered in tandem with the NSSI Screen developed by Co-I Kimbrel.
Beck Scale for Suicide Ideation (BSSI)	DV, Med	✓		✓	Widely-used self-report measure of intensity of thoughts and behaviors associated with suicide. Includes 2 additional items that ask about past suicide attempts as well as the level of suicidal intent during the most recent attempt. Prior research shows that endorsement of suicidal thoughts and behaviors can be greater on self-report questionnaires compared to interviews. Thus, this measure complements the suicide focused interviews.
Suicide Cognitions Scale-Brief	DV, Med	✓		✓	Self-report measure of suicide-related thoughts that load onto the following subscales: unsolvability, unlovability, and unbearability. Brief version was recently validated across 3 chronic pain samples (Bryan et al., 2016).
PTSD Checklist-5 (PCL-5)	Med	✓	✓	✓	Self-report of symptoms of PTSD during the previous month. Demonstrates high sensitivity and specificity in relation to a lengthy diagnostic interview for PTSD (CAPS), with which it was co-developed. Strong psychometric properties, including in numerous Project SERVE papers.
Patient Health Questionnaire-9	Med, DV	✓	✓	✓	Self-report measure used for screening, diagnosing, and monitoring depression. It incorporates DSM-IV diagnostic criteria (Question 9 screens for suicidal ideation; Kroenke, Spitzer & Williams, 2001).
Alcohol Use Disorders Identification Test (AUDIT)	Med	✓	✓	✓	Self-report measure to screen for alcohol-use disorders (Saunders, Aasland, Babor, Fuente, & Grant, 1993). 10-item measures adopted by VA as the gold-standard screening for alcohol use disorders in mental health and primary care clinics. Good internal consistency (α=.80 - .94) and test-retest reliability (*r*=.86), and strong concurrent validity with the MAST and CAGE screening measures (Babor et al., 2001).
Drug Abuse Screening Test (DAST)	Med	✓	✓	✓	Self-report measure to quantify drug misuse and related psychosocial impairment. Good internal consistency and concurrent validity with frequency of drug use over 12-months (Skinner, 1982). Moderately correlated with denial and social desirability. The instructions will be updated to more explicitly assess for misuse of opiates that may have been prescribed.
Substance Use Screen	Med	✓		✓	Form created for the current study that will be used to assess current and lifetime substance use (e.g., stimulants, cannabis, etc.)
TBI—Vasterling Assessment Interview	E, Med	✓		✓	This clinician-administered structured interview developed by Vasterling (2008) assesses the number, recency, type of injury, and clinical sequelae associated with traumatic brain injury during deployment. Total number of lifetime head injuries leading to any symptoms will also be assessed. TBI will be assessed at baseline for lifetime history and then re-assessed at the annual interview for any new TBIs that may have occurred during the past two years.
Ten-item Personality Inventory (TIPI)	PV	✓			10-item self-report measure of the Five-Factor Model of personality (Gosling, Rentfrow & Swann, 2003).
Patient Health Questionnaire–15 (PHQ-15)	Med, DV	✓		✓	Self-report (Kroenke, Spitzer & Williams, 2002) of somatic symptom clusters including pain (musculoskeletal, headaches), cardiac, gastrointestinal, respiratory, etc. that account for more than 90% of outpatient physical complaints (Kroenke, Arrington & Manglesdorff, 1990). The PHQ-15 had strong internal reliability in the initial validation (α=.80) and was associated with functional status and disability (Kroenke et al., 2002).
Chronic Pain Screen Quest.	Med	✓		✓	Self-report of pain type/intensity. Internal consistency in SERVE was .67.

Acceptance and Action Questionnaire (AAQ-II)	PV	✓	✓	✓	Self-report measure assessing acceptance, experiential avoidance (attempting to alter the form or frequency of unwanted internal experiences), and taking action despite experiencing unwanted private events (Bond, et al, 2011). Strong psychometrics in multiple SERVE publications (Meyer et al., 2013; 2018; in press, DeBeer, Meyer, et al., 2017).
Brief Experiential Avoidance Quest. (BEAQ)	PV	✓	✓	✓	The BEAQ is a single-factor item that assesses the modifiable construct of experiential avoidance (Gamez et al., 2013).
Self-Compassion Scale – Short Form (SCS-SF)	PV	✓	✓	✓	Self-report measure of self-compassion, consisting of a total scale score and six subscale scores: self-kindness, self-judgment, common humanity, isolation, mindfulness, and over-identified (Neff, 2003; Raes, Pommier, Neff, & Van Gucht, 2011). The SCS-SF is strongly correlated with the original long form (r=.97) and has the same 6-factor structure with one higher-order factor. Internal consistency was .86 for the whole measure, with subscale alphas ranging from .54 to .75 (Raes et al., 2011).
Difficulties in Emotion Regulation Scale (DERS-Brief)	PV	✓	✓	✓	Self-report measure (Bjureber et al., 2016) of 6 domains of emotion dysregulation: nonacceptance of emotional responses, difficulty engaging in goal-directed behavior, difficulty with impulse control, lack of emotional awareness, poor emotion coping strategies, and lack of emotional clarity.
Five Facet Mindfulness Questionnaire	PV	✓	✓	✓	Self-report measure assessing multiple facets of the modifiable factor of mindfulness. The FFMQ has demonstrated good construct validity and internal consistency. Good predictive validity in research with veterans.
World Health Organization Disability Assessment Schedule II (WHODAS 2.0)	DV	✓	✓	✓	Self-report assessment of functional disability with total score and 6 domains of functioning: understanding and communicating, mobility, getting along with others, life activities (i.e., work, education, household responsibilities), participation in society, and self-care (Üstün et al., 2010). Both global and specific areas of functioning are crucial in thoroughly understanding functional recovery, as Veterans may function well in one area and have difficulty in another. Moreover, some domains may be affected by contextual factors instead of representing functional capacity (e.g., work functioning in a struggling economy independent of impairment).
Inventory of Psychosocial Functioning (IPF) – Brief	DV	✓	✓	✓	Self-report measure (Co-I Marx et al., 2009; Bovin et al., 2018) of Romantic Relationships with a Spouse/Partner, Family, Work, Friendships and Socializing, Parenting, Education, and Self-Care. The short version has a .90 correlation with the full 80-item instrument (Co-I Marx, personal communication). Higher scores indicate greater functional impairment.
Quality of Life Scale (QLS)	DV	✓	✓	✓	Self-report (Burkhardt, et al., 1989) assessing how satisfied people are in areas distinct from health status (mate, physical well-being, relationships with others, social, community, and civic activities, personal development and fulfillment, recreation, and independence). Good internal consistency and high test-retest reliability (Burckhardt et al. 2003).
Values Tracker	DV	✓	✓	✓	Brief self-report measure of value engagement. Good predictive validity in research with chronic pain samples.
Meaning in Life Questionnaire	PV	✓		✓	Brief self-report assesses presence and search for meaning in life (Steger et al., 2006).
Social Connection Index	DV, Med	✓		✓	Self-report measure of frequency of contact with others, number of close friends and relatives, level of secure attachment in relationships, frequency of problems getting along with friends and family members.
Brief Loneliness Measure	DV, Med	✓		✓	Brief self-report measure of loneliness for use in large survey studies. Highly correlated with lengthier measures such as the UCLA Loneliness Scale.
Interpersonal Reactivity Index-Brief (B-IRI)	DV, Med	✓			Brief self-report measure of disposition to empathic responding; 2 subscales assess perspective taking and empathic concern. Good reliability and validity (Ingoglia et al., 2016).
Flexible Regulation of Emotional	DV, Med	✓			Self-report measure of ability to enhance and suppress both positive and negative emotions. Good convergent and divergent validity with depression, personality, resilience, and laboratory tasks measuring

Expression (FREE) Scale					emotion suppression and enhancement (Burton & Bonanno, 2016).
Perceived Ability to Cope with Trauma (PACT) Scale	DV, Med	✓			Self-report measure of trauma-focused and future-oriented coping. In addition, a coping flexibility score indicates greater use of both types of coping.
Differential Emotions Scale-IV (DES-IV)	DV, Med	✓			Self-report of frequency of emotional responses across 9 types of emotions: guilt, shame, fear, anger, shyness, self-hostility, contempt, disgust, sadness. Good reliability and associations with personality and MH symptoms (Izard et al., 1993). Modified to assess participants' emotional responses to thinking about their most traumatic and potentially morally distressing experiences.
Traumatic Life Events Questionnaire (TLEQ-Lite)	PV	✓		✓	24 items (Kubany et al., 2000); assesses frequency of exposure to 22 potentially traumatic events encountered outside of military service, resulting in a continuous trauma exposure score. The psychometric properties were carefully established in 5 studies, including a sample of combat Veterans (Kubany et al., 2000). Modified for this study to no longer assess DSM-IV criteria for PTSD Criterion A2, as this is no longer required in DSM-5, and to include an item assessing exposure to COVID-19 as a potential stressor.
Multidimensional Psychological Flexibility Inventory (MPFI)	PV	✓		✓	60-item self-report (Rolffs, Rogge, & Wilson, 2018) used to assess the dimensions of the psychological flexibility model that underlies Acceptance and Commitment Therapy
Expressions of Moral Injury Scale (EMIS)	DV				17-item self- report (Currier et al., 2018) to assess for problems associated with exposure to morally injurious events
Credibility & Expectancy Questionnaire	PV				Widely-used 6-item self-report measure of the credibility of the treatment approach and expectations for positive response to the treatment (Borkovec & Nau, 1972). Used in Dr. Meyer's prior ACT studies (Hermann, Meyer et al., 2016; Meyer et al., in press).
Client Satisfaction Questionnaire	DV				Widely-used 8-item self-report measure of treatment satisfaction (Larsen et al., 1979). Used in Dr. Meyer's prior ACT studies (Hermann, Meyer et al., 2016; Meyer et al., in press).
Working Alliance Inventory	PV				Widely-used, brief self-report measure of clients' perceptions of working alliance with therapist on 3 dimensions: goal, task, and bond (Horvath, 1981).
Parenting Stress Index Short Form (PSI-SF)	PV	✓	✓	✓	Veterans with a child between birth and 12 will be asked to complete this measure on the child they are most concerned about. Thirty-six items are divided into three domains: Parental Distress (PD), Parent-Child Dysfunctional Interaction (P-CDI), and Difficult Child (DC), which combine to form a Total Stress scale.
Quality of Marriage Index (QMI)	PV	✓	✓	✓	6-item self-report questionnaire used to measure relationship distress (Norton, 1983). The measure was developed based on an empirical analysis of the functioning and construction of marriage quality variables.
Saliva sample and saliva collection questionnaire	PV, Med	✓			DNA and other products will be extracted from saliva samples. A list of 13 questions will be asked during sample collection related to variables that can affect quality of saliva sample and associated biomarkers (e.g., time since last meal). Provision of saliva sample is optional.
Blood sample	PV, Med	✓			DNA and other products will be extracted from blood samples. Provision of blood sample is optional.
BL = Baseline; E = Eligibility; DV = Dependent/Outcome Variable; PV = Predictor Variable; Med = Mediator; CV = Covariate					

Training of Clinical Interviewers. Clinical interviews will be conducted by trained interviewers familiar with the assessment procedures and the culture of military service. The PI and trained doctoral staff members will conduct certifications in the proper administration of the clinical interviews and will provide ongoing, weekly supervision of interviews conducted. Further, all interviews will be video or audio-recorded through a VA computer using a microphone directly onto the secure, approved drive behind the VA firewall or using a FIPS 140-2 validated digital voice recorder. In any instance in which technical or logistical difficulties interfere with video recording, audio recording will be used. All video/audio files will be stored on the secure, approved drive

behind the VA firewall. FIPS 140-2 validated digital voice recorders will only be transported by research staff who have an approved Authorization to Transport memorandum on file with the Research Office. After being uploaded to these secure folders, audio files will be accessible to approved research staff. Approved research staff will listen to recordings for training purposes (e.g., practice coding, learn administration procedures), or for the purposes of assessing inter-rater reliability. An interviewer training manual has been developed, which details the training method, scoring procedures, and process for systematic DRG to ensure consistency across interviewers (Meyer, Morissette & Kimbrel, unpublished). Interviews (10% or more if necessary) will be rated for inter-rater reliability as an added measure. Recordings will also be coded for observable, clinically relevant behaviors.

Biological Markers.

Overview. Subjects will donate saliva and blood for genetic and biomarker research studies. Both saliva and blood will be collected because some biomarkers are known to be present in both blood and saliva. If we find a biomarker for PTSD symptoms in blood, and it is also in saliva, that would be a great advantage for monitoring. Also, there are species of proteins in saliva that are not carried in the blood, and which change with stress. These may also be biomarkers for PTSD symptoms. No clinically validated tests will be performed. The genetics/biomarker component of the protocol will be supervised by Dr. Rakeshwar Guleria (CoE Biomarkers and Genetics Core; Phase I, II, III), an expert in this area, in collaboration with the PI, Dr. Creech. See Appendix for Safety Survey. At the BL assessment, participants will be given the option of consenting to all study procedures or all procedures excluding the saliva/blood sample (depending on the phase) and genetic research.

Study participants will be donating their samples for biomarker and genetic-related studies. The samples (blood/saliva) will be collected from the study participants and will be analyzed for identifying molecular biomarkers for early diagnosis and prevention of traumatic brain injury and PTSD in our returning war Veterans. Genetic variation will also be studied between the patient vs. the control group of participants for predicting PTSD susceptibility and progression. The study participants will be donating their samples for the biomarker and genetics related studies. The process of biomarker identification and validation will be conducted in two stages 1) Unbiased approach (discovery) and 2) Targeted approach.

Stage I (unbiased approach): This is the discovery phase where samples will be analyzed globally to identify potential biomarkers (protein, genetic, epigenetic, metabolic, and immunological markers). Protein (proteomics) and metabolite (metabolomics) biomarkers will be screened with mass spectrometric analysis at the Mass Spectrometry Core facility, Baylor University, Waco, TX (under CTVHCS's MOU with Baylor). Genetic markers (allelic, mutations, CNV's, SNPs, miRNA) will be screened at the VA by using PCR, Real-Time Quantitative PCR, Droplet Digital PCR, and next-generation sequencing. Inflammation and immune biomarkers will be screened by flow cytometric analysis at the CoE Biomarkers & Genetics Core laboratory. If de-identified samples are sent outside the VA for analysis, we will follow all VA rules and regulations and obtain appropriate Research Service, IRB, safety and data monitoring approval.

Stage II (targeted approach): Once we narrow down the potential biomarkers, we will move to the qualification, verification, and validation steps where we will target the specific potential biomarker and proceed with a targeted screening approach. Once validated, the markers identified will be segregated according to susceptibility, diagnostic, and therapy biomarkers.

Sample Collection**:** Participants will donate saliva by passive drool, a method of pooling saliva in the mouth and pushing it through a straw or collection device into a collection tube. Staff will be trained to avert their eyes when participants are depositing saliva into the test tube to reduce potential embarrassment. Because many factors can influence salivary biomarkers, participants will complete a saliva questionnaire (included in Table 3 and appendices). The saliva samples will be stored in a cooler with an ice pack or in a refrigerator until transported to the Center of Excellence (Building 93), processed and stored until assay.

Subjects can also opt to donate blood by venipuncture by personnel trained in VA procedures for taking blood samples. All blood processing will take place at the VA by trained personnel. Compression bandages will be used to cover the puncture. Blood will be placed in 1 RNA (Paxgene Red-top), 1 DNA (Paxgene Blue-top), 2 purple top (plasma) and two red top (serum, activator coated), all coded, and stored in a cooler with an ice pack or refrigerator until transported to the Center of Excellence (Waco Building 93) within 4-6 hours of collection. If the participants have a fear of needles, blood will not be drawn in Phase III.

Tubes will either be frozen (RNA, DNA) or processed (redtop and purple top tubes) for cell protein and other constituents in Waco building 93 (2A113, 2A116, 2A117). DNA/RNA extraction from the DNA/RNA tubes will be performed by team members using DNA/RNA extraction kits and coded DNA/RNA samples will be stored at -20/-80 and in liquid nitrogen until testing. Blood will also be analyzed for immune and inflammatory markers (cluster of differentiation (CD) immunomarkers, chemokines, cytokines), as well as for other blood and saliva-based biomarkers. Remaining blood product samples will be stored at -20/-80^{0}C and in liquid nitrogen for future use, with appropriate IRB approval at CoE (Freezer Room 2A13). DNA genotyping and lab work will be performed in the wet lab within the CoE (Waco building 93; room 2A113, 2A116, 2A117). The results of any biomarker analysis will be saved in a coded, de-identified dataset and stored on VA computers on the secure CTVHCS Research Service-approved drives that will only be accessible to study staff.

Data Management:
Identifiers: A study ID number will be used to identify each participant across assessments.

Identifiers/linking data: A password protected master participant tracking spreadsheet will contain the linking information that matches the participant IDs to participant names. This spreadsheet will reside only on the secure research drive. Other PHI such as participant addresses and phone numbers (for follow-up contact), and date of participation will only be accessible to PI Creech and her research staff that is approved to work on the study. The Master tracker will be kept separately from study databases on the secure research drive. Paper files will be stored at the VISN 17 Center of Excellence in Waco, TX in Building 93, room 1A-137.

Confidentiality: No participant will be identified in any publications or presentations arising from this study. Records will be maintained in accordance with the Department of Veterans Affairs Record Control Schedule 10-1. It may be necessary or required for the study investigators to break confidentiality and release personal identifiers and health information when mandated by law. For example, state law requires health care workers to report any suspected abuse or neglect of a child, or person 65 years or older, or an adult with disabilities to the Texas Department of Family and Protective Services.

A Certificate of Confidentiality will be obtained from the National Institutes of Health prior to the commencement of research. The purpose of this certificate is to protect the identity of research subjects participating in studies that collect sensitive information. No information about participants will be released without their permission or where required by law (such as the examples given above).

All employees who are to handle data will be trained in confidentiality policies and procedures. If theft, loss, or other unauthorized access of sensitive data and non-compliance with security controls occur, study staff has been instructed to follow the CTVHCS standard operating procedure on incidence reporting.

Delineation of research tasks performed by VA and collaborators: All participant contact activities will take place on the Austin, Temple or Waco campuses of CTVHCS. Following approved CTVHCS methods for sharing a study dataset with collaborators, some secondary outcomes analyses may be performed by approved secondary users within and outside the VA through requests made to the SERVE Data Repository.

Primary users of the study dataset are those individuals listed on the study staff list and are those who will conduct pre-specified analyses consistent with the study's hypotheses and its primary, secondary and exploratory aims as described in the aims and analysis plan.

Disposition of the data: Paper files containing identifiers will be kept in locked file cabinets in a locked room at the Center of Excellence in Waco, TX. Coded paper files will be kept in separate locked file cabinets. Only approved study staff will have access to the files. Electronic data will be stored on the secure VA password-protected server with access restricted to research staff. These records will be maintained and retained in accordance with the Department of Veterans Affairs Record Control Schedule 10-1.

Incident Reporting: Any incidents affecting the security of the data such as theft, loss, or unauthorized access of sensitive data will be reported to the ISO and PO per VA regulations.
Data Use within CTVHCS: Only IRB approved personnel on the study staff list will have access to the data

collected in this study. Access to the study data will be terminated when personnel are no longer part of the research team. The primary repository of paper files generated by the study is the VHA VISN 17 CoE. Data to be transported to the CoE includes: consent documents and measures completed after each appointment. Study data collected at the Temple or Austin campus will be transported to the approved data storage location at the Waco Campus where it will be uploaded to the secure research drive. Personally-identifying information (e.g. Informed Consent Form with name and date of consent) will be kept in a separate locked carrying case from the data during transport.

Records destruction information: "All paper AND electronic documentation containing confidential, personally identifiable information, protected health information, and any other sensitive information will be disposed/destroyed per current VA regulations at the time of disposal/destruction of documentation."

Records retention information: "The required records, including the investigator's research records, must be retained until disposition instructions are approved by the National Archives and Records Administration and are published in VHA's Records Control Schedule (RCS 10-1)." All de-identified data will be managed in accordance with the VHA Handbook 1605.1 APPENDIX B. All original data will be stored at VA.

Reporting: Any incidents involving theft or loss of data or storage media, unauthorized access of sensitive data or storage devices or non-compliance with security controls will be immediately reported to the IRB chair, Privacy Officer and Information Security Officer.

Data Analysis Software: Data will be analyzed using the software programs that are already owned by the VA (e.g., SPSS, SAS, mPLUS, AMOS) either using local copies of the software or through VA Informatics and Computing Infrastructure (VINCI).

Data Collection. Data will be visually inspected for completeness by study interviewers at the time of collection. Data will be gathered in two ways: collected and entered using hard-copy assessment measures or through the use of Qualtrics, a secure web-based survey application. Qualtrics is a secure, web-based application for building and managing online surveys and databases. This system is similar to REDCap and is flexible enough to be used for a variety of types of research, and provides an intuitive interface for participants to complete surveys. It also offers easy data manipulations with audit trails for reporting, monitoring, and querying patient records, and an automated export mechanism to common statistical packages. As with REDCap, all web-based information transmission is encrypted. Data from Project SERVE: FX (00390) will be stored on VA servers, including data downloaded/exported from Qualtrics. Data will be entered and managed using statistical software (SPSS, SAS, Stata, R/S-Plus, and others) and through Research Electronic Data Capture (REDCap). REDCap is a service through the VA Information Resource Center (VIReC; for more information, please see: http://vaww.virec.research.va.gov/REDCap/Overview.htm). REDCap is a secure, web-based application for building and managing online surveys and databases. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team. The iterative development and testing process results in a well-planned data collection strategy for individual studies. The REDCap system provides secure, web-based applications that are flexible enough to be used for a variety of types of research, provide an intuitive interface for users to enter data and have real time validation rules (with automated data type and range checks) at the time of entry. These systems offer easy data manipulation with audit trails for reporting, monitoring and querying patient records, and an automated export mechanism to common statistical packages (SPSS, SAS, Stata, R/S-Plus). REDCap servers are housed in the secure, VA Information Technology Center on a VINCI server, located in Austin, TX. All web-based information transmission is encrypted. REDCap was developed specifically around HIPAA-Security guidelines. REDCap has been disseminated for use locally at other institutions and currently supports 240+ academic/non-profit consortium partners on six continents and over 26,000 research end-users (www.project-redcap.org). Interview and self-report data will be entered continuously by staff members as the data are collected. Data entry training will consist of both didactic sessions in which staff members are provided with information about the data entry system in place at the CoE as well as actual entry of mock data as a validity and accuracy check.

Data Sharing With Other Studies Comprising Project SERVE. Project SERVE: FX is one of several studies that will comprise the Project SERVE research program. Each study aims to independently contribute to scientific understanding of the impact of warzone experiences on OEF/OIF/OND Veterans. A data sharing agreement is requested between Project SERVE studies and a SERVE Data Repository has been established for future research. Data from Project SERVE will be included in the SERVE Data Repository.

AIMS AND HYPOTHESES.

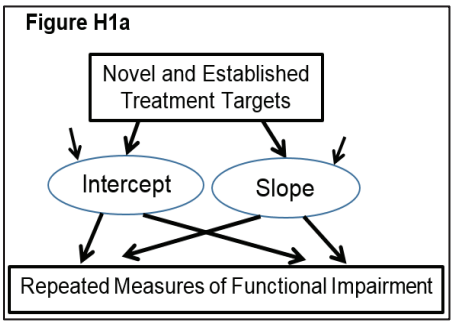
Specific Aim 1: Identify treatment targets that prospectively predict functional disability and self-directed violence (SDV) in post-9/11 Veterans with PTSD, depression, chronic pain, TBI, and/or AUD.

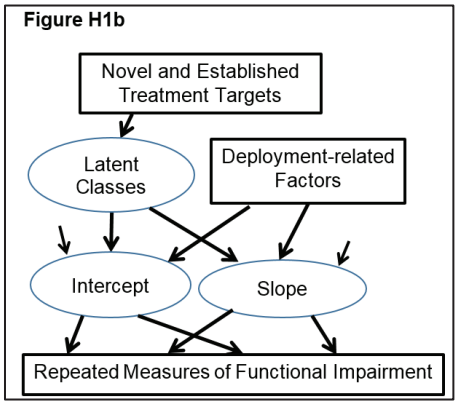
Hypothesis 1: Novel factors (mindfulness, perceived burdensomeness, thwarted belongingness, and moral injury) along with established treatment targets (psychological flexibility, self-compassion, and emotion regulation) will prospectively predict functional disability and SDV after accounting for covariates.

Analytical Plan.

Aim 1: The proposed analyses are grounded in the SERVE conceptual framework (Figure H1a). Our team has expertise in a variety of advanced statistical modeling procedures, including latent growth models, growth mixture models, longitudinal analyses, and measurement invariance. The design is based on a measurement model that collects predetermined, repeated assessments every 8 months over a two-year period. The effect of treatment will be examined via dummy variables in all hypotheses. We will use both traditional (e.g., maximum-likelihood regression) and advanced approaches (e.g., latent growth models, growth mixture models, and mediation models with bias-corrected bootstrap confidence intervals) to analyze the data. For example, to test Hypothesis 1a (H1a) in a traditional manner, principal component analysis (PCA) will be used to create a composite functional impairment factor. This approach will greatly reduce the number of tests conducted and provide us with a broad index of functional impairment. Variables used to create this factor score will include measures of functional impairment (WHODAS 2.0, IPF), QoL (QLS), and values-based behavior (VT). Change scores for these measures will be calculated and regressed onto the hypothesized predictors and covariates (including prior level of functional impairment) to test H1a. Latent growth modeling (LGM)—which allows for modeling of the change/growth trajectory of different variables assessed on multiple occasions across time—will also be used to analyze the data. We expect that scores on repeated measures will be correlated. Growth models take this dependency into account by treating repeated measures as separate variables, and fitting a proposed trajectory shape to the scores across time. Advantages of using LGM over other approaches include the flexibility of placing constraints on the model while allowing growth parameters describing participants' trajectories to serve as predictors or outcomes. LGM assumes that individuals come from a homogeneous population while Growth Mixture Modeling (GMM) allows multiple subpopulations to be inferred from the data. GMM is a general latent class analytical framework that has the capacity to model both random variation of the latent growth factors and the unknown heterogeneous subpopulations simultaneously. The proposed mediation effects will be examined with bias-corrected bootstrap confidence intervals that have been shown to produce the unbiased test with highest statistical power. We will ensure adequate data quality by evaluating normality and conducting descriptive, outlier, and psychometric analyses for each data wave. We will use alternative robust estimators (e.g., WLSM, WLSMV, MLM, and MLMV) when analyzing non-normal data. All SEMs including the LGM and mediation analyses will be evaluated with the chi-square test and commonly used fit indices such as RMSEA, SRMR, CFI and TLI. Additionally, for GMM, we will evaluate the results using the recommended information criteria (e.g., BIC, BLRT) and other related fit statistics (e.g., entropy). Analyses will be registered in the NIH clinical trials online database prior to data collection.

The statistical power of the hypothesized models was estimated using the Monte Carlo procedure in Mplus. For each power analysis, 1000 datasets were simulated following a hypothesized model that included a particular effect size of interest for each test. The model(s) of interest were then estimated for each dataset, and the proportion of datasets in which the null hypothesis was rejected was taken as the (empirical) power of the test. To examine the effect of the novel and established treatment targets on functional impairment over time in Hypothesis 1a, we will use LGM with the treatment targets measured at baseline predicting functioning





over time (Figure H1a). The statistical power of the target effect, the direct arrow from the treatment targets to the slope of functional impairment over time, is evaluated. Given the proposed sample size (500 participants with 4 repeated measures), the power for detecting a medium direct effect (based on our preliminary analyses) from the treatment targets to the slope of functional impairment is > .90. GMM will be used to test Hypothesis 1b (Figure H1b). Based on our preliminary studies, the statistical power for detecting a three-class solution is larger than .90 given the proposed sample size (500 participants). We calculated statistical power for the effects of the novel and established treatment targets on latent class membership. Assuming a small to medium effect size (odds-ratio = 1.82, which roughly corresponds to Cohen's d of 0.34), the power of the treatment targets on predicting class membership ranged from .72 to .91. In Hypothesis 1c, risk for SDV is measured in multiple ways including a continuous variable (severity of suicidal thoughts), a frequency/count variable (number of instances of NSSI), and a dichotomous variable (attempted suicide). A latent factor will be created and analyzed in Mplus which uses the MLR estimation to handle non-normally distributed variables. The longitudinal property of this latent factor will be examined via the longitudinal measurement invariance. Once the risk for SDV factor model is confirmed, we will regress it on the latent class membership (based on H1b results), hypothesizing that the most severely impaired class will predict greater risk of SDV. The proposed mediation model in Hypothesis 1d (i.e., the treatment targets mediate the effects of mental and physical wounds on functional impairment and risk for SDV over time) will be tested by using Mplus MODEL INDIRECT with bootstrap confidence intervals. By assuming a medium mediation effect, the corresponding statistical power is larger than .80 with our proposed sample size. We used conditions and parameters that are broadly based on our own data, prior clinical studies, and published Monte Carlo studies. Effect sizes estimates were in the small-to-medium range. The number of repeated measures is based on the current design. In brief, we are confident that the parameters and conditions are very close to our proposed study conditions.

Additional exploratory analyses will focus on the relationship between mental health symptoms and a range of health outcomes. As an initial step, we will use multivariable Cox regression to estimate hazard ratios and 95% confidence intervals for the development of heart failure by PTSD status.

Missing Data Management: Longitudinal designs pose several challenges with respect to missing observations (e.g., length of data collection, multiple assessment points, participant attrition). Based on our prior research and multiple methods of maximizing retention, we anticipate low attrition and minimal missing data. Nonetheless, we conservatively expect up to 20% missing data. Mplus, which uses full information maximum likelihood (FIML) estimation for handling missing data, will be used for analyses. FIML is a principled approach that is considered "state of the art" in missing data management. FIML is a maximum-likelihood based estimation procedure that directly estimates parameters and their standard errors for the full sample from the existing and limited data. Thus, there is no attempt to replace missing data values. Instead, as "maximum likelihood" suggests, the parameter estimates are derived in a manner that maximizes the likelihood that the data were drawn from the population of interest. FIML is the optimal procedure for handling missing data within both SEM and LGM frameworks primarily because it produces relatively unbiased parameter estimates and standard errors. In fact, using methods other than FIML in SEM requires justification.

HUMAN SUBJECTS RESEARCH AND PROTECTION FROM RISK

1. Risks to Subjects

A. Human Subjects Involvement and Characteristics: Up to 600 male and female OEF/OIF/OND Veterans enrolled for healthcare at the CTVHCS will be participants in Phase III. Veterans from all races/ethnic backgrounds will be recruited. Veterans with mental health conditions will be over-sampled. Participants will be

at least 18 years of age. The telephone screen will determine initial study eligibility. Eligible participants will be scheduled for a baseline assessment, at the beginning of which participants will complete a written informed consent form (ICF) for all Phases. Final eligibility will be confirmed at the baseline assessment. Participation is voluntary, with no penalty for withdrawal. Consistent with HIPAA and institutional IRB guidelines, the utmost care will be taken to protect the welfare and interests of human subjects. All key personnel are thoroughly trained in the conduct of human-subjects research. See also below "Protection Against Risk" and "Data Safety and Monitoring Plan."

B. Sources of Material: The baseline and annual follow-up assessments will be collected by questionnaire, clinical interview, and saliva/blood samples. In addition, questionnaire follow-up assessments will be mailed to participants 8- and 16-months post baseline; the Veteran will have the option to complete the follow-up assessment either by paper and pencil or online through Qualtrics. Participants who prefer to receive email reminders via the Qualtrics system will have their email addresses temporarily stored in the secure Qualtrics database using the "Contact List" feature. The Contact List is a feature within a PI's individual, password protected, online Qualtrics account. This feature allows the PI and approved study personnel to create a list of study participant email addresses. Only through this feature are study personnel able to send a survey link via an email from Qualtrics to participant's who request this method. Only approved study staff will have access to this online account and will be able to enter or see participant's email addresses. No PHI will be sent or received using this feature. The Contact List will simply store email addresses and this feature will allow for the distribution of survey links to every participant, which will not require participants to provide any identifying information. All email addresses will be deleted from the Qualtrics Contact List at the completion of the study. For further description of the Qualtrics security structure, please see the "Qualtrics Security White Paper." All data will be collected for research purposes only. The data will be protected as mandated by local IRB committees and the national HIPAA guidelines. Face-to-face interview and questionnaire data obtained during baseline and follow-up assessments by the research team will be stored in locked files with only code numbers to identify participant data. A list linking names with code numbers will be kept to ensure that no participants re-enter the protocol and to facilitate scheduling for follow-up assessments; this list will be kept electronically on the secure research drive. All research staff involved with the study will be made fully conversant with relevant ethical principles related to the conduct of human subjects research (including completion of HIPAA training and CITI training in human subjects research) and will be trained to be sensitive to the potential need for clinical referral.

In the event that an assessment conducted by members of the research team indicates that a participant is severely debilitated and/or needs a clinical referral (e.g., reports suicidality, homicidality, and/or severe symptomatology), the assessor will conduct a risk assessment, develop a safety plan (if necessary), and make an appropriate clinical referral. The PI will be notified of all such occurrences immediately. All CoE staff have been fully trained by a doctoral-level staff member or the local suicide prevention coordinator using the Operation SAVE (Signs, Ask, Validate, Encourage) program developed by the Canandaigua CoE. Emergency response (i.e. if the Veteran is actively suicidal or homicidal warranting crisis intervention) varies based on the campus in which the Veteran is being interviewed. In Waco, during regular business hours, Veterans can be escorted to the Mental Health Clinic for further evaluation, stabilization and hospitalization as necessary. After business hours, staff is instructed to call 911. In Temple, Veterans in crisis are brought to urgent care for evaluation, stabilization and hospitalization as indicated. In Austin, staff is instructed to call 911, as no emergency services are available on site. However, Veterans who would like immediate outpatient services can be referred to Primary Care Mental Health in Austin for same-day outpatient appointments.

In the event that a follow-up assessment received in the mail, online, telephone, or by VA approved video communication technology indicates that a participant is severely debilitated and/or needs a clinical referral (e.g., reports suicidality and/or severe symptomatology), the assessor will contact the PI immediately. The PI or trained staff member will then contact the participant to conduct a risk assessment, develop a safety plan (if necessary), and provide appropriate local treatment referral(s).

With respect to connecting Veterans with appropriate mental health services, a system of providing clinical referrals across each campus in which Veterans will be interviewed (Waco, Temple, Austin) has been established during the Project SERVE pilot study and continued in subsequent Phases. We anticipate that some Veterans will refuse referrals, particularly in light of data suggesting strong concerns about stigma among returning OEF/OIF Veterans (Hoge et al. 2004). We will make every effort to make Veterans feel

connected to the research study, which we hope will serve as an additional point of access to clinical services offered at CTVHCS. By establishing a relationship, coupled with data-driven check-ins on an ongoing and as-needed basis, we hope that Veterans who initially refuse services will eventually feel more comfortable accepting referrals. Certainly, study staff will be available at all times to forge a liaison with mental health services upon request.

In addition to interviews and self-report questionnaires, saliva/blood samples will be collected from participants. All specimens will be used strictly for research purposes. Providing a saliva/blood sample is optional and declining to provide a saliva/blood sample does not impact participation in the rest of the study.

With respect to the saliva sample, staff will be trained to avert their eyes when participants are spitting into the test tube to reduce the risk for potential embarrassment. The procedure will take approximately 1 minute. With respect to the blood draw, risks will be minimized by using personnel trained by the VA who will have a fully self-contained phlebotomy kit for each participant. Personnel draw 19 ml (= 4 teaspoons) of blood. The procedure will take approximately 10-15 minutes. Samples will be labeled with code numbers only and transported by study staff to the Waco VA Campus (Building 93: room 2A 113) for DNA extraction and storage. Participants will complete a layered informed consent process in which they will be informed of all procedures and will be given the opportunity to participate in the larger observational study while opting out of providing saliva/blood samples for later studies. Further, participants may specify that their DNA samples may not become part of the shared dataset/tissue repository.

C. Potential Risks: Potential risks include breach of confidentiality, coercion to participate, and possible discomfort from processing and retrieving memories of traumatic events. There is also some concern that a seriously impaired Veteran could be identified by the measures included in the interviews or the self-report questionnaires. As discussed in greater detail below, we believe that the likelihood of breach of confidentiality and coercion are low, given the steps we have taken to obviate these risks (e.g., numeric coding, informed consent). This study assesses sensitive information (e.g. alcohol and drug history). To protect confidentiality, we have obtained a Certificate of Confidentiality through the NIH for this research program, which will be amended to include Phase III. The risk of discomfort from discussion of mental health issues, including disclosure of traumatic material is moderate; however, the increased discomfort would be expected to be short-term and participants expressing severe distress would be referred for evaluation and treatment. The identification of a Veteran whose impairment is debilitating is expected to be a low-frequency occurrence. However, should an impaired Veterans be identified in the proposed project, appropriate referrals will be made. The saliva sample may cause embarrassment for some people. The risks of having blood taken from a vein in your arm are pain, bleeding, bruising, and rarely, infection at the site where the needle is inserted. Fainting or light-headedness may occur, but they seldom happen. If the Veteran is injured as a result of having blood drawn, VA will provide medical treatment for his/her research-related injury at no cost to the Veteran. There is a very remote risk that the Veteran's DNA sample might be obtained by someone who has no right to examine it, and enough information might be determined from DNA to identify him/her even if only a code is attached to the sample. There might be identity risks involved if this information falls into the wrong hands (e.g., the Veteran could be denied insurance coverage or employment because of certain genetic information about him/her). Federal laws and policies provide protection from discrimination by health insurance companies, group health plans, and most employers based on genetic information. A new federal law, the Genetic Information Nondiscrimination Act (GINA), will generally provide protection in the following ways: 1) Health insurance companies and group health plans may not request the Veteran's genetic information obtained from this research; 2) Health insurance companies and group health plans may not use the Veteran's genetic information obtained from this research when making decisions regarding his/her eligibility or premiums; and 3) Employers with 15 or more employees may not use the Veteran's genetic information obtained from this research when making a decision to hire, promote, or fire you or when setting the terms of employment. However, this new Federal law does not protect the Veteran against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

2. Adequacy of Protection From Risks

A. Recruitment and Informed Consent: Several recruitment strategies will be used to obtain a broad sample of OEF/OIF/OND Veterans. Participants will be recruited from the preceding longitudinal study, as indicated in the ICF. New participants will be recruited through advertisement at enrollment sites, vet centers, Veteran's networks and service organizations, through in-service presentations to primary care staff, mental health staff,

and other relevant VA staff (e.g., OEF/OIF/OND coordinators, etc.), and through the community (e.g. grocery stores, churches, shopping centers, and so forth). In-person recruiting will also be conducted at enrollment and community sites. In these cases, one or more research team members will sit at a table/booth in a high visibility area (e.g., a main VA lobby or outside of a grocery store) with a sign indicating that OEF/OIF/OND Veterans are being recruited to participate in a research study. Staff members will provide interested Veterans with a flyer (see attached flyer and brochure) about the study. In addition, Veterans interested in participating in the study will be given the option of providing staff members with their contact information so that they can be contacted by phone at a later point in time to complete a telephone screen interview.

In addition, as described in more detail above, we will request that IT/study staff conduct periodic searches for OEF/OIF/OND Veterans who meet some of our inclusion criteria (e.g. OEF/OIF/OND Veteran, diagnosis of PTSD or depression, no mental health disorder) so that we can reach out to returning Veterans to let them know that the study is being conducted.

Interested participants will complete a telephone screen. Eligible participants will be scheduled for a baseline assessment appointment, at the beginning of which informed written consent will be obtained. A cover letter will be mailed to the Veteran in advance of the baseline assessment appointment with directions and parking instructions. In addition, a copy of the Informed Consent Form (ICF) will be mailed to the Veteran along with a cover letter in advance of the appointment (time permitting depending on when appointment is scheduled) for the Veteran to read and consider participation in advance. Upon arrival, the Veteran will be asked if s/he had a chance to read the ICF, and if not, will be asked to read the consent form at that time. It should be noted that, regardless of whether or not participants read the ICF ahead of time, the study staff member will always explain the nature of the study to participants at the time of the baseline assessment, as well as the potential risks/benefits of participating in the study. Participants will be provided with a photocopy of signed forms. Related to the saliva/blood sample, the participant will be informed: 1) DNA will be extracted from their sample; 2) Researchers may use the participant's DNA to conduct studies of genetic markers in the future; 3) Researchers may conduct DNA studies with new technology in development that is currently unknown to the researchers; 4) Gene material and the gene information obtained will be used for research purposes only and will not be released to health insurance companies; 5) Researchers will not give the participant feedback or information about the results of his/her genetic testing; and 6) Participants can decline the saliva/blood sample and still participate in all other study procedures.

Written informed consent will not be obtained until the researcher is satisfied that the participant has a good understanding of the risks/benefits of participating in the study. The Veteran will be informed that s/he may discontinue participation at any time or revoke consent to the storage of DNA without any professional or personal consequences. We anticipate that participants will be in adequate health to attend and participate in all assessments. In order to maximize retention of participants in Phase III, we will offer the option of signing an informed consent form remotely for transfer participants who have moved out of the area. Following the phone screen, if the Veteran is interested in participation, he/she will be mailed the informed consent form and HIPAA authorization. Participants will be provided clear instructions for signing the forms, and a postage-paid envelope for returning them to the study team. Participants will be informed that study procedures will not begin until the forms have been received by a study team member. Any potential participant who wishes to travel to the VA Medical Center to provide informed consent in person will be allowed to do so, unless it is deemed unsafe for the veteran or study staff (e.g., due to COVID-19).

B. Protection Against Risk: Breach of confidentiality is unlikely because of our numeric coding system. Assessment procedures will be closely supervised by the PI. Study evaluators may identify a seriously impaired Veteran based on the measures proposed in this study. This will be addressed through risk assessment, safety planning, and clinical referral.

Issues related to coercion are unlikely, as Veterans who do not wish to participate in the study will not experience any impact on their care as Veterans. We will seek to protect Veterans from the emotional distress that might be aroused by the assessments in the following ways: (a) structured training and ongoing supervision of all assessment staff; (b) PI availability 24 hours per day, to respond to calls from participants who find themselves in crisis, and to assist in any necessary referrals; (c) referrals made for emergency or other inpatient or outpatient psychiatric services to identified local clinicians through existing referral mechanisms; and (d) Data Safety and Monitoring Plan (DSMP) and Data Safety and Monitoring Board (DSMB), described below.

To ensure the safety of potentially-impaired Veterans, a study investigator will review all assessments. The study investigators will have a roster of treatment providers specializing in the treatment of trauma, depression and substance abuse both in the VA and outside the VA. A list linking participant ID numbers to names will be on the secure Research and S:\CoE Data\FX drives, which will allow for identification of participants in the event that a Veteran evidences serious impairment on the assessment battery, so that an appropriate referral for intervention may occur, as needed. Hardcopy assessment information will be kept in a locked office (Building 93, 1A-137). Study identifiable information (ICF, HIPAA, payment forms, and contact information) are stored separately from coded hardcopy data.

Informed consent forms and forms with any identifiable information (e.g., payment records) will be kept in a locked file cabinet of a locked office (Building 93, 1A-137) with limited access at the Center of Excellence for Research on Returning War Veterans. Coded hardcopy phone screen data from both eligible and ineligible participants and assessment data will be kept in separate locked file cabinets from identifiable information (Building 93, 1A-137). Additionally, coded phone screen information will be placed in separate files to distinguish screen eligible/enrolled, screen eligible/not enrolled, and ineligible screens. Data may be temporarily (i.e., no more than 7 business days) stored at the Temple research space in locked offices, inside locked file cabinets, with identifying information separated from coded data using locked containers.

Video/Audio recordings will be recorded on FIPS 140-2 validated digital voice recorders that use VA-approved encryption, stored as .DS2 files, or using VA laptops, recorded directly onto the secure, approved drive, and transported by research staff who have an approved Authorization to Transport memorandum on file with the Research Office. Video/Audio files will be stored as electronic files in the secure, approved drive and on encrypted SD memory cards that are stored as hard copy data in the CoE data rooms (Building 93, 1A-137). Once video/audio files are transferred to the secure server folders and to the encrypted SD card, they will be erased from individual research staff members' digital voice recorders. Approved research staff will listen to video/audio-recordings on site using VA computers; thus, once video/audio files are transferred to storage, the only copies will exist on VA-secured servers (electronic) and in locked data rooms (hard copies on SD memory cards).

Coded data collected at other interview sites (Temple, Austin, CBOCs) will be transferred in a locked suitcase by a credentialed interviewer/research team member. All data will be marked with code numbers only. Informed consent forms, payment forms, and contact information with personally identifiable information (name, date of consent, SS#, etc.) will be transferred in a separate carrying case from the coded data (see Data Transport Agreements). For online data collection, a unique code will be assigned to participants. IP address will be blocked for additional protection, and no email addresses, names, or PHI will be collected. Research records will be retained until disposition instructions are approved by the National Archives and Records Administration and are published in VHA's Records Control Schedule (RCS 10-1). Any and all paper documentation containing confidential, personally identifiable information, protected health information, and any other sensitive information will be disposed/destroyed according to current VA regulations at the time of disposal/destruction of documentation. Original data will remain at VA. Only copies of de-identified data will be shared outside VA with study collaborators, after approval from the Privacy Officer as de-identified. We will request that collaborators share any newly-created variables. However, as the databases are de-identified, they will not be required to be returned for destruction.

Access to identifiable data will be terminated when staff are no longer part of the team. Procedures are in place for reporting any incidents (i.e., theft or loss of data or storage media, unauthorized access of sensitive data or storage devices or non-compliance with security controls) by reporting to respective parties (i.e., privacy officer and/or information security officer, IRB, first line supervisor).

Every effort will be made to keep information both private and confidential. Study records may only be disclosed in accordance with federal law, including the Federal Privacy Act, 5 U.S.C.552a, and its implementing regulations. Records may be reviewed by the U.S. Food & Drug Administration (FDA), other U.S. government agencies, Institutional Review Boards including the Central Texas Veterans Health Care System Institutional Review Board and by staff at these institutions that deal with research as part of their official duties. As a result, they may see participant names; however, they are also bound by rules of confidentiality.

3. Potential Benefits of the Proposed Research to Subjects and Others: There are no known benefits for the assessment study participants. It is possible that Veterans may benefit from clinical referrals received following

the clinical research assessment. In general, Veterans exposed to chronic and potentially-traumatic stress may benefit from the findings of this longitudinal project. Specifically, findings from the proposed project will inform efforts in the prevention of functional impairment in individuals at increased risk for developing symptoms from occupational exposure to chronic and potentially-traumatic stress. The anticipated risks of this project are considered reasonable given that this project will expand our knowledge of the effects of potentially-traumatic events, stress, and coping on Veterans and potentially lead to advances in the prevention and treatment of functional difficulties encountered during the readjustment process post-warzone.

4. Importance of the Knowledge to be Gained: The proposed project results may represent important advances in the study of functional recovery and impairment related to commonly-occurring disorders in OEF/OIF/OND Veterans, such as PTSD, depression, TBI, chronic pain, and substance-use disorders. Despite important epidemiological work in this area, relatively little is known about the specific biopsychosocial factors, including clinically relevant and modifiable treatment targets, that predict risk and resilience to these disorders in trauma-exposed populations. This programmatic line of research will help to elucidate those factors. Longitudinal examination of individuals at increased risk psychopathology based on varying levels of trauma exposure is essential for advancing our understanding of coping and recovery. This study will contribute to our overall understanding of the long-term psychological impact of combat exposure and empirically inform treatment development.

5. Data and Safety Monitoring Plan.

Due to the sensitive nature of the information collected during the observational study and the fact that clinical referrals may be made for a number of participants, we have established a DSMP. Given our team's expertise with the behavioral health of Veterans, we have well-established mechanisms for ensuring safety and confidentiality of referrals that have been in place during Phases I and II and will continue in Phase III. A final measure of governance designed to protect the participants in this project is the following DSMP.

The DSMP will consist of examination of the accruing study data for indications that participating Veterans are being appropriately referred for treatment when necessary. The PI and doctoral-level staff will provide ongoing supervision through weekly Diagnostic Review Groups (DRG), which will include discussion of referral information for each Veteran who is identified as having mental health difficulties. In addition, self-report data will be reviewed by the PI or her staff. Specifically, each time a participant completes the PHQ-9, item 9 (suicidality) will be visually scanned to make sure that participants are not endorsing suicidal intent. Any participants who are identified as at risk for suicidality (i.e., endorse "Several days" or "More than half the days" or "nearly every day" on PHQ-9 item #9 asking how often in the last two weeks the Veteran was thinking s/he would be better or dead or was wanting to hurt him/herself in some way) will be contacted by the PI or a trained clinician to conduct a clinical risk assessment, safety plan (if necessary), and appropriate clinical referral. Additionally, each time the participant completes the Treatment Involvement Form (TIF), it will be reviewed for serious adverse events occurring during the study period by the PI or trained study staff. The PI has the responsibility of reporting adverse events to the IRB, in accordance with federal regulations. If a participant is hospitalized in response to a crisis, determination as to continuation in the study will be handled on a case-by-case basis. Veterans who feel that participation in the study is overwhelming can certainly discontinue. Veterans will also be given the option of skipping an assessment point versus discontinuing. In many cases, it may be beneficial for the Veteran to continue, for example: 1) Although not a substitute for good clinical care, Project SERVE: FX can serve as an "extra set of eyes" to monitor how Veterans are doing over time; and 2) study discontinuation may feel penalizing for Veterans who have reported suicidality, when such reporting should be encouraged. Additionally, understanding suicidality over time is a crucial area of scientific research that has benefit for our understanding of the adjustment process following deployments, and for developing prevention programs for both Veterans and society at large.

Inclusion of Women, Minorities, and Children

1. Inclusion of Women. Both male and female Veterans who meet inclusion criteria will be recruited for participation in this study. We expect that the gender distribution in the proposed study sample will be similar to that in deployed samples. In SERVE FX-Phase I, we successfully oversampled women at the level of 33%, and 25% at Phase II. As women constitute 18.61% of recent Veterans residing in Texas, we will continue to

oversample to achieve 30% in Phase III. In order to maximize recruitment of women, we will actively recruit women through targeted advertisements and outreach efforts to women's groups within the VA and local Veteran's Service Organizations.

2. Inclusion of Minorities. We expect that completed response rates among minority participants will be similar to the breakdown of minorities in the armed forces residing in Texas (11.6% African-American and 16.4% Latino). We plan to collect data from all participants on their ethnic and racial self-identification. As with our efforts to maximize recruitment of women, we will actively recruit minority participants within Veterans, including outreach meetings with minority Veterans organizations (possibly outside the VA), where available.

3. Inclusion of Children. Adults ages 18 and older will be included in the current study.

COMPLETED PHASES

Phase I

A total of 309 VA-service-seeking returning OEF/OIF/OND Veterans were evaluated over a one-year period in Phase I. All data collection was completed in June 2014, and data was moved to the SERVE Data Repository on November 23, 2021. Primary activities for this study phase are no longer active, and any remaining biological samples have been destroyed.

Specific Aims

The specific aims of Phase I include: 1) examining the relationship between level of exposure to stressors (pre-deployment, deployment-related, and post-deployment) and functioning over time; 2) examining whether potentially malleable resilience factors predict higher levels of functioning in returning Veterans over time; 3) examining whether psychopathology predicts lower levels of functioning in returning Veterans over time; 4) testing the theoretical model that psychopathology partially mediates the effects of stress, social support, coping, and neurocognition on functioning over time; 5) examining whether changes in the use of healthy coping strategies, social support, post-deployment stress, and psychopathology predict changes in functioning over time; and 6) exploring whether stress, social support, coping, neurocognition, and psychopathology have differential effects on specific aspects of functioning (e.g., occupational, family, social, and physical functioning) over time.

Study Methods

This study will investigate the course of functioning over time among returning OEF/OIF/OND Veterans enrolled at CTVHCS. The primary outcome measures will assess multiple domains of functioning, including: 1) occupational functioning; 2) social relationships; 3) family functioning; 4) physical functioning; and 5) quality of life. Hypothesized predictors of functioning include: 1) level of exposure to deployment-related stressors, including potentially traumatic events (PTEs) and head injuries/traumatic brain injury (TBI); 2) level of pre-deployment stress and trauma exposure; 3) level of exposure to post-deployment stress and trauma, including “everyday” stressors; 4) modifiable psychological factors including coping, emotion regulation, self-compassion, attributional style, psychological flexibility, and mindfulness; 5) perceived social support; 6) psychopathology including PTSD and depression; 7) substance misuse; 8) physical health symptoms including chronic pain; and 9) exposure to morally injurious events. Hair samples will be collected for biochemical validation of drug use. Saliva samples will also be collected (on an optional basis) to examine genetic contributions.

Procedures

Phase I assessments occur at 0 (baseline), 4-, 8-, and 12-month time points. Veterans will complete an in-person baseline assessment lasting approximately 4-6 hours and a one-year follow-up face-to-face assessment lasting approximately 3-4 hours. All face-to-face assessments will be conducted in private rooms with a white noise machine so that interviews cannot be overheard, although participants may sit in a waiting room to complete their questionnaires (any questions that arise will be answered in a private area). The baseline and annual assessments include clinical assessments, self-report questionnaires, and a hair sample (for biochemical validation of drug use report). Veterans are required to provide a hair sample; thus, Veterans who decline to provide a hair sample decline to participate in the study.

Validity Checks

Self-report of substance use will be verified via analysis of hair samples gathered at BL and annual assessment. Although only 10% of samples will be analyzed, this sampling has been shown to increase accuracy of self-reported substance use (Marlatt & Gordon, 1985). Hair samples will be collected as per standard procedures recommended, and kits provided, by Omega Laboratories, Inc. Participants are given the option of providing a sample of head hair or from another part of the body (underarm, arm, leg, pubic). In the case of pubic hair, participants are instructed in how to take the hair sample and do this themselves in the bathroom. Hair (amount approximately the width of a pencil) is cut as closely as possible to the root and laid in a piece of tin foil (root in one direction), which is folded. Hair samples are then placed in a small sealed envelope, which is placed in a larger sealed envelope with associated paperwork marked with a code number only. A total of 10% of the samples will be shipped to Omega Laboratories, Inc. for testing. Hair samples are stored with other coded data in locked file cabinets until testing. Hair samples will be disposed/destroyed after testing.

Phase I Assessment Instruments. [DATA COLLECTION COMPLETED]

Measures/ Proposed Indicators	Purpose	Assessment Time Point			Description/Rationale
		BL	4/8m	12m	
Telephone Screen	E				Assesses inclusion/exclusion criteria.
Contact Information	Contact	✓	✓	✓	Collected to verify Veteran status in CPRS, scheduling, send appointment confirmation letter, contact for follow-up, etc.
Demographic Questionnaire & Military History Form	Demographic, PV	✓		✓	Assesses basic demographic and Veterans-specific characteristics (e.g., years of education, years of military service, family history of military service). Readministered at annual to assess changeable demographics (e.g. marital status, employment).
Medical History Form		✓		✓	Form created for the current study. Medical history will be evaluated with respect to participant health and family history.
Treatment Involvement Form	CV	✓	✓	✓	Form created for the current study that will be used to assess treatment involvement during the prior 4 months, including medical, psychiatric and psychological treatment, as well as supportive interventions (e.g. Alcoholics Anonymous, Narcotics Anonymous). Duration of untreated symptoms will be assessed.
Mini International Neuropsychiatric Interview (MINI) - Psychosis modules	E	✓		✓	Screening Interview for exclusionary criteria (bipolar disorder and psychosis unrelated to PTSD). Assessment of PTSD related to civilian events.
Clinician Administered PTSD Scale (CAPS)	Med, DV	✓		✓	Interview. Will assess current and lifetime PTSD using DSM-IV criteria. Criterion F assesses functional impairment associated with PTSD. Both categorical diagnoses and symptom severity ratings will be obtained. The CAPS format allows the interviewer to link PTSD symptoms to specific Criterion A events (i.e., a traumatic event that includes the experience of fear, helplessness or horror) and separately assesses for Criterion A1 (a potentially-traumatic event) and A2. Scoring according to criteria established by Weathers et al. (1994) has excellent retest and inter-rater reliability, and high sensitivity and specificity for PTSD diagnosis.
Structured Clinical Interview for DSM-IV (SCID)	Med, DV	✓		✓	Interview. Widely used. Will assess depression, generalized anxiety disorder, alcohol and drug use.
Wide Range Achievement Test 4th Edition - Word Reading Subtest (WRAT4)	CV, PV	✓			The WRAT4 word reading subtest (Wilkinson and Robertson, 2007) is a brief (2 minutes) test that provides an estimate of native intellectual potential that is considered to be unaffected by the onset of mental health problems. This will allow a measure of pre-deployment/pre-morbid intellectual potential to serve as both a predictor and as a covariate in analyses of neurocognitive performance, given previous findings of lower pre-military intellectual functioning among individuals diagnosed with PTSD (Kremen, et al., 2007; McNally & Shin, 1995; Vasterling, et al., 1997).
Neuropsych-ological screening	PV	✓		✓	A brief (35 minutes) neuropsychological assessment will be conducted, from which a composite neuropsychological functioning index will be computed. The influence of cognitive functioning on functional outcomes among returning Veterans is not fully understood. Whether influenced by combat exposure, TBI, mental health problems, or the complex interactions among them, impaired cognitive processing may impact risk, recovery, or lead to greater chronicity of functional impairment. Domains include: 1) basic processing speed and attentional and memory processes frequently observed among individuals with mild TBI, as well as psychiatric conditions including PTSD (Brewin, et al., 2007), substance abuse/dependence, and sleep disturbance; 2) working memory, which exhibits a robust relationship with a range of functional outcomes in psychiatric populations (Green, 1996) and may serve as a protective factor against development of PTSD (Parslow & Jorm, 2007); and 3) executive functioning,

					which is associated with impulsivity and PTSD (e.g., Vasterling, et al, 1998; Gilbertson et al., 2006). Domains will be assessed as follows: · Processing speed - Digit Symbol Coding (WAIS-IV), Trail Making Test A · Attention - Digits Forward and Backward (WAIS-IV) · Auditory working memory - Digits Forward and Backward (WAIS-IV) · Auditory learning and memory - California Verbal Learning Test 2nd Ed. (CVLT) · Executive functioning – Trail Making Test B, Stroop test The neuropsychological assessment will be re-administered at the annual assessment in order to assess changes in cognitive functioning that may have occurred during the past year.
TBI Assessment Interview	E, PV	✓		✓	This clinician-administered structured interview developed by Vasterling (2008) assesses the number, recency, type of injury, and clinical sequelae associated with traumatic brain injury during deployment. Total number of lifetime head injuries leading to any symptoms will also be assessed. TBI will be assessed at baseline for lifetime history and then re-assessed at the annual interview for any new TBIs that may have occurred during the past year.
Traumatic Life Events Questionnaire (TLEQ)	PV	✓		✓	23 items (Kubany et al., 2000); assesses frequency of exposure to 22 potentially traumatic events encountered outside of military service, resulting in a continuous trauma exposure score. The psychometric properties were carefully established in 5 studies, including a sample of combat Veterans (Kubany et al., 2000).
Deployment Risk and Resilience Inventory (DRRI)	PV	✓		✓	The DRRI (King, King, and Vogt, 2003) is a collection of 13 individual scales assessing pre-deployment, deployment, and post-deployment risk and resilience factors. The DRRI was recently validated for use with OIF Veterans (Vogt et al., 2008). The full DRRI will be readministered at the annual interview if participants have been deployed again. In addition, the social support scale of the DRRI will be re-administered to all participants at Annual 1 in order to obtain an ongoing assessment of social support across time.
RAND Peritraumatic Dissociative Experiences Q.	PV	✓		✓	8 items. Assesses dissociative experiences at the time of a military PTE. Demonstrated good retest reliability (r=.85), internal consistency (α = .83) and construct validity, and correlated moderately with PTSD symptomatology (Marshall et al., 2002).
Posttraumatic growth Inventory	PV	✓		✓	21 items (Tedeschi & Calhoun, 2005); factors include new possibilities, relating to others, personal strength, spiritual change and appreciation of life.
Full Combat Experiences Scale	PV	✓			34 items. Newly developed and adapted from the DRRI to assess experiences and trauma exposure in land combat situations such as OEF/OIF (Hoge et al., 2004). Will be re-administered if re-deployed.
PTSD Checklist-5 (PCL-5) Military and Civilian	Med	✓	✓	✓	20 items. Measures symptoms of PTSD during the previous month. Demonstrates high sensitivity and specificity for a CAPS diagnosis of PTSD. Prior research demonstrates the value of including both self-report and clinical interview assessment of PTSD (cf. National Vietnam Veteran Readjustment Study; Kulka et al., 1988).
Schedule of Recent Exper-iences (SRE)	PV	✓	✓	✓	42 items. The SRE (Holmes & Rahe, 1967) will be used to assess exposure to common, “everyday” stressful life events (e.g., job loss, relationship difficulties, illness or death of a loved one).
Beck Depression Inventory-II (BDI-II)	Med	✓	✓	✓	21 items; The BDI-II (Beck, Steer, Ball, & Ranieri,1996) is a widely-used measure of depressive symptoms with high internal consistency (Beck, Steer, Ball & Ranieri, 1996) and test-retest reliability (Beck, Steer, & Brown, 1996).
Depression, Anxiety, Stress Scales	Med	✓		✓	21 items; 3 empirically distinct subscales: depression, anxiety, and general stress. Reliable and valid measure of these constructs, and discriminates between anxiety and depression better than other commonly used indices (Antony et al., 1998;

					Brown et al., 1997; Lovibond & Lovibond, 1995)
Columbia Suicide Scale	DV	✓		✓	The Columbia Suicide Scale (Posner et al., 2008) is a state-of-the-art suicide assessment for individuals perceived to be at high risk for suicidality.
Daily Drinking Quest. Revised (DDQ-R)	Med	✓	✓	✓	Yields typical frequency (average number of drinking days per week), typical quantity (number of drinks/drinking day), week sum (total number of drinks during an average week). Binge drinking and tolerance questions added.
Rutgers Alcohol Problem Index (RAPI)	Med	✓		✓	23-items; measures the frequency of physical (e.g., had withdrawal symptoms, passed out or fainted suddenly), psychological (e.g., noticed a change in your personality, felt that you had a problem with alcohol), and social (e.g., caused shame or embarrassment to someone, had a fight, argument, or bad feelings with a friend) consequences experienced during the past three months (White & Labouvie, 1989). Internal reliability for the 23-item RAPI is excellent (α= .94; White & Labouvie, 1989).
Drug Abuse Screening Test (DAST)	Med	✓		✓	20-items to quantify drug misuse. Good internal consistency (alpha = 0.92) and concurrent validity with frequency of drug use over 12-months (Skinner, 1982). Moderately correlated with denial and social desirability. 92% of individuals with drug abuse scored greater than 10.
Fagerstrom Test for Nicotine De- pendence (FTND)	DV, Med	✓	✓	✓	6 items that quantify nicotine dependence that exhibits satisfactory internal consistency (α = .61), as well as convergent validity with biochemical indices of heaviness of smoking (Heatherton et al., 1991).
Brief COPE	PV	✓		✓	The widely-used Brief COPE assesses a range of behavioral and cognitive coping strategies (Carver, et al., 1989).
Acceptance and Action Questionnaire (AAQ-II)	PV	✓	✓	✓	10 items; The AAQ-II (Hayes, Bissett, et al, 2004) assesses acceptance, experiential avoidance (attempting to alter the form or frequency of unwanted internal experiences), and taking action despite experiencing unwanted private events. Lower scores indicate greater levels of experiential avoidance, whereas higher scores indicate greater experiential acceptance and willingness. The AAQ-II exhibits a single factor structure, good internal consistency (mean α = .83 across multiple samples) and test-retest reliability (α = .80 at 3 months, .78 at one year), and convergent associations with symptoms of depression (r = -.71), anxiety (r = -.58), and global distress (r = -.65).
Distress Tolerance Scale (DTS) – Emotional and Physical Distress Scales	PV	✓		✓	16 items (Simons & Gaher, 2005) assessing the extent to which participants can tolerate physical (6 items; e.g., “I’ll take fairly extreme measures to stop physical discomfort or pain”) and emotional (10 items; e.g., “I usually follow through with tasks that are emotionally upsetting”) distress. The ability to tolerate distress may explain why a disorder develops. For example, if one is low on distress tolerance, this may increase risk for reliance on other maladaptive coping strategies, particularly substance misuse.
Brief Resilience Scale	PV	✓		✓	6-item scale measuring resilience (Smith et al., 2008); ability to bounce back or recover from stress. Significantly correlated with 25-item Connor Davidson Resilience Scale.
World Health Organization Disability Assessment Schedule II (WHODAS II)	DV	✓	✓	✓	36 item self-report version assessing functional disability across 7 domains (understanding and communicating, getting around, getting along with people, life activities, work, participation in society, self-care) as well as a total score. The WHODAS-II is becoming widely used in investigations of functional disability with wide-ranging populations and is a primary measure in an ongoing VA/DoD study aimed at developing a measure of functional impairment in active duty service members and Veterans (Marx, PI, Schnurr and Hoge, Co-Investigators).
Inventory of Functional Impairment (IFI)	DV	✓		✓	87 items (Marx et al, 2009). The IFI yields an overall score and 7 subscales: Romantic Relationships with a Spouse or Partner, Family, Work, Friendships and Socializing, Parenting, Education, and Day-to-Day functioning. Higher scores indicate greater functional impairment. Preliminary analyses (n = 170) with Veterans show strong psychometric properties, including strong

					internal consistency (Cronbach's alpha ranging from .76 to .91) and construct validity.
Employment Survey (ES)	DV	✓	✓	✓	12 item self-report version adapted from the measure developed by Glynn and colleagues (Mueser, Glynn, and McGurk, 2006) to assess employment status, number of hours worked, income, reasons for not working or working less than full-time, satisfaction with various aspects of current employment, and stability of employment (number of jobs held, reasons for leaving previous jobs) since discharge from active duty military.
Quality of Life Scale (QLS)	DV	✓	✓	✓	16 items (Burkhardt, et al., 1989) assessing how satisfied people are in regards to 16 areas distinct from health status (mate, physical well-being, relationships with others, social, community, and civic activities, personal development and fulfillment, recreation, and independence). Good internal consistency and (alpha .82 to .92) and high test-retest reliability (r = .78 to .84; Burckhardt et al. 2003). Life satisfaction is a central goal of recovery and rehabilitation, and diminished quality of life may influence suicidality and other key outcomes.
Strengths and Difficulties Questionnaire (SDQ)	DV	✓		✓	25 items; Administered only to participants with one or more children living at home. Measures emotional and behavioral disturbance in children aged 4-17 (Goodman, 1997). Consists of 5 5-item subscales: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and pro-social behavior. First 4 scales sum to yield a total difficulties score. Strong psychometric properties (Muris et al., 2004), concurrent validity (i.e., highly correlated with CBCL; Klasen et al., 2000), good convergent validity with structured interviews (Goodman & Scott, 1999), and divergent validity (i.e., distinguishing psychiatric and community samples; Klasen et al., 2000). The proposed approach of using the CBCL annually and the SDQ at each time point should provide a thorough assessment of child psychopathology and functional dimensions over time.
NEO Five-Factor Inventory (NEO-FFI)	PV	✓		✓	60 items (Costa & McCrae, 1989); shortened version of the NEO PI-R. Reliable and valid measure of the five-factor model of adult personality. Good internal consistency for the five subscales (range .74 - .89).
Pain Disability Index		✓		✓	7-item instrument for measuring the impact that pain has on the ability of a person to participate in essential life activities.
Marlow-Crowne Social Desirability Scale	QA	✓		✓	10 item abbreviated version of the original Social Desirability Scale (Crowne & Marlowe, 1960) assessing the extent to which responses are influenced by social desirability. Measures the same construct as the full scale and has good internal consistency (Fraboni & Cooper, 1989; Strahan & Gerbasi, 1973).
Hair Sample	QA	✓		✓	To verify self-report of drug use, hair samples will be gathered at BL and annual assessments. The hair sample is a required component of the study. Participants will be told that hair may be tested for drug use; however, only 10% of samples will be analyzed for use of nicotine, cocaine, marijuana, opiates, amphetamines, phencyclidine, hydrocodone, hydromorphone, and oxycodone.
Saliva sample	PV, Med	✓			DNA and other products will be extracted from saliva samples. Provision of saliva sample is optional.
Monetary Choice Questionnaire (MCQ)	PV			✓	27-item instrument (Kirby, Petry, & Bickel, 1999) used to estimate the rate at which respondents discount the value of future rewards. Higher rates of discounting on this measure have been associated with both self-reported impulsivity and real-world engagement in impulsive behaviors.
BL = Baseline; BI-ANN = Bi-Annual; ANL = Annually; E = Eligibility; DV = Dependent/Outcome Variable; PV = Predictor Variable; Med = Mediator; CV = Covariate; QA = Quality Assurance/Validity Check					

Biological Markers

In Phase I, subjects will donate DNA/RNA/Saliva for genetic and research studies. No clinically validated tests will be performed. The genetics/biomarker component of the protocol will be supervised by Dr. Keith Young (CTVHCS Neuropsychiatry Research Program, Building 205, 3R05 and 3R08) and Dr. Rakeshwar Guleria (CoE Biomarkers and Genetics Core) experts in this area, in collaboration with the PI. See Appendix for Safety Survey. At the BL assessment, participants will be given the option of consenting to all study procedures or all procedures excluding the saliva/blood sample (depending on the phase) and genetic research.

For those who consent to that aspect of the study, participants will donate saliva by spitting into a coded Oragen™ tube at the assessment site. Staff will be trained to avert their eyes when participants are spitting into the test tube to reduce potential embarrassment. The saliva samples will be stored at room temperature in a locked - cabinet present inside a locked office (Building 93,1A-137) until transported at room temperature by team members to Dr. Young's lab in Temple or Waco Building 93 (rooms 2A 116, 2A 117), where the samples will be stored until DNA extraction and testing. Phase I genotyping will be performed at CTVHCS Temple Building 205 and Waco Building 93. According to the work load, the genotyping work will be divided between the two labs (Drs. Guleria & Young).

Aims and Hypotheses

Specific Aim 1. Identify whether a dose-response relationship exists between level of exposure to stressors and subsequent level of functioning.

Hypothesis 1a. Greater exposure to pre-deployment stress and trauma will predict lower levels of functioning concurrently and over time.

Hypothesis 1b. Greater exposure to deployment-related stress and trauma will predict lower levels of functioning concurrently and over time.

Hypothesis 1c. Greater exposure to post-deployment stressors will predict lower levels of functioning concurrently and over time.

Specific Aim 2. Examine whether potentially malleable resilience factors predict higher levels of functioning in returning OEF/OIF Veterans.

Hypothesis 2a. Greater use of healthy coping strategies (i.e., acceptance and active coping) will predict higher levels of functioning concurrently and over time.

Hypothesis 2b. Greater levels of social support will predict higher levels of functioning concurrently and over time.

Hypothesis 2c. Higher levels of neurocognition will predict higher levels of functioning concurrently and over time.

Specific Aim 3. Examine whether psychopathology predicts lower levels of functioning.

Hypothesis 3a. Greater PTSD-Depression symptoms will predict lower levels of functioning concurrently and over time.

Hypothesis 3b. Greater AUD symptoms will predict lower levels of functioning concurrently and over time.

Specific Aim 4. Test the theoretical model that psychopathology partially mediates the effects of stress, social support, coping, and neurocognition on functioning concurrently and over time.

Hypothesis 4a. The hypothesized model (Figure 1) in which PTSD-Depression and AUD symptoms fully mediate the effects of pre-deployment stress, post-deployment stress, and active coping on functioning and partially mediate the effects of neurocognition, deployment stress, acceptance, and social support on functioning will show significantly better fit to the data compared to any of the following alternative models: an independent main effects model, a fully mediated model, or a full partial mediation model.

Hypothesis 4b. PTSD-Depression symptoms will fully-mediate the effects of active coping, pre-deployment stress, and post-deployment stress on functioning and will partially-mediate the effects of deployment stress, acceptance, and social support on functioning.

Hypothesis 4c. AUD symptoms will partially mediate the effects of neurocognition on functioning.

Specific Aim 5. Examine the influence of changes in coping, social support, post-deployment stress, and psychopathology on changes in functioning over time.

Hypothesis 5a. Sustained use of healthy coping strategies (i.e., acceptance and active coping), or increases in healthy coping strategies, will predict higher levels of functioning over time.

Hypothesis 5b. Sustained higher levels of social support, or increases in social support, will predict lower levels of functioning over time.

Hypothesis 5c. Sustained higher levels of PTSD-Depression and AUD symptoms, or increases in PTSD-Depression and AUD symptoms, will predict lower levels of functioning over time.

Specific Aim 6. Explore whether stress, social support, coping, neurocognition, or psychopathology have differential effects on different facets of functioning (e.g., occupational, family, social, and physical functioning).

Hypothesis 6a. Neurocognition will be most strongly related to occupational functioning.

Hypothesis 6b. PTSD- Depression and AUD symptoms will be most strongly related to family functioning.

Planned Analyses

The purpose of the longitudinal design is to better understand the functional recovery of returning OEF/OIF/OND Veterans over time and to identify potentially-malleable risk and resilience factors associated with functioning. The study design is based on a measurement model that collects predetermined, repeated assessments every 4 months over a one-year period beginning with a baseline evaluation. Other than these measurement contacts, no experimental manipulations are planned, although participants may participate in treatment programs or be appropriately referred to treatment programs or other research studies during the course of this study. Treatment will be tracked using the *Treatment Involvement Form*, as this may influence course and outcome.

This study will provide a rich dataset from which we will be able to conduct numerous analyses as proposed here, as well as those that are exploratory in nature in order to maximize the impact of the proposed research. Various statistical software programs will be utilized to accomplish the study aims, as appropriate (e.g., SPSS, SAS, mPLUS, AMOS). VA software will be used. Licenses are supported by the VISN 17 CoE as well as local IT (as indicated in original grant budgets). We will also use access software through the secure VA VINCI system (e.g., SPSS). VINCI requires documentation of IRB approval before analyzing data on the VINCI system. With respect to the proposed primary hypotheses, structural equation modeling (SEM; Jöreskog, 1970, 1993) will be the statistical approach employed to examine the relationships among the variables. SEM is essentially a combination of factor analysis and path analysis (Kline, 2005). This type of statistical analysis was chosen to test the hypotheses because it has several advantages over traditional statistical techniques (e.g., multiple regression). For example, SEM corrects for measurement error, which, in turn, improves statistical power. SEM also allows both latent and observed variables to be evaluated within the same model, and it is an especially effective analytical procedure for studying complex relationships among many variables. However, the two most important advantages of SEM over other traditional statistical analyses are: 1) SEM enables users to conduct tests of entire models in a single analysis; and 2) *SEM allows for entire models to be tested against other competing models* (Kline, 2005). Given that the one of the primary aims of the current proposal is to provide a direct test of our hypothesized model of functional outcomes in returning Veterans (Specific Aim 4, Figure 1), SEM appears to be the most appropriate type of statistical analysis to employ as it will enable us to: 1) examine the overall fit of our hypothesized model to the data; and 2) statistically compare our hypothesized model to other competing models (e.g., a main effects only model).

A two-step modeling approach will be used to test each aim (Anderson & Gerbing, 1988; Kline, 2005). First, a confirmatory-factor analysis (CFA) measurement model will be computed to determine the degree to which the underlying latent constructs are statistically accounted for by their corresponding hypothesized observed variables. The hypothesized measurement model that we have proposed (see Table 3) is based on a combination of findings from our pilot data, previous research, and current theory and represents our best estimate of what the measurement model will be. If the hypothesized measurement models are supported by CFA, the structural relationships among the latent variables will be tested in the second step. If the initial hypothesized measurement model is rejected, the suggestions for model respecification offered by Kline (2005, pp 165 - 208) will be followed until an acceptable measurement model is found. Once an acceptable measurement model has been identified, the fit of the hypothesized structural model will be assessed with multiple goodness-of-fit indices, including the Root

Mean Square Error of Approximation (RMSEA), Standardized Root Mean Square Residual (SRMR), Comparative Fit Index (CFI), Normed Fit Index (NFI), and the Akaike Information Criterion (AIC). The hypothesized models will also be compared with other competing models using either the chi-square difference test for hierarchically-related models or the AIC for models that are not nested. Alpha will be set conservatively ($\alpha = .01$) for all analyses in order to minimize the probability of Type I error.

Specific Aims 1, 2, and 3, which hypothesize that stress, coping, neurocognition, and psychopathology will predict functioning in returning Veterans concurrently and over time will be initially tested within the context of an independent main effects model in which each of the hypothesized factors will be simultaneously regressed onto the functioning factor while accounting for the covariances among the predictors. Hypotheses will be considered to be rejected if the regression coefficients are either non-significant (i.e., > .01) or are in the opposite direction of our predictions. To test these hypotheses over time, an identical model will be constructed using level of functioning at 1-year follow-up as the primary outcome variable while co-varying for level of functioning at baseline. In addition, a Cross-Lag Panel design (Ecob, 1987; Farrell, 1994; King et al., 2000; Williams & Peodsakoff, 1989) will be employed to examine the autoregressive associations (i.e., the value of interest is assumed to be a function of the previous values plus a random component) and cross-lag associations between the predictors and functional impairment across time. For example, Figure 3 illustrates the structural aspects of a Cross-Lag Panel design based on two waves of assessments of post-deployment stress and functioning. Within this model, we will test the effects of post-deployment stressors from the prior time period on functioning in the subsequent time period, while accounting for the effects of functioning from the prior time period. Likewise we will test the effects of functioning from the prior time period on post-deployment stressors in the subsequent time period, while accounting for the effects of post-deployment stressors from the prior time period. The Cross-Lag Panel design will enable us to examine the possibility that there may be reciprocal relationships that occur over time involving the predictors of interest and functional impairment.

Specific Aim 4, which hypothesizes that psychopathology partially mediates the effects of stress, coping, and neurocognition on level of functioning in returning Veterans concurrently and over time, will be achieved by comparing the hypothesized model with several competing models, which include an independent main effects model, a fully-mediated model, and a complete partial mediation model. The overall fit of the hypothesized model will initially be assessed with multiple goodness-of-fit indices including RMSEA, SRMR, CFI, and NFI. Next, chi-square difference tests and AIC values will be used to compare the hypothesized model against the competing models. It is predicted that the hypothesized model will show good overall fit to the model (e.g., RMSEA < .05, CFI > .95) and that the hypothesized model will fit the data significantly better than the competing models. The regression coefficients for the hypothesized indirect pathways will also be examined for statistical significance (i.e., $p < .01$). The hypothesized model will also be tested over time. Specifically, level of functioning at year 1 follow-up will be regressed on to PTSD-Depression and AUD symptoms at 8-months, which, in turn, will be regressed on to ongoing stress, social support, acceptance, and active coping at 4 months and deployment stress, pre-deployment stress, and neurocognitive functioning at baseline. By testing the hypothesized model in this manner, we will be able to reduce the possibility that response bias during a particular assessment accounts for the hypothesized mediation results. Testing the model in this manner will also take into account the hypothesized causal ordering (i.e., stress, coping, social support, and neurocognition predict psychopathology, which, in turn, predicts functioning).

Specific Aim 5, which hypothesizes that changes in the use of healthy coping strategies, social support, post-deployment stress, and psychopathology will predict changes in functioning over time, will be achieved by using latent growth curve models (LGMs) to test hypotheses 5a – 5c. LGMs characterize the trends in growth and change functions for individuals over time (Figure 4). This analytic method assumes that individuals change at different rates and that underlying latent variables determine the overall level and shape of individual trajectories (Lawrence & Hancock, 1998; McArdle, 1998). LGMs can be fit using structural equation models, and are capable of describing the behavior or symptom status of individuals in terms of their initial measurement levels and by their trajectories of change from those levels. LGM techniques can also analyze variability in initial levels and trajectories across persons, while providing means to test the contribution of other predictor variables and constructs as determinants of the different levels and trajectories. LGM techniques offer great flexibility for modeling individual growth

trajectories and their effects on outcomes, while accounting for multiple covariates. LGM will be used to examine the degree to which changes in healthy coping, post-deployment stress, social support, and psychopathology predict changes in functioning over time. It is hypothesized that sustained use of healthy coping strategies and social support, or increases in healthy coping or social support, will predict higher levels of functioning over time, whereas sustained high levels of, or increasing levels of, post-deployment stress and psychopathology are hypothesized to predict lower levels of functioning over time.

Specific Aim 6, which proposes to explore whether the proposed risk and resilience factors have differential effects on specific aspects of functioning, will be achieved by testing the hypothesized model (or an alternative model found to provide the best overall fit to the data in relation to global functioning) in relation to each specific aspect of functioning at both baseline and at 1-year follow-up. That is, separate tests of the hypothesized model will be conducted for each specific aspect of functioning (e.g., occupational, family, social, physical). We hypothesize that neurocognition will be most strongly related to occupational functioning, whereas PTSD-Depression and AUD symptoms will be most strongly related to family functioning.

Power and Sample Size Considerations. SEM will be used as the analytic strategy for testing all hypotheses. MacCallum, Browne, & Sugawara (1996) describe a method for estimating the required sample size to achieve a given power estimate at specified degrees of freedom (*df*) for both close fitting (i.e., RMSEA = .05) and not close fitting (i.e., RMSEA = .08) models. These RMSEA values are chosen as points of estimate, since values below .08 are shown to indicate an acceptable but not necessarily close model fit to the data, and values below .05 are shown to indicate an acceptable and close fit to the data (Stieger, 1990; Browne & Cudek, 1993; Hu & Bentler, 1993). The method described by MacCallum and colleagues can also be employed to provide a power estimate for close and not-close fitting models. For the purposes of the current proposal, the software developed by Preacher and Coffman (2006) to calculate power from *df*, RMSEA, *N*, and alpha using the method described by MacCallum et al. (1996) were used to conduct a power analysis for the proposed study. For SEM equations, *df* are equal to the number of observations [i.e., observed variables * (observed variables + 1) / 2] minus the number of free parameters in the model. Due to the complexity of the proposed models, the *df* for our proposed models are high and range from 137 to 922 *df*, with differences among the models being largely accounted for by differences in model complexity and the number of observed variables included in each model. Power was estimated conservatively by using the model with fewest degrees of freedom to estimate power, as power increases with *df* (MacCallum et al., 1996). Setting alpha conservatively at .01, a final sample size of 300 participants (from 400 enrolled) would provide a power estimate of .997 for a close-fitting model with 137 *df* and .988 for a not-close fitting model with 137 *df*. In addition, in the event that there is even greater than expected attrition (i.e., attrition rates are greater than 20%), the proposed study would still remain well powered even if as much as 35% of the sample were lost to attrition. For example, leaving alpha set conservatively at .01, a sample size of 195 participants (65% of the original sample size) would still provide a power estimate of .936 for a close-fitting model with 137 *df* and .822 for a not-close fitting model with 137 *df*. These results are also consistent with Kline's (2005) rule-of-thumb that sample sizes of 200 or greater are generally well-powered for SEM analyses. Thus, by recruiting an initial sample of 400 participants, we will be well-positioned to retain a sufficiently large sample to remain well-powered throughout the duration of the study, even in the event that attrition rates are higher than expected.

Phase II

Five hundred and one OEF/OIF/OND Veterans were evaluated over a two-year period in Phase II. All data collection for this phase was completed in in June 2018, and data was moved to the SERVE Data Repository November 23, 2021. Primary activities for this study phase are no longer active, and any remaining biological samples have been destroyed.

Specific Aims

The specific aims of Phase II are to identify clinically-relevant, modifiable psychosocial factors that: 1) prospectively predict improvements in long-term functioning; (2) predict membership in latent class trajectories of functioning; and (3) predict transitions between trajectories of functioning.

Study Methods

This study will investigate the course of functioning over time among returning OEF/OIF/OND Veterans enrolled at CTVHCS. The primary outcome measures will assess multiple domains of functioning, including: 1) occupational functioning; 2) social relationships; 3) family functioning; 4) physical functioning; and 5) quality of life. Hypothesized predictors of functioning include: 1) level of exposure to deployment-related stressors, including potentially traumatic events (PTEs) and head injuries/traumatic brain injury (TBI); 2) level of pre-deployment stress and trauma exposure; 3) level of exposure to post-deployment stress and trauma, including "everyday" stressors; 4) modifiable psychological factors including coping, emotion regulation, self-compassion, attributional style, psychological flexibility, and mindfulness; 5) perceived social support; 6) psychopathology including PTSD and depression; 7) substance misuse; 8) physical health symptoms including chronic pain; and 9) exposure to morally injurious events. Hair samples will be collected for biochemical validation of drug use. Saliva/blood samples will also be collected (on an optional basis) to examine genetic contributions.

Procedures

Phase II assessments occur at 0, 8-, 16-, and 24-month time points. Veterans will complete an in-person baseline assessment lasting approximately 4-6 hours, and a two-year follow-up face-to-face assessment lasting approximately 3-4 hours. All face-to-face assessments will be conducted in private rooms with a white noise machine so that interviews cannot be overheard, although participants may sit in a waiting room to complete their questionnaires (any questions that arise will be answered in a private area). The baseline and annual assessments include clinical assessments, self-report questionnaires, and a hair sample (for biochemical validation of drug use report). Veterans are required to provide a hair sample; thus, Veterans who decline to provide a hair sample decline to participate in the study.

Validity Checks

Self-report of substance use will be verified via analysis of hair samples gathered at BL and annual assessment. Although only 10% of samples will be analyzed, this sampling has been shown to increase accuracy of self-reported substance use (Marlatt & Gordon, 1985). Hair samples will be collected as per standard procedures recommended, and kits provided, by Omega Laboratories, Inc. Participants are given the option of providing a sample of head hair or from another part of the body (underarm, arm, leg, pubic). In the case of pubic hair, participants are instructed in how to take the hair sample and do this themselves in the bathroom. Hair (amount approximately the width of a pencil) is cut as closely as possible to the root and laid in a piece of tin foil (root in one direction), which is folded. Hair samples are then placed in a small sealed envelope, which is placed in a larger sealed envelope with associated paperwork marked with a code number only. A total of 10% of the samples will be shipped to Omega Laboratories, Inc. for testing. Hair samples are stored with other coded data in locked file cabinets until testing. Hair samples will be disposed/destroyed after testing.

Phase II Assessment Instruments. [DATA COLLECTION COMPLETED]

Measures/ Proposed Indicators	Purpose	Assessment Time Point			Description/Rationale
		BL	8 & 16mo	24 mo	
Telephone Screen	E				Administered prior to the baseline assessment to determine initial eligibility. Assesses inclusion/exclusion criteria.
Contact Information	Contact	✓	✓	✓	Collected to verify Veteran status in CPRS, scheduling, send appointment confirmation letter, contact for follow-up, etc.
Service Connection (SC-S)	Demographic, PV	✓		✓	Assess service-connected disability.
Demographic Questionnaire & Military History Form (DHMQ)	Demographic, PV	✓		✓	Assesses basic demographic and Veterans-specific characteristics (e.g., years of education, years of military service, family history of military service). Re-administered at annual to assess changeable demographics (e.g. marital status, employment).
Patient Health Questionnaire–15 (PHQ-15)	Med, DV	✓	✓	✓	15-item self-report (Kroenke, Spitzer & Williams, 2002) of somatic symptom clusters including pain (musculoskeletal, headaches), cardiac, gastrointestinal, respiratory, etc. that account for more than 90% of outpatient physical complaints (Kroenke, Arrington & Manglesdorff, 1990). The PHQ-15 had

					strong internal reliability in the initial validation (α=.80) and was associated with functional status and disability (Kroenke et al., 2002).
Treatment Involvement Form (TIF)	CV	✓	✓	✓	Form created for the current study that will be used to assess treatment involvement during the prior interval, including medical, psychiatric and psychological treatment, as well as supportive interventions (e.g. Alcoholics Anonymous, Narcotics Anonymous). Duration of untreated symptoms will be assessed.
Mini International Neuropsychiatric Interview (MINI) - Psychosis modules	E	✓		✓	Screening Interview for exclusionary criteria (manic/hypomanic episode and psychosis unrelated to PTSD). Assessment of PTSD related to civilian events.
Clinician Administered PTSD Scale (CAPS)	Med, DV	✓		✓	Interview. Will assess current and lifetime PTSD using DSM-5 criteria. Criterion F assesses functional impairment associated with PTSD. Both categorical diagnoses and symptom severity ratings will be obtained. The CAPS format allows the interviewer to link PTSD symptoms to specific Criterion A events (i.e., a traumatic event that includes the experience of fear, helplessness or horror) and separately assesses for Criterion A1 (a potentially-traumatic event) and A2. Excellent retest and inter-rater reliability, and high sensitivity and specificity for PTSD diagnosis. Questions will reflect both DSM-IV for continuity across phases and new DSM-5 criteria.
Structured Clinical Interview for DSM-IV (SCID)	Med, DV	✓		✓	Interview. Widely used. Will assess mood disorders and alcohol use disorder. Frequency and quantities of drug use will be assessed. Questions will reflect both DSM-IV for continuity across phases and new DSM-5 criteria.
Wide Range Achievement Test 4th Edition - Word Reading Subtest (WRAT4)	CV, PV	✓			The WRAT4 word reading subtest (Wilkinson and Robertson, 2007) is a brief (2 minute) test that provides an estimate of native intellectual potential that is considered to be unaffected by the onset of mental health problems. This will allow a measure of pre-deployment/pre-morbid intellectual potential to serve as both a predictor and as a covariate in analyses of neurocognitive performance, given previous findings of lower pre-military intellectual functioning among individuals diagnosed with PTSD (Kremen, et al., 2007; McNally & Shin, 1995; Vasterling, et al., 1997).
TBI—Vasterling Assessment Interview	E, PV	✓		✓	This clinician-administered structured interview developed by Vasterling (2008) assesses the number, recency, type of injury, and clinical sequelae associated with traumatic brain injury during deployment. Total number of lifetime head injuries leading to any symptoms will also be assessed. TBI will be assessed at baseline for lifetime history and then re-assessed at the annual interview for any new TBIs that may have occurred during the past year.
Traumatic Life Events Questionnaire (TLEQ-Lite)	PV	✓		✓	23 items (Kubany et al., 2000); assesses frequency of exposure to 22 potentially traumatic events encountered outside of military service, resulting in a continuous trauma exposure score. The psychometric properties were carefully established in 5 studies, including a sample of combat Veterans (Kubany et al., 2000). Modified for this study to no longer assess DSM-IV criteria for PTSD Criterion A2, as this is no longer required in DSM-5.
Deployment Risk and Resilience Inventory (DRRI)	PV	✓	✓	✓	The DRRI (King, King, and Vogt, 2003) is a collection of 13 individual scales assessing pre-deployment, deployment, and post-deployment risk and resilience factors. The DRRI was recently validated for use with OIF Veterans (Vogt et al., 2008). The select scales of the DRRI will be readministered at the annual interview if participants have been deployed again. The social support scale of the DRRI will be administered to all participants at all time points, and the Exposure to Nuclear, Biological, or Chemical Agents- Modified (ENBCA-M) scale will be administered to all participants at 16 months.
Full Combat Experiences Scale (FCES)	PV	✓		✓	25 items. Newly developed and adapted from the DRRI to assess experiences and trauma exposure in land combat situations such as OEF/OIF (Hoge et al., 2004). Will be re-

					administered if re-deployed.
PTSD Checklist-5 (PCL-5) Military and Civilian	Med	✓	✓	✓	21 items. Measures symptoms of PTSD during the previous month. Demonstrates high sensitivity and specificity for a CAPS diagnosis of PTSD. Prior research demonstrates the value of including both self-report and clinical interview assessment of PTSD (cf. National Vietnam Veteran Readjustment Study; Kulka et al., 1988).
Schedule of Recent Experiences (SRE)	PV	✓	✓	✓	42 items. The SRE (Holmes & Rahe, 1967) will be used to assess exposure to common, "everyday" stressful life events (e.g., job loss, relationship difficulties, illness or death of a loved one).
Patient Health Questionnaire-9	Med, DV	✓	✓	✓	9-item measure used for screening, diagnosing, and monitoring depression. It incorporates DSM-IV diagnostic criteria (Question 9 screens for suicidal ideation; Kroenke, Spitzer & Williams, 2001).
Columbia Suicide Scale	DV	✓		✓	The Columbia Suicide Scale (Posner et al., 2008) is a state-of-the-art suicide assessment for individuals perceived to be at high risk for suicidality. Internal consistency ranged from .73 to .95 (Posner et al., 2011).
Alcohol Use Disorders Identification Test (AUDIT)	Med	✓	✓	✓	Administered at every time point to screen for alcohol-use disorders (Saunders, Aasland, Babor, Fuente, & Grant, 1993). 10-item measures adopted by VA as the gold-standard screening for alcohol use disorders in mental health and primary care clinics. Good internal consistency (α=.80 - .94) and test-retest reliability (*r*=.86), and strong concurrent validity with the MAST and CAGE screening measures (Babor et al., 2001).
Drug Abuse Screening Test (DAST-20)	Med	✓		✓	20-items to quantify drug misuse. Good internal consistency (alpha = 0.92) and concurrent validity with frequency of drug use over 12-months (Skinner, 1982). Moderately correlated with denial and social desirability. 92% of individuals with drug abuse scored greater than 10.
Fagerstrom Test for Nicotine De- pendence (FTND)	DV, Med	✓	✓	✓	6 items that quantify nicotine dependence that exhibits satisfactory internal consistency (α = .61), as well as convergent validity with biochemical indices of heaviness of smoking (Heatherton et al., 1991).
Brief COPE (b-COPE)	PV	✓		✓	The 28-item measure is widely-used Brief COPE assesses a range of behavioral and cognitive coping strategies (Carver, et al., 1989).
Acceptance and Action Questionnaire (AAQ-II)	PV	✓		✓	10 items; The AAQ-II (Bond, et al, 2011) assesses acceptance, experiential avoidance (attempting to alter the form or frequency of unwanted internal experiences), and taking action despite experiencing unwanted private events. The AAQ-II exhibits a single factor structure, good internal consistency (mean α = .83 across multiple samples) and test-retest reliability (α = .80 at 3 months, .78 at one year), and convergent associations with symptoms of depression (r = -.71), anxiety (r = -.58), and global distress (r = -.65).
Brief Experiential Avoidance Questionnaire (BEAQ)	PV	✓	✓	✓	15 items; The BEAQ is a single-factor item that assesses the modifiable construct of experiential avoidance (Gamez et al., 2013).
Self-Compassion Scale – Short Form (SCS-SF)	PV	✓	✓	✓	12-item self-report measure of self-compassion, consisting of a total scale score and six subscale scores: self-kindness, self-judgment, common humanity, isolation, mindfulness, and over-identified (Neff, 2003; Raes, Pommier, Neff, & Van Gucht, 2011). The SCS-SF is strongly correlated with the original long form (r=.97) and has the same 6-factor structure with one higher-order factor. Internal consistency was .86 for the whole measure, with subscale alphas ranging from .54 to .75 (Raes et al., 2011).
Attributional Style Questionnaire (ASQ)	PV	✓		✓	This 12-item self-report measure assesses attributions for positive and negative events along three causal dimensions: internal vs. external, stable vs. unstable, and global vs. specific (Peterson, Semmel, von Baeyer, Abramson, Metalsky, & Seligman, 1982). Internal consistency (α=.72-.75) and test-retest reliability (r=.58-.70) are adequate.
Difficulties in Emotion	PV	✓	✓	✓	36-item self-report measure (Gratz & Roemer, 2004) of multiple

Regulation Scale (DERS)					domains of emotion dysregulation. Comprised of 6 scales: nonacceptance of emotional responses, difficulty engaging in goal-directed behavior, difficulty with impulse control, lack of emotional awareness, poor emotion coping strategies, and lack of emotional clarity. Internal consistency (α=.84 to .93) and test-retest reliability (r=.57-.89) were strong (Gratz & Roemer, 2004). Individual subscale consistencies (range from α=.81 to .92) have also been strong (Perez et al., 2012).
Monetary Choice Questionnaire (MCQ)	PV	✓			27-item instrument (Kirby, Petry, & Bickel, 1999) used to estimate the rate at which respondents discount the value of future rewards. Higher rates of discounting on this measure have been associated with both self-reported impulsivity and real-world engagement in impulsive behaviors.
Endorsed and Anticipated Stigma Inventory (EASI)	Med	✓			Three of five 8-item scales that assess a variety of stigma-related beliefs within the broader categories of self- and public stigma will be used (beliefs about mental illness, mental health treatment, treatment seeking). The EASI was developed for use with military and Veteran populations. Evidence is available for the internal consistency reliability of these scales, with alphas ranging from .84 to .93. Scales have strong content validity, convergent and discriminant validity, and discriminative validity. Confirmatory factor analysis results support the proposed five-factor structure (Vogt et al., in press).
World Health Organization Disability Assessment Schedule II (WHODAS 2.0)	DV	✓	✓	✓	36-item self-report assessment of functional disability with total score and 6 domains of functioning: understanding and communicating, mobility, getting along with others, life activities (i.e., work, education, household responsibilities), participation in society, and self-care (Üstün et al., 2010). Both global and specific areas of functioning are crucial in thoroughly understanding functional recovery, as Veterans may function well in one area and have difficulty in another. Moreover, some domains may be affected by contextual factors instead of representing functional capacity (e.g., work functioning in a struggling economy independent of impairment).
Inventory of Psychosocial Functioning (IPF) [Previously named Inventory of Functional Impairment, IFI]	DV	✓	✓ (Brief)	✓	87-item self-report measure (Co-I Marx et al., 2009) of Romantic Relationships with a Spouse/Partner, Family, Work, Friendships and Socializing, Parenting, Education, and Self-Care. The short version has a .90 correlation with the full 80-item instrument (Co-Marx, personal communication). Higher scores indicate greater functional impairment. For the 80-item IPF, preliminary analyses (*n* = 236) with Veterans show strong psychometric properties, including excellent internal consistency (Cronbach's α ranging from .79 to .90) and concurrent validity with other measures of impairment and QoL, as well as PTSD and depressive symptoms (McQuaid et al., 2012). A 7-item brief version will be administered at 8- and 16-month.
Community Integration Questionnaire (CIQ)	DV	✓	✓	✓	This 15-item measure (Willer, Ottenbacher, & Coad, 1994) assesses frequency of participation in and ability to independently complete home, social, and goal-directed activities. The CIQ demonstrates excellent internal consistency (α=.83 to .97) and test-retest reliability (r=.91-.97). Although there is no gold-standard measure of community integration, this measure is recognized by the VA Working Group on Community Integration (Resnik et al., 2012).
Quality of Life Scale (QLS)	DV	✓	✓	✓	16 items (Burkhardt, et al., 1989) assessing how satisfied people are in 16 areas distinct from health status (mate, physical well-being, relationships with others, social, community, and civic activities, personal development and fulfillment, recreation, and independence). Good internal consistency and (alpha .82 to .92) and high test-retest reliability (r = .78 to .84; Burckhardt et al. 2003).
NEO Five-Factor Inventory (NEO-FFI)	PV	✓			60 items (Costa & McCrae, 1989); shortened version of the NEO PI-R. Reliable and valid measure of the five-factor model of adult personality. Good internal consistency for the five subscales (range .74 - .89). New participants only.

Employment Survey (ES)	Demographic, DV	✓	✓	✓	12 item self-report version adapted from the measure developed by Glynnand colleagues (Mueser, Glynn, and McGurk, 2006) to assess employment status, number of hours worked, income, reasons for not working or working less than full-time, satisfaction with various aspects of current employment, and stability of employment (number of jobs held, reasons for leaving previous jobs) since discharge from active duty military.
Health-Promoting Lifestyle Profile II (HPLP-II)	PV	✓		✓	52-item questionnaire that measures frequency of health-promoting behaviors in several domains: physical activity, spiritual growth, health responsibility, interpersonal relations, nutrition, and stress management. The total score (α= .94) and each of the subscales (α= .70-.87) demonstrate good internal consistency.
Interpersonal Needs Questionnaire (INQ)	DV	✓			18-item self-report measure that assess thwarted belongingness and perceived burdensomeness (Van Orden et al., 2012). The INQ has demonstrated good convergent validity, internal consistency and concurrent validity (Van Orden et al., 2012).
Modified Habits Questionnaire 4 (MHQ-4)	DV	✓			4-item questionnaire assessing self-injurious behavior
Nash Moral Injury Events Scale (MIES)	PV		✓	✓	9-item self-report questionnaire developed as a measure of potentially morally injurious events (Nash, Carper, Mills, Au, Goldsmith, & Lizt, 2013). The MIES has excellent internal consistency, both the overall scale and the 2 subscales showed temporal stability, and early research found preliminary support for the construct validity (Nash, et al., 2013).
Moral Injury Questionnaire- Military Version (MIQ-M)	PV		✓	✓	20-item self-report measure for assessing morally injurious experiences or MIEs among military populations (Currier, Holland, Drescher, & Foy, 2013). Research supports the factorial, concurrent, and incremental validity of the MIQ-M for use in both clinical and research contexts (Currier, et al., 2013).
Family Assessment Device 12 (FAD)	PV		✓	✓	12-item self-report questionnaire, widely used as a measure of general family functioning (Epstein, Baldwin, & Bishop, 1983). Measure is noted to have adequate test-retest reliability and cut-off scores which differentiate between clinician –rated healthy and unhealthy families (Miller, Epstein, Bishop, & Keitner, 1985).
Quality of Marriage Index (QMI)	PV		✓	✓	6-item self-report questionnaire used to measure relationship distress (Norton, 1983). The measure was developed based on an empirical analysis of the functioning and construction of marriage quality variables.
State Shame and Guilt Scale (SSGS)	PV		✓	✓	10-item self-report questionnaire used to assess phenomenological aspects of shame and guilt (Marschall, Saftner, & Tangney, 1994).
Gratitude Questionnaire-6 (GQ-6)	PV			✓	6-item self-report measure of trait gratitude. Items are rated on a 7-point scale from 1 = strongly disagree to 7 = strongly agree. (GQ-6; McCullough, Emmons, & Tsang, 2001)
Hair Sample	QA	✓		✓	To verify self-report of drug use, hair samples will be gathered at BL and annual assessments. The hair sample is a required component of the study. Participants will be told that hair may be tested for drug use; however, only 10% of samples will be analyzed for use of nicotine, cocaine, marijuana, opiates, amphetamines, phencyclidine, hydrocodone, hydromorphone, and oxycodone.
Saliva sample	PV, Med	✓		✓	DNA and other products will be extracted from saliva samples. Provision of saliva sample is optional.
Blood sample	PV, Med	✓		✓	DNA and other products will be extracted from blood samples. Provision of blood sample is optional.
BL = Baseline; E = Eligibility; DV = Dependent/Outcome Variable; PV = Predictor Variable; Med = Mediator; CV = Covariate; QA = Quality Assurance/Validity Check					

Biological Markers

Subjects will donate saliva and blood for genetic and biomarker research studies. Both saliva and blood will be collected because some biomarkers are known to be present in both blood and saliva. If we find a biomarker for PTSD symptoms in blood, and it is also in saliva, that would be a great advantage for

monitoring. Also, there are species of proteins in saliva that are not carried in the blood, and which change with stress. These may also be biomarkers for PTSD symptoms. No clinically validated tests will be performed. The genetics/biomarker component of the protocol will be supervised by Dr. Keith Young (CTVHCS Neuropsychiatry Research Program, Building 205, 3R05 and 3R08) and Dr. Rakeshwar Guleria (CoE Biomarkers and Genetics Core) an experts in this area, in collaboration with the PI. See Appendix for Safety Survey. At the BL assessment, participants will be given the option of consenting to all study procedures or all procedures excluding the saliva/blood sample and genetic research.

Subjects will donate saliva in a coded Oragen tube at baseline and in a 1ml test tube at follow-up. Staff will be trained to avert their eyes when participants are spitting into the test tube to reduce potential embarrassment. The Oragen saliva test tubes will stored in Building 93 (2A 113) until transported by team members to Dr. Young's lab in Temple and the small tube collected at follow-up will be frozen at -80* in Waco Building 93 (2A 113). Subjects can also opt to donate blood by venipuncture by personnel trained in VA procedures for taking blood samples. Compression bandages will be used to cover the puncture. Blood will be placed in one yellow top, one red top (no additives), one purple top, 1 RNA (Paxgene Red-top) and 1 Green-top tubes (Plasma-lithium-heparin), all coded, and stored at 4 degrees on ice until separation (green top) or frozen (RNA and Yellow top). The original green top tube will be recapped and all tubes frozen in temporary storage at the VA lab, Dr. Young's lab or Waco Building 93 (rooms 2A 116, 2A 117). Whole blood in the green-top EDTA tubes will be spun and supernatant separated into three test tubes (coded). Blood products will be temporarily stored in a freezer at -20 and will be periodically (depending on patient flow) transported by automobile by team members with data transport waivers, or by VA clinical lab transport to be stored at the Temple VA clinical lab until transfer to Dr. Young's lab (Building 205, 3R05 and 3R08 or to Waco Building 93, 2A 113, 2A 116, 2A 117). Blood from redtop and purple top tubes will be processed for cell protein and other constituents in Waco building 93 (2A 113, 2A 116, 2A 117). All blood preparation will take place at the VA by trained personnel. DNA/RNA extraction from the DNA/RNA tubes will be performed by team members using DNA/RNA extraction kits (Amplicon: Building 205, 3R05 and 3R08). Coded DNA/RNA samples will be stored at -20/-80 and in liquid nitrogen until testing (Building 205, 3R05 and 3R08). Blood product samples will be stored at -20/-80 and in liquid nitrogen for future use, with appropriate IRB approval (Building 205, 3R05 and 3R08). Initial genotyping (Stage 1 and 2) and lab work will be performed in Dr. Young's lab (Temple Building 205, 3R05 and 3R08). The results of the genotyping will be saved in a coded, de-identified dataset and stored on VA computers on the secure CTVHCS Research Service-approved drive and S:\CoE Data\FX drive that will only be accessible to study staff. Below is a 3-phase description of the genetics research.

If research staff do not have access to phlebotomy service (or if, for example, participants have a fear of needles), no blood will be drawn in Phase II. Instead, participants can volunteer to donate a second saliva sample in Phase II, using Oragen™ DNA tubes as in Phase I. Oragen™ test tubes do not need to be frozen, and will be stored at room temperature (Building 93, 1A-137, 2A 113) until transport by team members to Dr. Young's lab in Temple for long-term storage at RT (Building 205: 3R05 and 3R08).

<u>Stage 1:</u>

SERT (SLC6A4). We will perform SERT genotyping with a triplex/double digestion PCR protocol as adapted from Young et al., 2006 and Wendland et al., 2006 to genotype for the 5HTTLPR + rs25531 variants, the inton 2 VNTR 9, 10 and 12 repeats (IN2) and the Ile425Val a-g mutation (Ile/Val425). The digestion protocol using HpaII and BccI yields Sa, Sg, La, Lg, IN2-9, IN2-10, IN2-12, Ile425, Val425. All possible haplotypes will constructed from the variants and used in the analysis. Although the Sg and Val 425 are quite rare (0.25%), we expect to genotype a few subjects with these variants subjects (0.5%). We will carefully monitor information on the additional Leu425 (and other) functional polymorphism(s) to ascertain whether resequencing will be required. Genotyping will be performed at CTVHCS Temple Building 205.

<u>Stage 2:</u>

5HT-2A, 5HT1A, 5HT6, CRHR1, CRHR1, MAOA, P11, FKBP5, GR, GNB3, CRH, TPH1, TPH2, BDNF, TrkB, microRNA panel (exigon mirnome panel or equivalent). Phase 2 SNP genotyping and Plasma/lymphocyte RNA/methylation/hormone assays will be performed serially on ABI TaqMan SNP Genotyping Assays (Applied Biosystems, Inc., Foster City, CA) and bead-based saliva hormone assays

in duplicate with negative controls. TaqMan fluorogenic 5'nuclease assay (Applied Biosystems) using a final volume of 5ul (2 ng genomic DNA and 2.5ul TaqMan Universal PCR Master Mix) will be used. Thermal cycle conditions (508C for 2 min, 958C for 10 min, 40 cycles of 928C for 15 sec and 608C for 1 min) in 384-well plates processed in a Dual 384-Well GeneAmp PCR System 9700 (Applied Biosystems) with endpoint fluorescent readings performed on an ABI PRISM 7900 HT Sequence Detection System (Applied Biosystems). For assessment of haplotype coverage, we will use International HapMap project (release 19 October 2005 2006-01-24 or later), which remaps release 19 based on NCBI Build 35 coordinates.

Stage 3:

SNP, gene expression, copy number analysis, gene epigenetic modifications, protein analysis, and deep resequencing. We will use commercially available SNP chips, microarray panels or commercial resequencing to assay for additional for polymorphisms in all genes and for microRNA and gene expression changes. Pooled samples may be used initially to investigate clinical subsets. Data from SNPs will be used to generate haplotype data which will be assayed for linkage and association as above.

Aims and Hypotheses

Specific Aim 1: Identify clinically-relevant, modifiable psychosocial factors that predict improved functioning over time.

Hypothesis 1a: Higher levels of acceptance, self-compassion, and positive attributions, and better emotion regulation will predict improved functioning over time after accounting for the covariates (number of TBI exposures, combat exposure, time since deployment, physical health symptoms).

Specific Aim 2: Identify clinically-relevant, modifiable psychosocial factors that predict membership in latent class trajectories of functioning.

Hypothesis 2a: Higher levels of acceptance, self-compassion, and positive attributions, and better emotion regulation will predict membership in the least impaired trajectory after accounting for the covariates.

Hypothesis 2b: Lower levels of acceptance and self-compassion, and greater negative attributions and emotion dysregulation will predict membership in the most impaired trajectory after accounting for the covariates.

Specific Aim 3: Identify clinically-relevant, modifiable psychosocial predictors of transitions between trajectories of functioning.

Hypothesis 3a: Higher levels of acceptance, positive attributions, self-compassion, and emotion regulation will predict recovery (i.e., moving to a less impaired trajectory) after accounting for the covariates.

Hypothesis 3b: Lower acceptance and self-compassion and higher levels of negative attributions and emotion dysregulation will predict chronicity (i.e., staying on an impaired trajectory) after accounting for the covariates.

Planned Analyses

We will use both traditional (e.g., maximum-likelihood regression) and advanced approaches (e.g., latent growth models, parallel process models, growth mixture models, latent transition models) to analyze the data. For example, to test Aim 1 in a traditional manner, principal component analysis (PCA) will be used to create a composite functional impairment factor (see Preliminary Studies section for data in support of this approach). This approach will greatly reduce the overall number of tests conducted and provide us with a broad index of functional impairment. Variables used to create the functional impairment factor will include measures of functional disability (WHODAS 2.0, IPF), community reintegration (CIQ), quality of life (QLS), and mental health problems (e.g., CAPS, SCID, PCL-M, BDI-II). Either a clinical interview (i.e., CAPS, SCID) or self-report measure (PCL-M, BDI-II) will be used to assess mental health problems depending upon the time point (interviews for the post-deployment, baseline, and 24-month time points, self-reports for the 8- and 16-month time points). Change scores will then be calculated and regressed onto the hypothesized predictors and covariates (including prior level of functional impairment) to test Hypothesis 1a.

Advanced approaches for longitudinal data analysis will be employed in the current proposal that generally fall under the latent growth modeling (LGM) framework (Bollen & Curran, 2006; Preacher et al., 2008), which allows modeling of the change/growth trajectory of different variables assessed on multiple

occasions across time. Generally, scores on the repeated measures will be correlated due to the fact that they are measures of the same participants over time. The growth models take this dependency into account by treating the repeated measures as separate variables, and fitting a proposed trajectory shape to the scores across time. The initial status and growth rate of the growth trajectory are modeled as latent variables (i.e., growth factors). The means of the latent variables represent the overall starting point and the overall growth rate of the population, respectively. The variances of the growth factors capture the variability of individual growth trajectories. The advantages of using LGM over other approaches include the flexibility of placing constraints on the model while allowing growth parameters describing participants' trajectories to serve as predictors of other variables as well as growth models (Bollen & Curran, 2006; Preacher et al., 2008).

LGM assumes that individuals come from a homogeneous population while latent class growth analysis (LCGA; Nagin, 1999; 2005) allows multiple subpopulations to be inferred from the data. However, LCGA imposes an unrealistic restriction that the random variations of the latent growth factors within classes are not modeled (Muthén, 2004; Palardy & Vermunt, 2010). Combining LCGM and LCGA, Growth Mixture Modeling (GMM) is a more general modeling framework that has the capacity of modeling both random variation of the latent growth factors and the unknown heterogeneous subpopulations simultaneously. Latent transition models (LTMs) are related to growth mixture models but study changes in class membership rather than growth of observed variables (Collins & Lanza, 2010). For reasons of compactness and ease of understanding, we present path diagrams of the main analyses below rather than their multi equation algebraic equivalents.

Power Analysis. Research questions are translated into testable hypothesized models and are presented below in path diagrams. The corresponding statistical power of the hypothesized models was estimated using the Monte Carlo procedure available in Mplus (Muthén & Muthén, 1998-2012). For each power analysis, 1000 datasets were simulated following a hypothesized model. This model included a particular effect size of interest for each test. The model(s) of interest were then estimated for each dataset, and the proportion of datasets in which the null hypothesis was rejected was taken as the (empirical) power of the test (L. K. Muthén & Muthén, 2002).

Hypotheses 1a. The regression models used to test hypothesis 1a (H1a) will be well-powered (>.99) to detect effect sizes of the magnitude we expect to find (i.e., medium to large) based on our preliminary analyses. To examine the effect of the change in the malleable/modifiable factors on the change/improvement in the long term functional recovery, we propose using a parallel growth model (Cheong, MacKinnon, & Khoo, 2003) as presented in Figure H1ab in which linear growth models are specified for individual modifiable factors functional recovery. The statistical power of the target effect, the direct effect from the slope of the modifiable factor to the slope of the long term functioning (i.e., the bolded arrow in Figure H2ab), is evaluated. Given the proposed sample size (500 participants with 5 repeated measures), the empirical power for detecting a medium direct effect from the slope of modifiable factor to the slope of long term functioning is larger than .90.

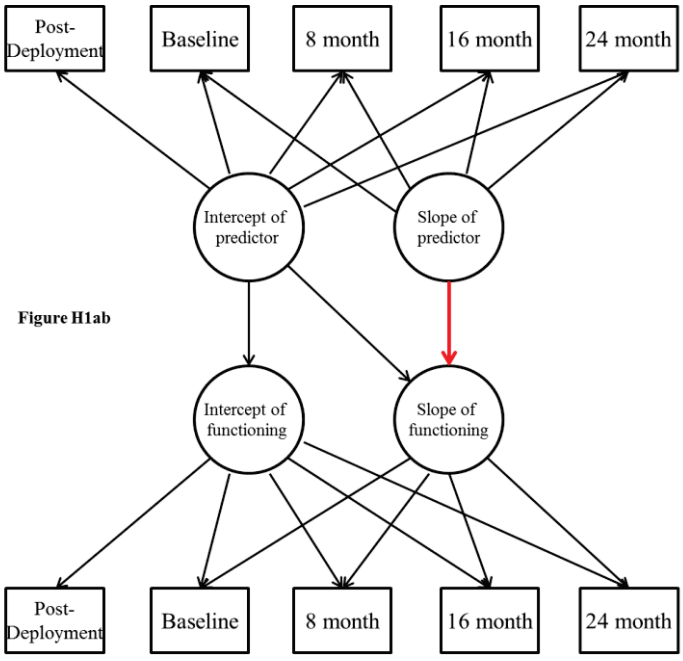


Figure H1ab

Hypotheses 2a & 2b. These two hypotheses can be examined by using GMM as presented in Figure H2ab. Based on the results from the preliminary studies, the statistical power for detecting a three-class solution is larger than .90 given the proposed sample size (500 participants). We also calculated statistical power for the effects of the modifiable factors on latent class membership. Assuming a small to medium effect size (odds-ratio = 1.82, which roughly

corresponds to a Cohen's *d* of 0.34), the empirical power of the modifiable factors on predicting class membership ranged from .72 to .91.

Hypotheses 3a & 3b. These two hypotheses can be examined by using the sequential process GMM (L. K. Muthén & Muthén, 2012) as presented in Figure H3ab. These power analyses used similar growth factor parameters from hypotheses 2a and 2b, and assumed a small transition probability of .20. Measurement invariance of the latent class formed by the first three time points and that formed by the last two time points was assumed. The statistical power for detecting transitions from latent trajectory class 1 to latent trajectory class 2 was larger than .79 given the proposed sample size (500 participants). We also calculated statistical power for the effects of the modifiable factors on predicting transitions. Statistical power for one modifiable factor predicting one or more transitions was larger than .72, assuming small to medium effect sizes (odds-ratios ranging from 1.6 to 2.7).

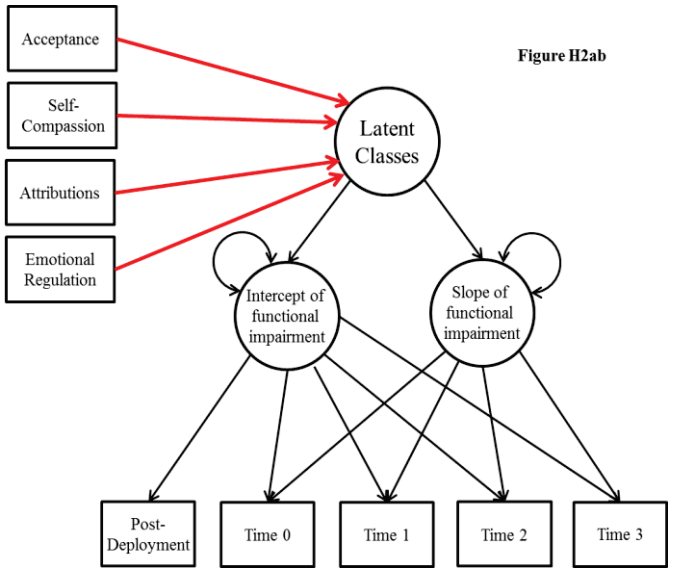


Figure H2ab

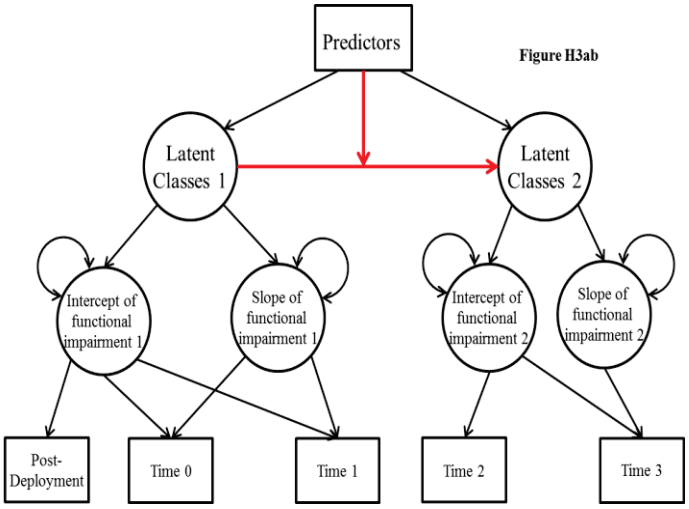


Figure H3ab

Missing Data Management. Longitudinal designs, by their very nature (i.e., the length of data collection, the presence of multiple assessment points), pose challenges regarding missing observations, with partial participation and participant attrition being of particular concern. Based on past research by this study team with other populations who showed high levels of responsibility in meeting study obligations, we anticipate that retention rates will be good and that missing data will be minimal. Nonetheless, a limited amount of missed data are anticipated to occur. Based on our pilot data, we expect the amount of missing data to be 20% or less. In addition, we will implement multiple methods to reduce participant attrition (e.g., reminder and follow-up calls, thank you notes, incentives; cf. Kleschinsky et al., 2009; Scott et al., 2006). We will also implement data screens using Mplus (Muthen & Muthen, 2009) to characterize and elucidate patterns of missing data. When missing data do occur, full information maximum likelihood (FIML) estimation will be used to estimate parameters and standard errors. FIML is a principled approach to missing data management that is considered "state of the art" by leaders in the field of missing data management (e.g., Schafer & Graham, 2002). FIML is a maximum-likelihood based estimation procedure that directly estimates parameters and their standard errors for the full sample from the existing and limited data. Thus, there is no attempt to replace missing data values (e.g., Arbuckle, 1996; Hedeker & Gibbons, 1994, 1997; Horn & McArdle, 1980; McArdle & Bell, 2000; Neale et al., 1999). Instead, as the term "maximum likelihood" suggests, the parameter estimates are derived in a manner that maximizes the likelihood that the data were drawn from the population of interest (Kline, 2005). FIML is the optimal procedure for handling missing data within both SEM and LGM frameworks, and, in fact, using estimation methods other than maximum likelihood in SEM requires explicit justification (Kline, 2005; Hoyle, 2000). The primary advantage of using FIML over other procedures is that it produces relatively unbiased parameter estimates and standard errors (Schafer & Graham, 2002).

IMPACT

Due to a change in PI, on December 18, 2019, the treatment arm of Phase III of this study (aka: IMPACT) was put on hold, and ultimately closed prior to the RCT stage. Sixteen veterans were enrolled into the adaptation and refinement stages of IMPACT. All data collection for this arm was completed by February 2020. Primary activities for this arm of the study are no longer active. Data from IMPACT will be moved to the SERVE Data Repository with the rest of the Phase III data at the completion of the study.

Specific Aims

A sub-study is integrated into the scientific aims in which we will translate knowledge gained in prior Phases regarding modifiable factors that predict functional impairment as well as in Dr. Meyer's broader treatment outcome research program to adapt an intervention specifically designed to promote functional recovery among the most severely functionally impaired war veterans. This study component is referred to as: Intervening on Modifiable Predictors using Acceptance and Commitment Therapy (IMPACT). IMPACT involves use of a Successive Cohort Design (SCD) to refine Acceptance and Commitment Therapy for promoting functional recovery (ACT-FX). ACT is an empirically-supported, acceptance and mindfulness-based form of behavior therapy that has been used with a range of mental and physical health conditions commonly experienced by war veterans. We will first pilot ACT-FX with two cohorts of 5 participants each and refine it based on veteran and clinician feedback. We will then select 90 participants from the longitudinal study and randomly assign them into either ACT-FX or mental health treatment as usual (TAU) while continuing the longitudinal assessments for long-term follow-ups. The over-arching goal of this research is to provide data to inform evidence-based prevention and treatment programs designed to assist returning Veterans with achieving optimal functioning upon reintegrating into civilian life. The specific aims of IMPACT are: 1) develop, refine, and evaluate the feasibility and acceptability of Acceptance and Commitment Therapy specifically designed to improve functioning in Veterans (ACT-FX); 2) evaluate if participation in ACT-FX leads to the emergence of a new trajectory class that is characterized by long-term functional recovery.

Description of ACT-FX

ACT-FX will be an adaptation of the ACT treatment model aimed at reducing functional impairment associated with any combination of the most common mental and physical wounds of war. ACT is a mindfulness-based behavioral treatment in which the primary goal is improved functioning. In ACT, clients are guided through a series of behavioral and experiential exercises focused on six core processes: mindful awareness, emotional acceptance, defusion from maladaptive thoughts, self-as-context, clarification of personal values, and committed action. The theory underlying ACT posits that low levels of psychological flexibility, which arises from lack of connection with the present moment, experiential avoidance, and disengagement from values-based behavior, leads to functional impairment across a range of mental and physical health problems. Such a transdiagnostic approach appears essential given high comorbidity in severely impaired Veterans. ACT is currently being disseminated across VA as an evidence-based treatment for depression. Moreover, several studies support the efficacy of ACT for several of the other most common mental and physical health conditions experienced by war veterans that are, in turn, associated with functional impairment and disability. As part of Aim 1, our expert treatment adaptation team (Drs. Meyer, Vowles, Walser, Morissette, DeBeer, and Elliott) will integrate PI Meyer's ACT manual that focuses on promoting recovery in Veterans with co-occurring PTSD-AUD with content drawn from Co-Is Vowles' and Walser's ACT manuals focusing on reducing functional impairment associated with chronic pain and depression, each of which has empirical support. An integrated session overview and treatment blueprint (i.e., the values and goals worksheet) have also been developed (see appendices). ACT-FX will be an individual, outpatient psychotherapy, with sessions occurring approximately weekly for approximately 12 sessions. Each session includes: 1) mindfulness training; 2) review of between-session mindfulness practice and behavioral assignments; 3) new content and experiential exercises; and 4) development of values-consistent behavioral assignments to improve functioning. Daily mindfulness practice will be facilitated by audio recording in-session exercises and using free mindfulness websites, apps, and CDs. Veterans will document their between-session practice using paper-and-pencil logs. Veterans will be given the option to invite a support person (e.g. spouse or significant other) to sit in on a session Thus, the number of sessions will typically be 12 or 13, though it is possible that some veterans may require an additional session or two if, for example, a session needs

to be completed over the course of two weeks due to time constraints or other logistical factors. Based on feedback that we receive from veterans during stages 1 and 2, we may decide to modify the ACT-FX treatment protocol to include additional sessions (e.g., up to 16 sessions).

Study Methods and Procedures

Veterans enrolled in the Phase III longitudinal study who meet a few additional eligibility criteria will be recruited into the successive cohort treatment component of the Phase III study (Aims 2 and 3; total n = 100). Participants who are eligible and who elect to enroll in the treatment portion of the study will participate in outpatient psychotherapy. This treatment is currently designed as 12 one-hour-long treatment sessions with ACT-FX over 3 to 4 months, though treatment length may be modified based on veterans' feedback, followed by a post-treatment assessment that will be virtually identical to the 8- and 16-month follow-up assessments in the observational study, and for those in the treatment adaptation phase only, a 30 minute Veterans' Experiences Qualitative Interview conducted post-treatment. The Successive Cohort Design (SCD) method involves several steps:1) identifying a promising, theory-driven treatment approach; 2) developing or adapting initial treatment manuals, supporting materials (e.g., handouts), and measures; and 3) iterative revisions based on qualitative and quantitative data collected through providing the treatment to successive cohorts of patients. We already identified the general treatment approach (ACT) and reported on its utility in promoting recovery in people living with depression, chronic pain, and co-occurring PTSD-AUD.

Stage 1: Adaptation. Our treatment adaptation team will continue the process of forming ACT-FX by integrating our existing ACT manuals focusing on promoting recovery in Veterans living with PTSD, AUD, depression, and chronic pain, and by integrating principles of TBI rehabilitation, resulting in a personalized intervention to promote broad functional recovery. Clinician and Veteran qualitative feedback provided from the first Veteran cohort (n = 15) will provide the treatment adaptation team with recommendations for improvements. We will consider changes to the sequencing of treatment sessions and whether to add a session(s). Also, where therapist feedback suggests, additional or refined questions for the semi-structured interview guide (see Appendix) will be used for subsequent Veteran interviews. For Veteran feedback, individual qualitative interviews will be conducted immediately following completion of ACT-FX. The current interview guide is a modified version of the interview guide used during our ACT for PTSD-AUD study. A Co-I experienced in qualitative interviewing will conduct all recorded phone interviews, and lead coding and analysis of the interviews. Project staff will provide live transcription as close to verbatim as possible as a safeguard in the event of a recording failure. Following each interview, staff will review and edit transcriptions using recordings to ensure completeness. Guiding our analytic approach, we will use an integration of matrix and grounded theory techniques. Immediately following interviews for each treatment cohort, the coders will independently use a summary template to capture key information relevant to key domains from the interview guide relevant to guiding treatment adaptation (e.g., Treatment Initiation, Engagement, Experiences). Summaries will then be compared in a matrix, and discrepancies resolved by consensus. These matrices will be reviewed and compared across participants in each cohort. In the second round of coding, grounded theory analysis will be used to identify new or emergent themes. The coders will review transcripts and repeatedly meet to discuss an identify novel themes emerging in the data. This will result in a secondary set of inductively derived codes. Once this coding schema is finalized, the coders will code transcripts independently using qualitative software. Discrepancies during this round of coding will be reviewed to allow for discussion toward consensus. The final content of thematic codes will then be reviewed with constant comparison among participants to identify Veteran attitudes and perspectives to inform potential revisions for further adapting ACT-FX. Qualitative findings be presented to the treatment adaptation team to aid in modifications to the ACT-FX manual.

Stage 2: Treatment refinement. We will treat a second cohort (n = 15), followed by using the same methods described above in Stage 1 to guide additional modifications. Data regarding retention, client satisfaction, qualitative content, therapist adherence, therapist competence, and treatment outcomes will also be reviewed and compared with Stage 1 to verify that prior modifications had the intended benefits.

Stage 3: Pilot RCT. We will conduct a pilot RCT of the refined ACT-FX protocol compared to mental health TAU with 90 Veterans (45 per group). The goals of the pilot trial are to evaluate feasibility

(enrollment with randomization, treatment completion) and acceptability (treatment satisfaction). We will also examine whether changes in the treatment targets are correlated with changes in outcomes.

Description of TAU and randomization. Our preliminary data indicate that most SERVE participants who will be eligible for the pilot RCT already receive mental health TAU through VA. Among Veterans randomized to TAU, those already receiving TAU will continue in TAU. Those who are not already receiving TAU will be offered a clinical referral to address the Veterans' most pressing mental or behavioral health concern (e.g., to the PTSD clinic or to primary care-behavioral health for pain management). Offering such referrals has been our procedure throughout SERVE. Because of the complexity of our target population, TAU will involve a variety of interventions. In accordance with recommendations for tracking TAU in RCTs, a brief (5 minute) weekly phone call will be conducted with TAU participants to closely track their use of VA and non-VA mental health services using our treatment involvement form. Our statistician Dr. Kwok will use permuted-block randomization with varying block sizes to determine treatment assignment.

Treatment Discontinuation

Treatment will be discontinued for participants who: (1) become actively suicidal or homicidal; engage in an uncontrolled episode of alcohol or drug use that requires immediate treatment, (2) require inpatient psychiatric treatment and further study treatment is determined to be clinically inappropriate, (3) resume or initiate a relationship in which they are being physically or sexually abused, or (4) fail to attend 3 consecutive therapy sessions without a reason judged by their therapist to be acceptable. For intent-to-treat purposes, all participants, including those who terminate early, are followed at mid-treatment, post-treatment, and 3-month follow-up.

Assessment schedule for the IMPACT SCD study

For participants treated in Stages 1 and 2, measures collected during their baseline assessment from the longitudinal assessment study will also serve as their pre-treatment assessment. For participants treated during the Stage 3 pilot RCT, measures collected during their 8-month follow-up will form the majority of their pre-treatment assessment. Supplementary pre-treatment measures will also be administered during the initial IMPACT appointment. Waiting until participants complete their 8-month follow-up to enroll in the pilot RCT standardizes the follow-up duration for Veterans in the pilot RCT, and allows us to confirm that newly enrolled Veterans' level of functional impairment has remained high across two time-points before treating them. Participants in the pilot RCT will complete a post-treatment assessment upon completion of treatment approximately 4 months following randomization lasting 1 hour, which will closely mirror the 8- and 16-month follow-ups from the Aim 1 study. These participants will complete the 16- and 24-month follow-up assessments (i.e., 4- and 12-months post-treatment) as part of the Aim 1 study, which will allow us to assess the durability of treatment effects, including whether booster sessions may be warranted. Assessors blind to treatment condition will complete the final assessment that includes interviews.

IMPACT Assessment Instruments. [DATA COLLECTION COMPLETED]

Measures/ Proposed Indicators	Purpose	Description/Rationale
Interpersonal Needs Questionnaire (INQ) [a,b]	PV	Self-report measure that assess thwarted belongingness and perceived burdensomeness (Van Orden et al., 2012). The INQ has demonstrated good convergent validity, internal consistency and concurrent validity (Van Orden et al., 2012).
Beck Scale for Suicide Ideation (BSSI) [a,b]	DV, Med	Widely-used self-report measure of intensity of thoughts and behaviors associated with suicide. Includes 2 additional items that ask about past suicide attempts as well as the level of suicidal intent during the most recent attempt. Prior research shows that endorsement of suicidal thoughts and behaviors can be greater on self-report questionnaires compared to interviews. Thus, this measure complements the suicide focused interviews.
Suicide Cognitions Scale-Brief [a,b]	DV, Med	Self-report measure of suicide-related thoughts that load onto the following subscales: unsolvability, unlovability, and unbearability. Brief version was recently validated across 3 chronic pain samples (Bryan et al., 2016).
PTSD Checklist-5 (PCL-5) [a]	Med	Self-report of symptoms of PTSD during the previous month. Demonstrates high sensitivity and specificity in relation to a lengthy diagnostic interview for PTSD (CAPS),

		with which it was co-developed. Strong psychometric properties, including in numerous Project SERVE papers.
Patient Health Questionnaire-9 [a]	Med, DV	Self-report measure used for screening, diagnosing, and monitoring depression. It incorporates DSM-IV diagnostic criteria (Question 9 screens for suicidal ideation; Kroenke, Spitzer & Williams, 2001).
Alcohol Use Disorders Identification Test (AUDIT) [a]	Med	Self-report measure to screen for alcohol-use disorders (Saunders, Aasland, Babor, Fuente, & Grant, 1993). 10-item measures adopted by VA as the gold-standard screening for alcohol use disorders in mental health and primary care clinics. Good internal consistency (α=.80 - .94) and test-retest reliability (*r*=.86), and strong concurrent validity with the MAST and CAGE screening measures (Babor et al., 2001).
Drug Abuse Screening Test (DAST) [a]	Med	Self-report measure to quantify drug misuse and related psychosocial impairment. Good internal consistency and concurrent validity with frequency of drug use over 12-months (Skinner, 1982). Moderately correlated with denial and social desirability. The instructions will be updated to more explicitly assess for misuse of opiates that may have been prescribed.
Acceptance and Action Questionnaire (AAQ-II) [a,b,c]	PV	Self-report measure assessing acceptance, experiential avoidance (attempting to alter the form or frequency of unwanted internal experiences), and taking action despite experiencing unwanted private events (Bond, et al, 2011). Strong psychometrics in multiple SERVE publications (Meyer et al., 2013; 2018; in press, DeBeer, Meyer, et al., 2017).
Brief Experiential Avoidance Quest. (BEAQ) [a,b,c]	PV	The BEAQ is a single-factor item that assesses the modifiable construct of experiential avoidance (Gamez et al., 2013).
Self-Compassion Scale – Short Form (SCS-SF) [a]	PV	Self-report measure of self-compassion, consisting of a total scale score and six subscale scores: self-kindness, self-judgment, common humanity, isolation, mindfulness, and over-identified (Neff, 2003; Raes, Pommier, Neff, & Van Gucht, 2011). The SCS-SF is strongly correlated with the original long form (r=.97) and has the same 6-factor structure with one higher-order factor. Internal consistency was .86 for the whole measure, with subscale alphas ranging from .54 to .75 (Raes et al., 2011).
Difficulties in Emotion Regulation Scale (DERS-Brief) [a]	PV	Self-report measure (Bjureber et al., 2016) of 6 domains of emotion dysregulation: nonacceptance of emotional responses, difficulty engaging in goal-directed behavior, difficulty with impulse control, lack of emotional awareness, poor emotion coping strategies, and lack of emotional clarity.
Five Facet Mindfulness Questionnaire [a]	PV	Self-report measure assessing multiple facets of the modifiable factor of mindfulness. The FFMQ has demonstrated good construct validity and internal consistency. Good predictive validity in research with veterans.
World Health Organization Disability Assessment Schedule II (WHODAS 2.0) [a]	DV	Self-report assessment of functional disability with total score and 6 domains of functioning: understanding and communicating, mobility, getting along with others, life activities (i.e., work, education, household responsibilities), participation in society, and self-care (Üstün et al., 2010). Both global and specific areas of functioning are crucial in thoroughly understanding functional recovery, as Veterans may function well in one area and have difficulty in another. Moreover, some domains may be affected by contextual factors instead of representing functional capacity (e.g., work functioning in a struggling economy independent of impairment).
Inventory of Psychosocial Functioning (IPF) – Brief [a]	DV	Self-report measure (Co-I Marx et al., 2009; Bovin et al., 2018) of Romantic Relationships with a Spouse/Partner, Family, Work, Friendships and Socializing, Parenting, Education, and Self-Care. The short version has a .90 correlation with the full 80-item instrument (Co-I Marx, personal communication). Higher scores indicate greater functional impairment.
Quality of Life Scale (QLS) [a]	DV	Self-report (Burkhardt, et al., 1989) assessing how satisfied people are in areas distinct from health status (mate, physical well-being, relationships with others, social, community, and civic activities, personal development and fulfillment, recreation, and independence). Good internal consistency and high test-retest reliability (Burckhardt et al. 2003).
Values Tracker [a]	DV	Brief self-report measure of value engagement. Good predictive validity in research with chronic pain samples.
Meaning in Life Questionnaire [a,b]	PV	Brief self-report assesses presence and search for meaning in life (Steger et al., 2006).
Social Connection Index [a,b]	DV, Med	Self-report measure of frequency of contact with others, number of close friends and relatives, level of secure attachment in relationships, frequency of problems getting along with friends and family members.
Brief Loneliness Measure [a,b]	DV, Med	Brief self-report measure of loneliness for use in large survey studies. Highly correlated with lengthier measures such as the UCLA Loneliness Scale.
Interpersonal Reactivity Index-Brief (B-IRI) [a,b]	DV, Med	Brief self-report measure of disposition to empathic responding; 2 subscales assess perspective taking and empathic concern. Good reliability and validity (Ingoglia et al., 2016).

Multidimensional Psychological Flexibility Inventory (MPFI) [a,b]	PV	60-item self-report (Rolffs, Rogge, & Wilson, 2018) used to assess the dimensions of the psychological flexibility model that underlies Acceptance and Commitment Therapy
Expressions of Moral Injury Scale (EMIS) [a,b]	DV	17-item self- report (Currier et al., 2018) to assess for problems associated with exposure to morally injurious events
Credibility & Expectancy Questionnaire [b]	PV	Widely-used 6-item self-report measure of the credibility of the treatment approach and expectations for positive response to the treatment (Borkovec & Nau, 1972). Used in Dr. Meyer's prior ACT studies (Hermann, Meyer et al., 2016; Meyer et al., in press).
Client Satisfaction Questionnaire [a]	DV	Widely-used 8-item self-report measure of treatment satisfaction (Larsen et al., 1979). Used in Dr. Meyer's prior ACT studies (Hermann, Meyer et al., 2016; Meyer et al., in press).
Working Alliance Inventory [d]	PV	Widely-used, brief self-report measure of clients' perceptions of working alliance with therapist on 3 dimensions: goal, task, and bond (Horvath, 1981).
Note: [a] = Included in post-treatment assessment for those participating in the IMPACT treatment component; [b] = pre-treatment assessment, [c] administered weekly during IMPACT; [d] administered after session 2 and again at post-treatment only for those receiving ACT-FX		

Participants

Veterans will be recruited (total n = 100 across 3 stages) from the ongoing longitudinal assessment study. Additional inclusion criteria are: 1) Veterans will have a global disability (mean item) score on the WHODAS 2.0 of 0.89, which is 1 SD above the mean of our large non-psychiatric sample of Veterans from SERVE and VA Boston during both of their last 2 assessments; and 2) Those enrolling in the pilot RCT must be willing to be randomized. Additional exclusion criteria are: 1) recent (1 month) or anticipated change in psycho-pharmacological treatment. Veterans may stay on current medications but will be asked to refrain from changes to the extent possible based on safety; 2) for those randomized to ACT-FX, current participation in another form of individual or group psychotherapy; 3) logistical circumstances that would interfere with study completion; 4) Presence of a non-alcohol substance use disorder (SUD) deemed to be the primary focus of treatment. Those with a principal AUD will be eligible. Additional diagnoses of non-alcohol SUD are allowed, unless they are deemed the principal focus of treatment. Potentially eligible Veterans who score above the clinical cutoff on the DAST will be asked additional questions during the eligibility screening to determine whether they meet criteria for a principal non-alcohol SUD (see phone screen); and 5) AUD/SUD of sufficient severity that residential, rather than outpatient, treatment is indicated based on potential safety concerns associated with withdrawal. This determination will be made by the PI, with consultation from the Veteran's existing treatment providers, as appropriate. We will begin the treatment adaptation (Stage 1) and refinement (Stage 2) by recruiting transfer participants who have already been assessed over time immediately following their baseline assessment. The pilot RCT will include both transfer and newly enrolled Veterans.

Recruitment and Retention

We expect that our total sample of 500 eligible Veterans will include 360 experiencing sufficient functional impairment to be eligible to participate in IMPACT (210 transfers and 150 new Veterans), of whom we will attempt to enroll 100. This plan is highly feasible based on PI Meyer's prior ACT for PTSD-AUD study completed at CTVHCS. In addition to being compensated for their time completing the assessments for the longitudinal assessment study as described above, IMPACT participants will be compensated as follows: Those in the adaptation phase will be paid $40 for completing the post-treatment assessment $10 for completing weekly assessments at each study visit, and $40 for completing the post-treatment qualitative interview ($200 total). Those in the pilot RCT will be paid $25 for completing supplemental pre-treatment measures, $40 for completing the post-treatment assessment, and $10 for completing weekly assessments at each study visit ($175 total). During the treatment adaptation and refinement stages, the weekly assessment will involve completing the AAQ-II and BEAQ and documenting completion of between-session assignments as part of ACT-FX. During the pilot RCT, those assigned to the ACT-FX group will be compensated $10 weekly for completing the AAQ-II and BEAQ and documenting between-session assignments; those assigned to TAU will be compensated for completing the AAQ-II and BEAQ and documenting ongoing treatment involvement (by phone).

Training of study therapists

Doctoral-level therapists will provide the treatment under Dr. Meyer's supervision. Dr. Meyer has served as both a national training consultant and as a regional trainer in VA's national training program in ACT

as an evidence-based treatment for depression. He will train and supervise the study therapists following the process used in this national roll-out training program. This process includes an in-person training workshop, weekly case consultation, and ratings on ACT core competencies on all sessions for the first case. Treatment sessions will be video or audio-recorded. Following the initial training case, 20% of subsequent sessions will be rated for competency and adherence. Weekly case consultation will continue throughout the study.

Aims and Hypotheses

Specific Aim 1: Develop, refine, and evaluate the feasibility and acceptability of a transdiagnostic, personalized ACT-based behavioral therapy (ACT-FX) specifically designed to improve functioning in Veterans.

> *Hypothesis 1:* ACT-FX will be feasible and acceptable to Veterans with complex mental and physical wounds of war.

Specific Aim 2: Evaluate if participation in ACT-FX leads to the emergence of a new trajectory class among Veterans in Project SERVE that is characterized by long-term functional recovery.

> *Hypothesis 2:* ACT-FX treatment will predict membership in a new trajectory class characterized by functional recovery compared to Veterans receiving TAU who will continue to exhibit flat or worsening trajectories.

Planned Analyses

Aim 1: All randomized participants will be included in these analyses. ACT-FX will be considered feasible and acceptable if: 1) we are able to recruit, enroll, [and randomize] the target sample within the specified timeframe; 2) given our complex sample, we have treatment completion rates > 60% based on completing > 9 treatment sessions. Our treatment completion rate was 67% in our ACT for PTSD-AUD pilot trial, which is high for this population, despite our stringent completion criterion; and 3) client satisfaction ratings are equivalent or better (maximum of d = .2 lower) than those for Veterans randomized to TAU.

Aim 2: We will test whether ACT-FX is associated with the emergence of a functional recovery trajectory by re-running the GMM analyses described above (H1b), focusing on treatment involvement as a predictor. Our preliminary analyses indicate that we have previously detected latent class memberships comprised of similar numbers of participants even without an intervention. Thus, we should be able to detect emergence of a recovery class should ACT-FX yield effects similar to our pilot work.