Cognitively Augmented Behavioral Activation for Veterans with Comorbid mTBI/PTSD

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Principal Investigator/Study Chair: Daniel Storzbach, Ph.D and Amy Wagner, Ph.D

Abstract

Veterans returning from the current conflicts in Iraq and Afghanistan exhibit high rates of comorbid mTBI/PTSD. Given the comorbidity and neuropsychiatric symptom overlap of these disorders, it can be difficult to determine whether problems and disruptions in functioning are due to mTBI, PTSD, or both. Hence, it is challenging for providers to know how to prioritize these patients' clinical issues and how to effectively treat them. Currently, there are no evidence-based treatments for comorbid mTBI/PTSD. Further, it is unclear to what extent existing treatments for each disorder can be adherently and effectively implemented for the other. As such, most current treatment recommendations suggest a holistic or integrated approach to treatment for comorbid mTBI/PTSD targeting symptoms and functionality rather than underlying etiology. We are proposing a treatment for comorbid mTBI and PTSD that directly targets daily functioning and quality of life. The primary objective of this study is to evaluate the efficacy of Cognitively Augmented Behavioral Activation (CABA), a new hybrid treatment for veterans diagnosed with comorbid mild Traumatic Brain Injury (mTBI) and posttraumatic stress disorder (PTSD). The study's specific goals are to determine whether: 1) CABA reduces PTSD symptoms in veterans with mTBI/PTSD, 2) CABA reduces cognitive-related functional impairment in veterans with mTBI/PTSD, 3) CABA results in improvements in depression symptoms, cognitive functioning, and quality of life in veterans with mTBI/PTSD; and 4) CABA is an acceptable treatment for veterans with mTBI/PTSD**.** The overall goal is to develop an evidence-based manualized treatment for comorbid mTBI/PTSD that can be readily implemented in Veterans Health Administration (VHA) treatment settings. The study design makes use of the convergent availability of resources at the two participating Veterans Administration Medical Centers (VAMCs) in Portland, Oregon, and Seattle, Washington to conduct a Randomized Controlled Trial (RCT) of CABA. The study will recruit a total of 192 veterans ≤ 55 years of age, 96 participants at each site, enrolled at participating VAMCs who are diagnosed with both mTBI and PTSD. Inclusion criteria will be 1) Veterans ≤ 55 years of age enrolled at one of the participating VA sites who are able to provide informed consent, 2) Diagnosis of PTSD based on the Clinician Administered PTSD Scale (Blake et al., 1990), 3) Positive screen on the Structured Interview for Collecting Head Trauma Event Characteristics as outlined by the VA/DoD Clinical Practice Guideline for Management of Concussion/mTBI and positively endorsed any of the Neurobehavioral Symptom Inventory (NSI) cognitive symptoms items (items 13-17), 4) English speaking, able to attend treatment (if in CABA condition) and assessment sessions, and willing to refrain from additional mental health treatment during the first 3 1/2 months of the active phase of treatment if they are assigned to the CABA condition, and 5) Willingness to participate in audio- recorded sessions. Exclusion criteria will be 1) Current diagnosis of moderate or severe substance (alcohol) use disorder using DSM-5 criteria within the past 30 days, 2) Current Bipolar or psychotic disorder (requirement to refrain from additional treatments might be harmful), 3) Veterans with a history indicated by medical record review of a diagnosis of moderate, severe, or penetrating TBI, or self- reported history on the Structured Interview for Collecting Head Trauma Event Characteristics of TBI with PTA greater than 24 hours or LOC greater than 30 minutes, 4) Active suicidal intent indicating significant clinical risk, which would suggest that a treatment specifically targeting this intent was indicated clients who report suicidal ideation without imminent risk will be admitted into the study, 5) Initiated psychotropic medication, including Prazosin, within 4 weeks or changed dosage within 2 weeks prior to the first assessment, as this would make it difficult to determine which treatment contributed to change in the CABA condition; additionally, started or changed dosage of sleep medication or low dosages of tricyclic antidepressant or trazodone for pain or sleep within 1 week prior to the first assessment. Participants could be re-considered for eligibility after stability on medication was achieved. Enrollees will be asked, but not prohibited, to hold the doses of the current medications stable over the course of enrollment (though changes in medications after enrollment will not exclude them from on-going participation), 6) Auditory or visual impairments that would compromise ability to participate cognitive rehabilitation group or benefit from compensatory strategies. Eligible participants will be randomly assigned to either the CABA or Treatment as Usual (TAU) group. Participants in the CABA group will receive the CABA intervention via telehealth (video or telephone) during the first 14 weeks of their participation in the study, whereas TAU participants will continue to receive TAU (usual care in a PTSD specialty treatment clinic, but no CABA) during their participation in the study. Both groups will undergo evaluations at baseline, 7 weeks (mid-treatment), and 14 weeks (post-treatment). During their study participation, all participants will continue to receive their usual medical care.

List of Abbreviations

AIC	Akaikes Information Criterion
ANOVA	Analysis of Variance
BA	Behavioral Activation
BDI-II	Beck Depression Inventory, Second Edition
CABA	Cognitively Augmented Behavioral Activation
CAPS-IV	Clinician Administered PTSD Scale
CCT	Compensatory Cognitive Training
CD	Compact Disc
CIQ	Community Integration Questionnaire
CSQ	Client Satisfaction Questionnaire
CogSMART	Cognitive Symptom Management and Rehabilitation Therapy
Co-PIs	Co-Principal Investigators
COWAT	Controlled Oral Word Association Test
CPT	Cognitive Processing Therapy
CSRD	Clinical Sciences Research Development
CST	Cognitive Strategies Training
CVLT-II	California Verbal Learning Test-2nd Edition
df	degrees of freedom
D-KEFS	Delis-Kaplan Executive Function System
DoD	Department of Defense
DSMB	Data and Safety Monitoring Board
DVA	Department of Veterans Affairs
GW	Gulf War
HCS	Health Care System
HIPAA	Health Insurance Portability and Accountability Act
HLM	Hierarchical Models
HVLT-R	Hopkins Verbal Learning Test – Revised
IADL	Independent Activities of Daily Living
ICC	Intra-class Correlation Coefficient
ICD	International Classification of Disease
IRB	Institutional Review Board
IQ	Intelligence Quotient
IOM	Institute of Medicine
MCI	Mild Cognitive Impairment
MCQ	Memory Compensation Questionnaire
MS	Multiple Sclerosis
MSNQ	Multiple Sclerosis Neuropsychological Screening Questionnaire
MINI	Mini International Neuropsychiatric Interview
mTBI	Mild Traumatic Brain Injury
NP	Neuropsychological
Neuro-QOL	Quality of Life in Neurological Disorders
NIMH	National Institute of Mental Health
NINDS	National Institute of Neurological Disorders and Stroke
NOS	Not Otherwise Specified
NSI	Neurobehavioral Symptom Inventory
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OND	Operation New Dawn

PCCS	Portland Cognitive Strategies Scale
PCL-C	PTSD Checklist – Civilian Version
PCL-M	PTSD Checklist – Military Version
PDA	Personal Digital Assistant
PE	Prolonged Exposure
PI	Principal Investigator
PRMQ	Prospective-Retrospective Memory Questionnaire
PTSD	Post Traumatic Stress Disorder
PEHRC	Portland Environmental Hazards Research Center
RBANS	Repeatable Battery for Assessment of Neuropsychological Status
RMASS	Research Management and Study Skills
RR&D	Rehabilitation Research and Development
RRM	Random Regression Model
SAS	Statistical Analysis Software
SD	standard deviation
SDS	Severity Dependence Scale
ShDS	Sheehan Disability Scale
SLS	Satisfaction with Life Scale
SS	Error Sum of Squares
TBI	Traumatic Brain Injury
TAU	Treatment as Usual
TMT	Trail Making Test
TRAC	Trigger Response, Alternative Coping
TRAP	Trigger Response, Avoidance Pattern
UC	Usual Care
VAMC	Veterans Affairs Medical Center
VAPORHCS	Veterans Affairs Portland Health Care System
VAPSHCS	Veterans Affairs Puget Sound Health Care System
VASDHS	Veterans Affairs San Diego Healthcare System
VHA	Veterans Healthcare Administration
VISNS	Veterans Integrated Service Networks
VVC	VA Video Connect
WAIS-III	Wechsler Adult Intelligence Scale-3rd Edition
WAIS_IV	Wechsler Adult Intelligence Scale-4th Edition
WRAT-4	Wide Range Achievement Test-4th Edition
WMS-4	Wechsler Memory Scale-4th Edition

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1.1 Study Personnel

Principal Investigator/Study Chair (and Portland Site PI): Daniel Storzbach, Ph.D, VAPORHCSVAPORHCS 503-220-8262 x56497; Daniel.storzbach@va.gov

Co-PI/Study Chair:
Amy Wagner, Ph.D, VAPORHCSVAPORHCS
503-220-8262 x33365; Amy.wagner@va.gov

Seattle Site PI:
Kathleen Pagulayan, Ph.D, VAPSHCS
206-768-5321; Kathleen.pagulayan@va.gov

Co-Investigators:

- Megan Callahan, Psy.D, VAPORHCS: Interventionist, Multisite Study Coordinator
  503-220-8262 x50525; Megan.Callahan@va.gov
- Marilyn Huckans, Ph.D, VAPORHCS
  503-220-8262 x54689; marilyn.huckans@va.gov
- Matthew Jakupcak, Ph.D, VAPSHCS
  206-277-1853; matthew.jakupcak@va.gov
- Mai Roost, Ph.D VAPORHCS; Interventionist
  503-220-8262 x58308; mai.roost@va.gov
- Maya O'Neil, Ph.D, VAPORHCS: Multisite Data Manager
  503-220-8262 x54522; maya.oneil@va.gov
- Halina Kowalski, MA, MFT, NCC, LPCI, VAPORHCS; Interventionist
  503-220-8262 x53013 Halina.kowalski@va.gov

Consultants/Contractors:

- Jennifer Vasterling, Ph.D, Boston VAMC
  Consultant
  857-364-6522; jennifer.vasterling@va.gov
- Jesse Fann, Ph.D, University of Washington Department of Psychiatry
  Consultant
  206-685-4280; fann@u.washington.edu
- Shah Golshan, Ph.D UCSD
  Contracted Study Statistician
  858-822-7737; sgolshan@ucsd.edu

2.0 Introduction

mTBI and PTSD are highly prevalent and frequently comorbid among Veterans. Studies estimate that 15-23% of those who have served in Iraq and Afghanistan have experienced TBIs[1], the majority of which are defined as mild traumatic brain injuries (mTBI). Many of these individuals sustain more than one mTBI over the course of their deployments[2], often with little recovery time between exposures due to the demands of a combat zone. Both of these factors (multiple concussions and insufficient recovery time) increase the risk for persisting cognitive difficulties frequently seen in this population[3.] Posttraumatic stress disorder (PTSD) is one of the most common mental health disorders among Veterans of wartime service, affecting approximately 15% of Veterans across eras[4.] In their comprehensive review, Carlson et al.[5] report an overall prevalence of comorbid TBI and PTSD among OIF/OEF Veterans at 5-7%. Significantly, individuals with TBI are at increased risk for developing PTSD[6]. Among Veterans with histories of TBI, rates of PTSD range from 33-65%[5,7], with rates highest among those seeking clinical care. Both mTBI and PTSD are associated with significant functional disability and high personal, social, and health care costs[8], with accumulating evidence that their comorbidity exacts an even greater impact on functionality than either disorder alone[9].

The reasons for comorbidity between PTSD and mTBI are complex, likely related to both causal factors and neuropsychiatric symptom overlap between disorders (Vasterling, Bryant, & Keane, 2012). First, many events (e.g., motor vehicle accidents, combat explosions) that increase the risk of TBI can also be psychologically traumatic. Modern warfare involving multiple deployments and high rates of blast exposure has greatly increased Service Members' risk of TBI and PTSD[10]. There is evidence for similar neuroanatomical underpinnings for TBI and PTSD. Neuroimaging studies suggest the same brain regions are affected in both TBI and PTSD (including prefrontal cortex, hippocampus, and amygdala)[10,11]. Neurobiological processes believed most affected by TBI have been linked to the development and course of PTSD, such as problems with executive control, affect regulation[12,13] and memory encoding and integration[14]. The overlap between mTBI and PTSD may be accounted for at least in part by overlap in symptoms, regardless of etiology. Core symptoms of PTSD and postconcussive syndrome include problems with concentration/attention, memory, sleep disturbance, and irritability[15,16]. Moreover, cognitive complaints and objective neurocognitive deficits are common among individuals with PTSD, even in the absence of TBI history[11,17].

Comorbidity and neuropsychiatric symptom overlap pose challenges for the treatment of individuals with both mTBI and PTSD. There are no established evidence-based treatments or treatment guidelines for individuals with comorbid mTBI and PTSD[10,18] due in large part to the complexity of this population and uncertainty about specific causal or maintaining factors. For example, given the comorbidity and symptom overlap, it can be difficult to determine whether problems and disruptions in functioning are due to mTBI, PTSD, or both[10,19], and hence, how to prioritize treatment (e.g., what to treat first). Further, it is unclear to what extent existing treatments for each disorder can be adherently and effectively implemented for the other. For instance, the two evidence-based treatments for PTSD that are widely disseminated throughout the VA are Cognitive Processing Therapy[20] and Prolonged Exposure[21]. Both are considered "trauma processing"

therapies and require a moderate degree of cognitive resources and assume normative learning and emotion regulation abilities. It is possible that cognitive deficits that occur with mTBI could interfere with these treatments[22,23], though this is not well-studied. Preliminary studies provide some evidence that individuals with mTBI can engage in and benefit from PE and CPT[24,25], yet controlled trials have not been conducted and the impact of these treatments on cognitive symptoms remains unknown.

Likewise, it is conceivable that treatment of cognitive problems related to mTBI could be impeded by symptoms specific to PTSD, such as avoidance and emotion dysregulation[26], though no study has evaluated treatment for mTBI-related problems among individuals with comorbid mTBI/PTSD. There are few studies evaluating treatment for mTBI-related cognitive impairment alone, due in large part to controversies regarding definition and measurement of mTBI and etiology of cognitive difficulties[27]. Investigators from our research group[28] conducted a non-randomized pilot study examining the efficacy of cognitive strategy training in OEF/OIF Veterans with mTBI for whom PTSD symptom severity was also evaluated (by the PTSD Checklist). Average pre-treatment levels of PTSD were above clinical cut-off for syndromal PTSD. At post-test, Veterans reported significant improvement of cognitive symptom severity, depression, and quality of life; however, no changes were evident in PTSD severity.

Further complicating treatment decisions, current theories suggest the symptoms of mTBI and PTSD are interrelated by two-way relationships, creating multiple "vicious cycle" feedback loops such that mTBI and PTSD have the potential to become mutually self-sustaining[27,28,29]. For instance, comorbid PTSD and mTBI-initiated cognitive problems could result in maladaptive behaviors that reduce postdeployment occupational and social functioning, leading to increased stress that exacerbates PTSD and cognitive problems; increased stress and cognitive problems then result in further vocational decline (or unemployment) and relationship problems, and so on. Also implicated in these theories are the impacts of additional common comorbidities with mTBI, and PTSD, including chronic pain, depression, and functional impairment due to physical injuries[30]. As such, most current treatment recommendations suggest a holistic or integrated treatment approach for comorbid mTBI/PTSD targeting symptoms and functionality rather than etiology[10,31.]

Veterans with mTBI and PTSD may benefit from alternative, present-centered approaches that emphasize first improving daily functioning, quality of life, and related patient-centered outcomes.
Based on population complexities and heterogeneity, difficulties in isolating causal and maintaining factors, and recommendations in the field, we are proposing a treatment for comorbid mTBI and PTSD that directly targets daily functioning and quality of life. There are additional reasons to consider alternative, present-centered approaches. In the treatment of PTSD, there exist numerous barriers to the provision of evidence-based, trauma-processing therapies[32]. Among Veterans, commonly reported barriers include stigma about seeking mental health care, difficulties accessing care, and competing life circumstances (e.g., childcare[33]). Of those who do seek care there is substantial drop-out from trauma-focused treatments (upwards of 50%[34]) with an overall recovery rate for such treatments estimated at 40% when non-completers are considered[35]. Further, there is evidence that many Veterans are disinclined to talk about past traumatic experiences[36] and instead have a preference for present-focused, skills-based interventions[37]. Present-centered treatments have been found to be efficacious in the treatment of PTSD with less treatment drop-out and comparable long-term outcomes relative to trauma focused treatments[38,39]. Additional provider- and systems-level barriers to the provision of trauma-focused treatments include insufficient training/confidence and time. Even in the VA where

most clinicians in PTSD specialty clinics have been trained in CPT or PE, a recent national survey found that fewer than 30% of patients were receiving these treatments[40]. Hoge[35] has estimated that, due to issues of tolerability, evidence-based trauma-focused PTSD treatments will only reach about 20% of all Veterans in need. Though not yet studied, barriers to care may be even greater among those with comorbid mTBI and PTSD due to their increased functional disabilities. To increase the reach of mental healthcare services, additional treatments are needed that are more accessible to the large numbers of Veterans with PTSD and comorbid mTBI/PTSD not currently accessing or benefitting from care.

Our proposed treatment for comorbid mTBI/PTSD, Cognitively-Augmented Behavioral Activation (CABA) combines and builds on our previously independent treatment development efforts. Next we describe our independent research followed by our collaborative work and the focus of this proposal.
Cognitive Interventions for mTBI. Dr. Huckans and colleagues initially developed an 8-week manualized treatment (Cognitive Strategies Training, CST) for cognitive symptoms associated with mTBI, consisting of group interactive didactics, in-class discussions, and activities which introduce participants to a variety of internal strategies and external aids designed to help them manage problems with memory, attention, planning, and organization. CST aims to increase overall functionality among individuals with mTBI by encouraging participants to apply their new skills to areas in their lives that are most adversely impacted by cognitive problems. Based on this initial work, CST was revised and renamed Compensatory Cognitive Training (CCT). Outcome data for both the open trial of the initial treatment[28] and the subsequent randomized controlled trial of CCT (VA funded through RR&D Merit Review, Storzbach, PI) are strong. CCT participants are demonstrating significant reductions in cognitive symptoms and depression. Importantly, participants have not shown significant reduction in symptoms of PTSD, suggesting the need for PTSD-specific treatment components. For further details see the Preliminary Studies section.

Behavioral Activation for PTSD. Wagner and Jakupcak have developed an adaptation of Behavioral Activation therapy (BA) for PTSD for the large number of Veterans who decline, drop out of, or do not have access to trauma-focused treatments. BA is a well-established treatment for depression[41,42,43,44] that targets patterns of avoidance and involves the identification and enactment of activities that are reinforcing to the individual and consistent with his/her long-term goals[45]. As such, case formulations and treatment planning are ideographic and patient-centered, based on empirically-supported principles of change. *The rationale for the application of BA to PTSD is based on the central role of avoidance in the development and maintenance of PTSD[46], and is consistent with contemporary views of mental disorders which identify unifying constructs, including avoidance, across a range of disorders[47].* Similar to *in vivo* exposure typical of CBT treatment for PTSD, engaging in goal-directed activity may allow for re-learning to conditioned trauma-related cues. BA differs from *in vivo* exposure in that the focus is specific to activities that are consistent with Veterans' goals, as opposed to those that are avoided because they elicit fear or anxiety.

Initial studies from our research group showed BA significantly reduced PTSD symptoms among both civilians[48] and military Veterans[49,50,51]. Importantly, researchers outside of our group have also found beneficial effects of BA for the treatment of PTSD[52,53,54]. Our most recent version of BA builds on previous work and was recently evaluated in a dual-site, randomized controlled trial of BA for PTSD compared to Treatment as Usual (PTSD specialty care) (Wagner & Jakupcak, CSR&D VA Merit Review). Results showed that BA significantly reduced PTSD symptoms with strong effect sizes and demonstrated some superiority over specialty PTSD

treatment (see Preliminary Studies for details). Moreover, findings also indicate that Veterans who screened positive for mTBI demonstrated an attenuated response to BA, underscoring the importance of augmenting this treatment with additional strategies to address the unique needs of those with mTBI/PTSD.

Pilot Data on Our Combined Intervention (Cognitively-Augmented Behavioral Activation, CABA) are Promising. *CABA is an integration of CCT for mTBI-related problems and BA for PTSD. Our rationale for combining CCT and BA is based on compatibilities in their structures and approach and the unifying focus on increasing functionality. Further, although not the focus of the current study, previous research on BA suggests this integration could address additional comorbities of the mTBI/PTSD population, including depression[42] and pain-related problems[55].* CABA is a 10-session treatment delivered in weekly 90 minute individual therapy sessions. At its core, CABA involves using Behavioral Activation to identify meaningful goals and activities while simultaneously learning cognitive strategies to aid in working towards those goals. The initial phase of CABA is devoted to psychoeducation about mTBI and PTSD, the rationale for BA, and lifestyle strategies that can improve cognitive functioning and mood. Cognitive compensatory skills are taught in each subsequent week that include internal and external strategies to help manage problems with memory, attention, and executive functions. The participant and provider spend portions of each session applying the cognitive skills to managing real life situations and increasing behavioral activation in the service of personal goals. Pilot data on 5 Veterans indicate that CABA significantly reduces PTSD, depression, and cognitive symptoms. Treatment details and pilot data are provided below.

Relevance of the proposed work to the VA Patient Care Mission

Demonstrating that an intervention specifically designed for the treatment of comorbid mTBI/PTSD is effective for both PTSD and cognitively-related functional impairment would be a significant innovation addressing a large gap in currently available treatments for Veterans. If found to be efficacious, the CABA treatment could be quickly disseminated to all VHA facilities. The CABA intervention would not only be useful in PTSD specialty care clinics, but could also be implemented in rehabilitation settings such as Polytrauma or Neuropsychology Clinics, specifically targeting Veterans with mTBI/PTSD who may not seek out traditional mental health treatment. The program's portability and ready availability make it immediately possible to deliver evidence-based treatment specifically designed for Veterans with comorbid mTBI/PTSD. Future studies will compare CABA to alternative treatments toward further identifying the most effective treatments for mTBI/PTSD. **Our proposed study is consistent with one of the explicitly stated missions of RR&D which is to ensure that Veterans achieve maximal recovery from combat-related neurotrauma by addressing co-occurring conditions or "polytrauma."**

PRELIMINARY STUDIES AND CURRENT STATUS OF THE FIELD

The proposed study is a continuation of multiple collaborative efforts at VA Portland HCS and Puget Sound HCS. A series of studies investigating treatments for traumatic psychological effects of battlefield deployment has culminated in the piloting of a new intervention, Cognitively Augmented Behavioral Activation (CABA), specifically designed for treatment of Veterans with comorbid mTBI/PTSD. Wagner and Jakupcak have been pursuing modifications of Behavioral Activation therapy to target PTSD as well as comorbid PTSD and depression among both civilian and Veteran populations. They recently completed a VA-funded (CSR&D, Merit Review) for a dual-site (Portland and Seattle VAs) randomized controlled trial of BA for the treatment of

PTSD among OIF/OEF Veterans. Concurrent with Wagner and Jakupcak's research on BA for PTSD, Storzbach and Huckans have been conducting research on cognitive rehabilitation for Veterans with mTBI. In 2007, Dr. Huckans developed and initiated the CST pilot study at VAPORHCS. Subsequently, Dr. Storzbach's currently ongoing 3-year 4-site (VA Portland HCS, VA Puget Sound HCS, VA San Diego HCS, and Boise VAMC) randomized controlled trial of CCT was funded through a VA Merit Review award. The study evaluates the efficacy of a manualized, 10-week, CCT group intervention for OEF/OIF Veterans with cognitive disorder resulting from mTBI.

Behavioral Activation for Veterans with PTSD[49]. Feasibility and effectiveness of BA for PTSD was examined in a sample of 11 Veterans from a VA outpatient PTSD clinic in this pre-post open trial pilot study. The sample was primarily male, Vietnam era Veterans all meeting diagnostic criteria for PTSD. Given the chronic nature of PTSD in this sample, BA was delivered in its comprehensive (i.e, 16-session) format. There was a statistically significant reduction in PTSD symptom severity, with five Veterans demonstrating reliable symptom reductions on the Clinician-Administered PTSD Scale for DSM-IV (CAPS-IV)[56] that ranged from 12 to 44 points (M = 21.6). Six of ten Veterans demonstrated symptom reduction on the PTSD Checklist[57] and one demonstrated an increase in symptom severity. The decrease in PTSD scores was consistent with small to medium effect sizes. These results provide initial support for the application of BA for the treatment of PTSD among Veterans. Change was evident among Veterans with chronic symptoms of PTSD and complex psychiatric profiles, suggesting stronger results would be likely among less chronic and severe populations.

Behavioral Activation as an early intervention for PTSD among recently injured trauma survivors[48]. This study is an initial examination of BA for the treatment of PTSD among civilian survivors of traumatic injury. The intent was to provide BA as an early intervention in an ecologically valid (real-world) manner. Participants were 8 patients recruited from the surgical ward of a Level 1 trauma center, who met diagnostic criteria for PTSD one month post-trauma, randomly assigned to either BA or treatment as usual (TAU). This was an ethnically diverse sample of men and women, ages 18-65. In consultation with the lead author of the behavioral activation manual (Dr. Christopher Martell), the components of comprehensive BA were modified to be delivered in 4-6, 90 minute sessions. In addition, the psychoeducational materials were modified to include descriptions of PTSD symptoms and to emphasize the role of avoidance in PTSD. The BA group demonstrated significantly greater reductions in PTSD (as measured by the PCL) than the control group (t = 2.07; one-tailed $p < .05$; unbiased Hedges's g = 1.27) and there was a trend for the BA group to score better than the control group on a measure of physical functioning (t = 1.89; one-tailed p = .05; unbiased Hedges's g = 1.16). These preliminary data added to the promise of BA as an effective alternative for the early intervention of PTSD.

Behavioral Activation as a primary-care based treatment for PTSD and depression among OIF/OEF Veterans[50]. This preliminary study examined treatment-satisfaction and potential therapeutic benefits of BA as a primary care-based treatment for PTSD and depression among OIF/OEF Veterans. Eight Veterans were enrolled, 6 completed at least four sessions, and 5 Veterans completed post-treatment and 3-month follow-up assessments after receiving 5-8 weekly sessions of Behavioral Activation delivered in a specialty post-deployment primary care clinic. The BA manual was similar to that used by Wagner and colleagues[48], with the provision of additional sessions (up to 8) in an effort to strengthen treatment effects. Participants demonstrated a significant reduction in PTSD over time as assessed by both the Clinician Administered PTSD Scale[56] (F(2,3) = 10.66, $p < .05$, d = 1.44, with an average drop in CAPS scores of 23.2 points) and PTSD Checklist[57] (F(2,3) =

24.97, $p < .05$, $d = 1.87$). Effect sizes for change in depression and quality of life were strong ($d = 1.28$ and .62, respectively) though not statistically significant. Importantly, treatment satisfaction ratings were high.

Behavioral Activation as an alternative treatment for PTSD among OIF/OEF Veterans (Wagner & Jakupcak, in preparation). This VA-funded Merit study (CSR&D) examined our 8-session (individual therapy) adaptation of Behavioral Activation (BA) for PTSD among returning OIF/OEF Veterans. Utilizing a randomized controlled design and two sites (Portland and Seattle VAs), BA was compared to Treatment as Usual (TAU), defined as referral to PTSD Specialty Clinics (TAU treatment was not controlled to allow for maximum flexibility in treatment planning and to reflect actual practice in PTSD specialty clinics; all TAU providers were trained in either Prolonged Exposure (PE), Cognitive Processing Therapy (CPT), or both, and Veterans were offered a minimum of 8 individual therapy appointments). Our primary aim was to determine whether BA is effective in reducing PTSD and depression symptoms and therefore is an effective alternative treatment for veterans with PTSD (e.g., for Veterans who do not want or cannot access trauma processing treatments). Therefore, we examined within-group as well as between-group effects. Participants were evaluated for PTSD, depression, and treatment satisfaction at pre- and post-treatment as well as 3-month follow-up.

Eighty Veterans (40 in each group) were enrolled in the study. Repeated measures analyses showed strong treatment effects over time for PTSD across groups as measured by both the CAPS and PCL (see Table 1), indicating that both BA and treatment within PTSD specialty clinics are effective in the treatment of PTSD. Effect sizes for time (eta^2) were moderate (CAPS=.42; PCL=.43). Time effects were also evident for depression as measured by the BDI (eta^2=.19). There was a significant group by time interaction for the PCL (eta^2=.08), such that **Veterans receiving BA reported greater reductions in PTSD on this measure compared to those in TAU**. Relevant to the current proposal, exploratory analyses were performed by adding history of mTBI to the above model. There was not a significant three-way interaction. However, two-way interactions of mTBI by time (F=3.3, p=.041, eta^2=.07) and treatment by time (F=3.47, p=.036, eta^2= .08) suggest that across groups, individuals without a history of mTBI did significantly better, though did not maintain treatment gains over time to the same extent as those with a history of mTBI. Treatment satisfaction ratings were high for both groups and comparable. These data strongly support the effectiveness of BA as an alternative treatment for PTSD among returning Veterans (i.e., that it is <u>at least</u> as effective and acceptable as specialty PTSD treatment that includes PE or CPT), and further support the rationale for our combined intervention for individuals with both PTSD and TBI.

Table 1. Pre- and Post-Treatment and 3-month follow-up Scores (means, standard deviations)

	BA			TAU				Time x
	Pre	Post	3-mo	Pre	Post	3-mo	Time F	Group F
CAPS	72.7 (14.5)	54.7 (24.1)	57.7 (26.0)	79.4 (16.0)	62.6 (27.5)	56.5 (26.5)	31.0**	ns
PCL	58.6 (7.7)	43.3 (12.8)	48.8 (14.4)	58.1 (8.6)	49.8 (13.1)	47.3 (13.4)	32.24**	3.8*
BDI-II	24.2 (7.0)	18.7 (11.7)	21.0 (12.0)	24.4 (8.2)	20.3 (9.4)	18.3 (10.4)	10.1**	ns

CAPS = Clinician Administered PTSD Scale; PCL = PTSD Checklist; BDI-II = Beck Depression Inventory; **p<.01; *p<.05

Cognitive Strategies Training CST (CST) Pilot Study[28]: Please see published study in Appendix 4 for details. Study findings demonstrated beneficial effects of CST has on self-reported cognitive functioning,

increased use of compensatory strategies and aids, and reduction of psychiatric symptoms. This study was used to support the proposal for the multi-site VA Merit Review study that is currently ongoing (see below).

Current CCT multi-site Merit Review study: The study aims to evaluate the efficacy of a manualized, 10-week, group intervention (Compensatory Cognitive Training, CCT) for OEF/OIF Veterans with cognitive disorder resulting from mTBI. A modification of CST, CCT consists of weekly 120-minute group sessions over 10 weeks. The CCT curriculum is an expansion of CST that includes non-overlapping elements of a similar manual developed by Elizabeth Twamley and her colleagues at the San Diego VA[59] in particular: skills to manage sleep problems, fatigue, headaches, anxiety/mood difficulties, improve active listening, and promote relaxation and mindfulness. CCT also added the use of behavioral analyses (as in BA) to individualize the treatment and interventions and therefore improve outcomes. Study design is a randomized controlled trial, comparing CCT to usual care (UC). The study is expected to conclude in 2013. Participants in the CCT group receive the CCT intervention during the first ten weeks of their participation in the study, whereas UC participants continue to receive usual care (which can include medical, pharmacological, and psychotherapeutic care, but no CCT intervention) during study participation. Both groups undergo evaluations at baseline, 5 weeks (midway through CCT), 10 weeks (immediately after CCT completion), and 15 weeks (5 weeks after CCT completion). Interim pre- and post-treatment cognitive results are shown in Table 2.

Table 2. Early interim results of CCT study from participants receiving CCT (n = 20)

	Pre-Tx score	Post-Tx score	df	t	p-value	Cohen's d
HVLT-R	44.58 ± 12.38	54.89 ± 6.39	19	-4.06	.001	1.05
Digit Span	8.50 ± 2.67	10.80 ± 2.71	19	-4.20	<.001	.85
Letter Fluency	9.90 ± 3.29	12.05 ± 2.30	19	-5.48	<.001	.96
Category Fluency	10.60 ± 3.19	12.15 ± 3.00	19	-2.87	.01	.50

Note: Data expressed as mean total score ± standard deviation unless otherwise noted.

Cognitively-Augmented Behavioral Activation (CABA) clinical pilot study: CABA was developed by members of our research team (Dr. Roost, with feedback by Drs. Storzbach and Wagner) and combines central components of both BA for PTSD and CCT (see "Experimental Intervention" below for a detailed description of CABA; see Appendix 2 for a draft of CABA). CABA is a 10-week manualized treatment for comorbid TBI/PTSD, delivered in 90 minute individual sessions. A clinical pilot study, which began in 2011, is being conducted in order to evaluate the effectiveness of this novel approach for individuals with comorbid TBI/PTSD. To date, 5 participants have completed the treatment. All participants were OEF/OIF male Veterans with PTSD and cognitive complaints with mean age of 37. All Veterans completed the 10-week treatment; however, one participant did not complete the post-assessment due to the birth of his baby. The high adherence rate noted during the clinical pilot study is reflective of CABA's acceptability and tolerability. Pre- and post-assessment measures (one week prior to and one week following treatment) included the BDI-II; PCL-M; NSI; MSNQ; PRMQ; MCQ; WAIS IV Matrix Reasoning; TMT A and B; and RBANS List Learning, Story Memory, Digit Span, List Recall, Story Recall, and Figure Recall. Analyses revealed a significant reduction in depression (BDI-II; $t=3.978$; $p<0.05$), PTSD (PCL-M; $t=3.015$; $p<0.05$), cognitive complaints (NSI; $t=7.816$; $p<0.01$), and attention/organization problems (MSNQ; t=3/757; $p<0.05$) after the CABA intervention. All effect sizes (Cohen's d) were large: 0.86 for the BDI-II, 0.94 for the PCL-M, 1.61 for the NSI, and 1.26 for the MSNQ.

There was a trend for better performance on most objective neuropsychological measures (RBANS; TMT A & B; WAIS-IV Matrix Reasoning) after the CABA intervention; however, none reached statistical significance.

OIF/OEF/OND Veterans are targeted for this project due to the fact that Veterans returning from the current conflicts in Iraq and Afghanistan exhibit high rates of comorbid mTBI/PTSD for which evidence-based treatments do not currently exist. The study targets outpatients in that treatment for both mTBI and PTSD outside of this study occur regularly within the VA clinical setting via outpatient appointments. Veterans must be adults to serve and thus the Veterans we recruit will all be 18 years or older. Seniors over 65 with cognitive complaints will be excluded due to increased risk of age related mild cognitive impairments as opposed to mTBI which would confound our results. There will be no other restrictions on age, ethnicity, or race, and both men and women will be included. Recruitment fliers will specifically include the statement, "women and members of minority groups are encouraged to participate." Of the OEF/OIF/OND veterans with mTBI, 95% of veterans are reported to be male. Seventy-percent of these veterans reported their race to be white, while 19% reported as non-white. The race of 11% of these veterans was categorized as unknown. This breakdown of gender and race is similar to populations seen in studies of OEF/OIF veterans with mTBI conducted by this research group. Thus, we would expect to recruit a similar population that would be representative of OEF/OIF veterans with mTBI.

3.0 Objectives

The primary objective of this study is to evaluate the efficacy of CABA for Veterans with comorbid mTBI/PTSD. The overall goal is to develop an evidence-based manualized treatment that can be readily implemented in VHA treatment settings. The study will use a randomized controlled design to address the following specific aims and hypotheses:

Specific Aim 1: To determine if CABA reduces PTSD symptoms.
Specific Aim 2: To determine if CABA reduces cognitive-related functional impairment.
Specific Aim 3: To determine if CABA is associated with additional positive clinical effects in patient-centered outcomes, including improved mood, adaptive cognitive function, and quality of life.
Specific Aim 4: To evaluate the overall acceptability of this treatment.

Primary hypotheses:
1a) CABA treated comorbid mTBI/PTSD-diagnosed Veterans will demonstrate significantly decreased PTSD symptom severity compared to those receiving Treatment as Usual (TAU), defined as standard PTSD specialty care.
1b) CABA treated comorbid mTBI/PTSD-diagnosed Veterans will display significantly decreased cognitive-related functional impairment compared to those in the TAU group.

Secondary hypotheses:
2a) CABA treated comorbid mTBI/PTSD-diagnosed Veterans will demonstrate additional significant improvements in patient-centered outcomes including depression symptom severity, cognitive symptoms, usage of cognitive strategies, and quality of life compared to a TAU group.

2b) Those receiving CABA will report significantly higher treatment satisfaction than those receiving TAU.

Exploratory Investigation to Provide Guidance for Future Research Directions: Exploratory analyses will examine possible mediator and moderator variables and secondary outcome variables, including measures of neuropsychological test performance and general functioning. We will also investigate whether CABA- associated treatment gains are maintained over a 6 month follow-up period (the 6 month follow-up is discontinued when the assessments/interventions are completed over telehealth).

4.0 Resources and Personnel

The study design makes use of the convergent availability of resources at the VA Portland Health Care System (VAPORHCS) and VA Puget Sound Healthcare System (VAPSHCS) in Seattle, WA where the research will be conducted. The treatment intervention will be conducted at both sites. A private room will be available at each site to ensure the confidentiality of participants. Office space is available at both medical centers for the safe and confidential storage of materials.

The following table includes a list of personnel who will work on the study including their roles, affiliations, and responsibilities.

Name	Affiliation	Role	Access to PHI?	Duties
Daniel Storzbach,Ph.D	VAPORHCS	Principal Investigator/Study Chair AND Portland Local Site	YES	Overall multisite study oversight; Portland Local site study oversight
Amy Wagner, Ph.D	VAPORHCS	Co-Principal Investigator/Study Chair	YES	Overall multisite study oversight
Kathleen Pagulayan, Ph.D	VAPSHCS	Seattle Local Site PI	YES	Seattle local site study oversight

Megan Callahan, Psy.D	VAPORHCS	Co-Investigator / Multisite Study Coordinator	YES	Overall multisite study management, provide the study intervention, recruit subjects, obtain ICF, administer surveys/interviews Provide the study intervention, recruit subjects, obtain ICF, administer surveys/interviews
Marilyn Huckans, Ph.D	VAPORHCS	Co-Investigator / Interventionist	YES	Provide the study intervention and assist multisite PI's.
Jennifer Vasterling, Ph.D	Boston VA	Co-Investigator / Consultant	NO	Consult on the study
Jesse Fann, Ph.D	University of WA	Co-Investigator / Consultant	NO	Consult on the study
Matthew Jakupcak, Ph.D	VAPSHCS	Co-Investigator / Interventionist	YES	Provide the study intervention and assist the Seattle Site PI.
Mai Roost, Ph.D	VAPORHCS	Co-Investigator / Interventionist	YES	Provide the study intervention and assist the Portland Site PI
Maya O'Neil, Ph.D	VAPORHCS	Co-Investigator / Multisite Data Manager	YES	Will provide data analysis support locally (VAPORHCS)
Shah Golshan, Ph.D	UCSD	Co-Investigator / Statistician	NO	Will conduct randomization and overall interim and final data analyses
Halina Kowalski, MA	VAPORHCS	Co-Investigator	YES	Provide the study intervention and recruit subjects, obtain ICF, administer surveys/interviews

Randomization procedures as well as overall multisite study interim and final data analyses will be conducted by our contracted statistician, Shah Golshan, Ph.D who is affiliated with University of California, San Diego. Dr. Golshan will receive a "limited data set" copied in encrypted format sent via secure email. The "limited data set" is defined as such for inclusion of patient assessment dates and otherwise would be considered de-identified. A Data Use Agreement will be pursued between the VAPORHCS and Dr. Golshan recognizing the agreement of the terms for use of this data which shall be transmitted and accessed strictly for data analysis purposes pursuant to the goals of this study.

5.0 Study Procedures

5.1 Study Design

Overall design:

We propose a dual-site randomized controlled trial comparing Cognitively Augmented Behavioral Activation (CABA) with a treatment as usual control group (TAU). The study design makes use of the convergent availability of resources at the participating VAs (Portland and VA Puget Sound). VA Puget Sound has two divisions, Seattle and American Lake, and all study activities may take place at either division. Participants will be Veterans ≤ 55 years of age (both male and female) with comorbid mTBI/PTSD enrolled for outpatient medical services at these VAs. A total of *192* participants will be recruited, 96 at each site. As described in the "Overall Clinical Trial Plan" section, participants in CABA will receive the CABA intervention via telehealth during the first 14 weeks of study participation, whereas TAU participants will receive usual care (no CABA intervention) during study participation (but will be offered CABA at no cost after the end of the study). In order to adhere to a national VA performance measure that requires 8 sessions to be delivered over a 14-week period, participants will be contacted by phone by a blinded assessor for the mid-treatment assessment 7 weeks after the onset of treatment. Allowing 14 weeks to complete a 10-session treatment protocol accounts for cancellations and missed sessions. Participants will then be seen for a follow-up assessment 14 weeks after initiating treatment. During their study participation, all participants will continue to receive their usual medical care. Due to the COVID-19 pandemic and hospital restrictions for in-person visits, all study operations will be conducted remotely. A detailed description of this plan is described in the following section.

Overall Clinical Trial Plan:

Experimental intervention: Cognitively Augmented Behavioral Activation (CABA). CABA combines key elements of BA for PTSD and CCT. In its comprehensive form as a treatment for depression[45], BA includes several key features, including orientation to the rationale and components of treatment, careful tracking of the patient's mood and relationship between activities and mood through behavioral analyses, identification of reinforcing goals and activities, identification of patterns of avoidance that block attainment of these goals and activities, and strategies for engaging the individual in alternative coping that increases behaviors that are reinforcing. This treatment was originally developed to be delivered in 16-24 weekly sessions. When proposing a study to examine the efficacy of BA for PTSD, Dr. Amy Wagner, a PI on this study, consulted

with the lead author of the behavioral activation manual, Dr. Martell. As a result of this consultation, the components of comprehensive BA were modified to be delivered in 8 60-minute sessions. The decision to condense the treatment was based in part on the early intervention focus of this work. The aim was to develop a treatment that was easier to complete for Veterans and easier to deliver in primary care settings, thus increasing the potential for future dissemination. Support for the effectiveness of BA delivered in a condensed format is supported[48,50,64]. In BA for PTSD, the psychoeducational materials were modified to include descriptions of PTSD symptoms and to emphasize the role of avoidance in PTSD. Activity scheduling was maintained as the central organizing tool, with emphasis placed on increasing activities consistent with the individual's short- and long-term goals and values. Since the presence of physical injury (which can be a result of trauma) can lead to new restrictions in activities (short term, long term, or permanent), greater attention was spent on goal identification and development. During behavioral analyses, attention was given to the full range of factors that may contribute to avoidance in those with trauma histories, including fear, pain, physical limitations, secondary emotions (e.g., shame), threat- and danger-related cognitions. To the extent that a patient's substance use can similarly be conceptualized as avoidant behavior [65], it can be targeted in this intervention as well.

Cognitive rehabilitation therapy used in CABA is taken from the Compensatory Cognitive Training (CCT) manual, which is a group intervention currently being used in Dr. Storzbach's Merit Review Study aimed at treating mTBI in Veterans. The CCT treatment manual is an integration of two previous treatment manuals: COGSMART at San Diego VAMC and CST at VAPORHCS. The CCT intervention is designed to be practical, portable, low-tech, and engaging to clients. The goal is to help participants develop new habits that will help them with real-world situations relevant to cognitive functioning. The 10-week CCT intervention is comprised of weekly two-hour sessions including interactive didactics, in-class discussions, and activities which introduce participants to a variety of lifestyle strategies, internal and external/environmental cognitive strategies, and external aids designed to help them manage problems with memory, attention, and executive functions. Participants are required to use a memory prosthetic of their choosing, either a paper day planner or an electronic calendar. Participants are given class handouts and weekly home exercises so they can practice and implement skills in their daily life. Participants are encouraged to practice the new skills during activities that relate to their most important life goals. Home exercises are discussed at subsequent sessions so that participants can receive feedback and troubleshoot application of new skills to their specific real life goals and problems. Participants receive extensive training in and practice with their day planners, with a particular focus on how the day planner can facilitate their use of other compensatory strategies taught in group (e.g., writing down important information for later reference, breaking tasks down into smaller steps, prioritizing healthy habits and other important life goals, using worksheets to aid with goal planning and problem solving).

CABA is designed as a 10-session treatment, to be delivered in 90" individual sessions (see Appendix 2 for a draft of the CABA manual). Due to the COVID-19 pandemic, these sessions will be provided via telehealth, including VA Video Connect (VVC, or alternative VA-approved video-based platform) or telephone.. CABA is shorter in duration than CCT because it is delivered individually. It is longer than the BA for PTSD manual because of the added CCT elements. The overlap between elements of CCT and BA for PTSD allows for a shorter treatment than would be required if each treatment were delivered independently. At its core, CABA involves using behavioral activation to identify meaningful goals and activities while simultaneously learning cognitive strategies to aid in working towards those goals. The initial stage of CABA will be devoted to psychoeducation on mTBI, psychoeducation on PTSD and BA, and lifestyle strategies that

can improve cognitive functioning and mood. After the initial phase, the Veteran will learn new cognitive compensatory skills each week that incorporate internal and external strategies to help manage problems with memory, attention, and executive functions. Participants are required to use a memory prosthetic of their choosing, either a paper day planner or an electronic calendar like a PDA or smart phone. Each participating site will offer paper day planners to participants. As part of this skills training, the Veteran and the provider will spend portions of each session applying the cognitive skills to real life situations. In CABA, the real life situation to which the cognitive skills will be applied will be chosen through the identification of goals and activities, which is a BA-specific intervention. For example, each week the Veteran and provider will work on scheduling activities that are reinforcing to the Veteran. If the cognitive skill for the week is learning to use a day planner, for homework that week the Veteran will apply the skill of using a day planner to aid in completion of the scheduled activity. When the Veteran returns the following week, the initial portion of the session will be spent reviewing the homework and problem-solving any barriers that the Veteran had with regard to completing the homework. As in BA for PTSD, attention is given to avoidance patterns (as well as cognitive factors) that may be interfering with increasing activation and goal attainment and to improving overall functionality. Behavioral analyses are maintained as a central tool for individualizing goals and interventions.

Control Intervention: Treatment as Usual (TAU). TAU refers to the usual care for PTSD and mTBI provided in the VA clinics represented in our study. The VA sites employ routine screening for PTSD and mTBI, and providers at both sites are familiar with the VA Clinical Practice Guidelines for the treatment of PTSD and mTBI. Actual clinical practice varies between sites and between providers within sites, as is typical of the VA health care system in general. In order to standardize the practices of the two sites as much as possible and ensure that the practices reflect typical practices across VA medical centers, participants assigned to TAU will be first offered a referral for PTSD specialty treatment at each site (e.g, to the PTSD Clinical team at the Portland site and either the Deployment Health Clinic or the PTSD Outpatient Clinic at the VA Puget Sound). Across these PTSD specialty clinics, psychosocial treatment options include skills focused interventions (e.g., skills for managing PTSD, either in group or individual modalities) and trauma-processing therapies. Emphasis is on providing evidenced-based psychotherapy for PTSD, and most providers are trained in and provide Prolonged Exposure (PE) and/or Cognitive Processing Therapy (CPT). TAU participants may also receive pharmacotherapy, either within PTSD specialty clinics or from primary care providers. To equate quantity of treatment across conditions, participants in TAU will be offered an evidence based treatment for PTSD (i.e., PE or CPT) which consists of 8-12 structured sessions designed to be delivered over a 14-weeks. Per our informed consent, we make Veterans aware of other treatments available and we are asking participants to not engage in CPT or PE concurrent to participating in CABA. However, at the end of participation, all Veterans will have the option of referral to CPT/PE. To ensure adequate attention to TBI-related difficulties, it will be directly communicated to the assigned PTSD care provider, referring provider, and primary care provider that the Veteran has been diagnosed with mTBI and may benefit from further assessment and treatment of mTBI-related difficulties. Cognitive problems are typically addressed in the Polytrauma, Neuropsychology, and Speech Pathology clinics and referrals to these clinics will be unrestricted. Therefore, TAU can be considered “optimized” usual care. Wewill record all treatment received.

Procedures: Patients who screen positive for comorbid mTBI/PTSD may be offered a flyer describing the study by their provider. The flyer will include phone numbers to contact the study coordinator. By partial waiver of informed consent for screening purposes, interested participants can also be referred to the

study team by the participant's provider to be contacted for prescreening or, at VA Puget Sound, can be identified through the Repository and Registry for Behavioral Neuroscience Research.

Clinical providers may refer interested patients and document their willingness to be contacted by the study through CPRS via their progress notes and using templated language provided to them (See Appendix G). Clinicians may also send referral information via encrypted email with the same templated documentation (or comparable documentation that the Veteran is interested in hearing more about the study and gives permission for research staff to contact them). Following a chart review and preliminary phone screen to determine eligibility, potential participants will be scheduled for an initial telehealth (by video or telephone) appointment during which they will be consented to the study. Consented participants will be instructed to return the informed consent form (ICF) and Authorization for Use and Release of Individually Identifiable Health Information Collected for VHA Research (HIPAA form) to the study team using a prepaid and preaddressed envelope. Once received, a study team member will complete an assessment appointment with the participant via telehealth. After all eligibility criteria are met and the assessment is complete, If telehealth appointments are conducted via VA Video Connect (VVC) platform, participants may receive automated reminders and appointment links over email, consistent with procedures for clinical appointments using VVC. the study statistician will randomly assign eligible participants to one of the two treatment options and will notify the site study coordinator about randomization status. The site study coordinator or other appropriate research team member, will contact the participants to inform them of their group assignment. Those assigned to CABA will be contacted by their therapist and tele-or video-therapy will commence. Those assigned to TAU will be offered a referral for PTSD specialty care. The assessors will be blind to group status throughout the study whenever possible. Consistent with a national VA performance measure that requires 8 sessions to be delivered over a 14 week period, participants will be contacted by phone by a blinded assessor for the mid-treatment assessment 7 weeks after the onset of treatment. Allowing 14 weeks to complete a 10 session treatment protocol accounts for cancellations and missed sessions. Participants will then be seen for follow-up assessments 14 weeks after initiating treatment. In order to minimize drop-out and maximize retention of individuals for intent-to-treat analyses, extensive efforts will be made to stay in contact with all study participants, including individuals who drop out of treatment. CABA participants who are deemed nonresponders or relapsers (do not evidence at least a 20% reduction in PTSD or cognitive symptoms) at the post-assessment or follow-up assessment (or an increase in suicidality or substance abuse), and other participants as clinically appropriate, will be offered alternative treatment or appropriate referrals.

Blinding: Subject and facilitator blinding is not feasible due to the study design: a treatment group vs. a usual care group. The assessors will be blind to group status throughout the study.

Randomization: Randomization tables will be prepared by Dr. Golshan, the statistician, at the beginning of the study, and he will notify the site study coordinator of the participant's randomization status. Over the course of the study, Dr. Golshan will monitor enrollment; if imbalance occurs, he will recommend appropriate adjustment.

Risks to Subjects

a. Human Subjects Involvement and Characteristics

Participants will be 192 Veterans ≤ 55 years of age receiving clinical care at the VAPSHCS and VAPORHCS

(Portland and Vancouver campuses) and affiliated clinics, who meet diagnostic criteria for comorbid mTBI/PTSD. Employees or students, pregnant women, economically and/or educationally disadvantaged persons, and terminally ill patients will be included. Based on the nature of the intervention, it is anticipated that this treatment will present minimal risk to these populations. Individuals with impaired decision making capacity, illiterate, or who have limited or no English language proficiency will be excluded on the basis of possible diminished cognitive ability that would compromise their involvement in this treatment. Prisoners will be excluded from the study as a result of this study being conducted on an outpatient basis only. There will be no restrictions on, ethnicity, or race, and both men and women will be included. Recruitment fliers will specifically include the statement, "women and members of minority groups are encouraged to participate." Additional inclusion criteria include: 1) Diagnosis of PTSD made by use of the Clinician Administered PTSD Scale (Blake et al., 1990); 2) screened positive for mTBI on the Structured Interview for Collecting Head Trauma Event Characteristics as outlined by the VA/DoD Clinical Practice Guideline for Management of Concussion/mTBI and positively endorsed any of the Neurobehavioral Symptom Inventory (NSI; Cicerone & Kalmar, 1995) cognitive symptoms items (items 13-17); 3) English speaking, willing to attend weekly treatment telehealth sessions (if randomized to the CABA condition) and the follow-up assessments, and willing to refrain from additional treatment for PTSD during the first 3 1/2 months of the active phase of treatment if they are assigned to the CABA condition; and 4) willingness to participate in audio-recorded sessions.

b. Sources of Materials

Several sources of information will serve as data for the study, including neuropsychological assessments and standardized diagnostic interviews and questionnaires administered by study personnel, audiotaped treatment sessions for individuals assigned to the CABA group (to be used for supervision, determination of adherence and competence in the intervention, achieving reliability in ratings of adherence and competence and training purposes), daily monitoring forms for individuals in the CABA group, and information from medical records. Other than the information derived from the medical records, data will be collected solely for research purposes. However, because of the clinically-relevant nature of much of this information, patients will be informed that these data may be reported in their medical record, as clinically indicated. Data will be labeled with a code number that is unique to each patient in the study. All hard copy data will be stored in locked filing cabinets in locked rooms, while all electronic data will be stored in password-protected files in a limited access folder on the secure VA network drive. Data may be temporarily stored in a locked filing cabinet at the American Lake division until it can be transported to the Seattle VA. Data will be transported between American Lake and Seattle divisions by study staff in HIPAA-compliant locked containers. Each study site will maintain a key code that links that site's patients with their coded identifier. This key code will be stored separately from all other study data and available and maintained only to the multisite co-PIs, the site PI's, the multi-site project coordinator, and the site coordinators and research assistants. Any materials with protected health information (e.g., Informed Consents) will be stored in separate locked filing cabinets from coded materials to ensure the security of patient privacy.

c. Potential Risks

Minimal risk is anticipated with the current investigation. The psychotherapeutic intervention under investigation is consistent with the treatments recommended in the VA/DoD Clinical Care Guidelines for the treatment of PTSD and mTBI. Participants randomized to TAU will have identical opportunities for treatment as non-research patients. Regarding research risk, participants may experience anxiety and/or distress during the assessment procedure and during the course of treatment. Participants may also experience discomfort as a result of being audio recorded during the course of therapy. Participants also might not experience symptomatic relief from the intervention. Potential study participants will be informed that they may choose not to participate in the study without risk to their medical care, and that similar interventions not being evaluated in the study are available in the facility without participation in the research.

All study personnel who conduct the assessments and interventions will be qualified, trained, and closely supervised by the co-Principal Investigators (co-PIs). Participants will be provided with emergency contact numbers. All participants will be clearly informed of their right to withdraw from the study at any point without adversely impacting their routine medical, psychiatric, or psychotherapeutic care.

Safety monitoring will be performed by the study staff who conduct interviews, administer assessment questionnaires, conduct psychological and cognitive assessments, and conduct interventions. Adverse events will be reported immediately to the co-PIs, who will examine the patient and determine if any additional evaluation or treatment is needed. The co-PIs will recommend termination of participation, provide appropriate referrals, and engage in follow-up if substantial decline in functioning is observed. Referral will also be offered to non-responders and any participant who requests further treatment. The co-PIs will ensure that adverse events are properly reported to the IRB. The co-PIs will review all cumulative adverse events quarterly to determine if there are any systematic problems as the co-PIs will be ultimately responsible for all safety monitoring conducted for this study.

Although the proposed study poses no serious risks to participants, participants may notify research personnel about pre-existing mental health issues that have not been previously identified by other VA providers. Therefore, participants will be referred to the VA's Mental Health Division for further assessment and/or treatment if a previously undiagnosed psychiatric disorder is identified. We will inform participants of this procedure as part of the informed consent process and participants must agree to this procedure to be eligible to participate in the study. This ensures that we can adequately manage any pre-existing clinical issues that become apparent through subject evaluation.

Adequacy of Protection from Risks

a. Protection Against Risk

Trained, closely supervised staff will conduct the assessments and the intervention. Assessors conducting diagnostic psychiatric interviews will have at least one year of graduate experience or equivalent work experience, and therapists will be master's or doctoral level. Drs. Wagner and Storzbach, licensed clinical psychologists, will review weekly therapy tapes and attend to any difficulties encountered. In addition, participants will be provided with emergency contact numbers. Finally, all participants will be clearly informed of their right to withdraw at any point and Drs. Wagner and Storzbach will recommend termination of participation (and provide appropriate referral and follow-up) if substantial decline in functioning is observed (including significant increase in alcohol or drug use). Referral will also be offered to nonresponders and any participant who requests further treatment. Specific procedures will be maintained to maximize the likelihood that participant research related material will secure and confidential. Data will be stored in locked filing cabinets and computer databases, without names or other potentially identifiable information attached; identifiable information will be kept separately and a coding system will be used to link data and identifiers.

All SAE's, UAP's, and protocol deviations occurring at either site will be communicated to the Co-PI's immediately and necessary documentation will be submitted to the CIRB within stipulated timeframes and via designated channels in accordance with the VA Central IRB Table of Reporting Requirements.

All study personnel will follow the policies and procedures for suicide prevention and management of suicidal behavior and its aftermath anywhere within the medical center or on the premises as outlined in the VAPORHCS Medical Center Memorandum No. 11-04 and in Memorandum TX-74 for Seattle both included in the study Suicide behavior protocol, Appendix A.

Imminent risk Protection: The following protocol applies to participants who express indication of imminent risk or clinical emergency; this includes concerns about suicidality and homicidality.

Participants may express indicators of risk either to the study clinician or to the study assessor; the protocol differs for each of these groups and is discussed below:

For study clinicians: If a participant presents to his/her study clinician/Interventionist with a clinical emergency (e.g. suicidality), the study clinician should address the situation as clinically appropriate. Concerns about imminent risk should be prompted by an examination of the participant's response to item #9 on the BDI (score > 2) and/or clinical inquiry. The clinician must assess and intervene within the study treatment protocol but is not limited by the parameters of the protocol in cases of imminent risk. Instead, in such cases, clinicians should address these situations consistent with optimal standards of care including hospitalization if required (see Suicidal/Homicidal Behavior Protocol in Attachment A).

In addition, any concerns of imminent risk among participants in the CABA condition are to be immediately communicated to the site investigators (Daniel Storzbach, Ph.D. at the VAPORHCS and Kathleen Pagulayan, Ph.D., at the VAPSHCS), including the course of action taken. The site PIs will review such cases and determine if additional intervention is necessary. This review and/or evaluation is not required of participants in the control group as they will be receiving usual VA care and evaluation and intervention for imminent risk will follow standard VA procedures.

For study assessors: Study assessors should follow the Suicidal/Homicidal Behavior Protocol under the following conditions: if a participant presents with a score of 2 or higher on item 9 on the Beck Depression Inventory, or when there is other information that suggests that the person may be at risk. Assessors must also contact the site investigators who will determine if additional intervention is necessary; this review and/or evaluation is not required of participants in the control group as they will be receiving usual VA care and evaluation and intervention for imminent risk will follow standard VA procedures. Participants may be connected via a "warm transfer" with the National Veterans Crisis Line or be instructed to go to their nearest medical facility's emergency department.

c. Potential Benefit of the Proposed Research to the Subject and Others

Participants in both the CABA and TAU conditions may experience a reduction in PTSD and/or TBI symptoms as benefit to participation in this study, though those assigned to CABA may experience a greater reduction in PTSD and/or TBI symptoms. Given that many Veterans with comorbid mTBI/PTSD do not respond well to current EBTs for PTSD because their cognitive problems interfere with their ability to optimally engage in treatment, this study may offer a treatment option for those who would not otherwise benefit from care and the benefit of this combined treatment would be available first to those assigned to the CABA conditions and then offered to TAU participants after their completion of the study. The risk of increased anxiety or distress (in the assessment or treatment components of the study) is balanced by the potential benefit of reduced distress and anxiety over time for study participants. Further, since the provision of CABA is also expected to reduce long- term health care utilization, this intervention may also lessen the burden of primary care providers.

d. Importance of Knowledge to Be Gained

In order to more effectively meet the mental health needs of Veterans with mTBI/PTSD, the present study aims to evaluate the effectiveness of a new hybrid treatment, Cognitively-Augmented Behavioral Activation for the treatment of PTSD, cognitive-problems, and functional impairment. Demonstrating that an intervention specifically designed for the treatment of comorbid mTBI/PTSD is effective for both PTSD and cognitively-related functional impairment would be a significant innovation that would address a large gap in currently available treatments for Veterans. If the treatment is found to be efficacious, the CABA manual could be

quickly disseminated to all VHA facilities. The CABA intervention would not only be useful in PTSD specialty care clinics, but could also be implemented in rehabilitation settings such as Polytrauma or Neuropsychology Clinics, specifically targeting Veterans with mTBI/PTSD who may be hesitant to seek out traditional mental health treatment. With the program's portability and ready availability, it will immediately be possible to deliver evidence-based treatment for Veterans with comorbid mTBI/PTSD.

e. Data Banking

Participants will be given the option to have their data banked for future research use in the Neuropsychology Data Repository Study #3508 managed by Dr. Maya O'Neil, housed at the VA Portland Health Care System and overseen by the VAPORHCS IRB. Seattle participants may have the option to bank their data in an additional repository for future research use. This banking system, Repository and Registry for Behavioral Neuroscience Research, is managed by Dr. Elaine Peskind at the VA Puget Sound Health Care System and overseen by the VA Puget Sound Mental Illness Research, Education, and Clinical Center and VA Puget Sound IRB. All future research of data maintained within a research data repository will only occur after further Institutional Review Board and/or other applicable approvals to ensure the protection privacy. Participants are not required to provide this permission and not providing this permission will have no impact on their participation in the study, i.e., granting permission is not a condition of participating in the study.

5.2 Recruitment Methods

Subject recruitment and feasibility: Participants will be 192 male and female Veterans ≤ 55 years of age referred for PTSD treatment who meet diagnostic criteria for comorbid mTBI/PTSD. Participants will be recruited from the healthcare clinics of the VA Portland Health Care System and VA Puget Sound Health Care System. Potential participants will be recruited through clinic referrals at participating VA's, flyers, recruitment events and patient medical record review followed by recruitment letters sent to patients who meet the requisite pre-screening criteria.

Identification and recruitment of participants is detailed to occur in one of four ways:

1) By Referral from provider: Study personnel will seek provider referrals from VA outpatient clinics, including MIRECC mTBI/Behavioral Specialty Clinic, Neurology, Primary Care, Mental Health, Neuropsychology, Rehabilitation Medicine, Polytrauma, and others; VA community-based outpatient clinics (CBOCs); local area Veterans centers; and National Guard and Reserve units. We will seek these provider referrals in conversations with colleagues, by word of mouth, by email, and via presentations from study staff to appropriate clinical staff. Providers will be given detailed information about study inclusion/exclusion criteria, recruitment process, and treatment goals. They will also be given templated language to use in CPRS notes if Veterans have agreed to be contacted by study staff. Participants will be referred to the study by their provider through CPRS and documentation of their consent to be contacted by the study will be documented in CPRS by the referring provider.

   We may identify potentially eligible participants by reviewing weekly care panels of providers who provide services for Veterans with a history of mTBI and/or PTSD using administrative and manual CPRS review data pulls. Providers of potentially eligible Veterans identified by review of care panels

with upcoming appointments may be contacted via encrypted email to inform them about the study and to invite them to discuss the study with the potentially eligible Veteran(s).

2) By Flyer and other advertising methods: Study staff will be responsible for disseminating IRB-approved flyers at hospital health fair and hallway information tables as well as bulletin boards; at presentations by investigators; via emails to clinicians and staff; in highly trafficked areas and clinic waiting areas. The study may also be advertised on VA Puget Sound research kiosks; VA Portland and Puget Sound electronic reader-boards; websites, and in newsletters. Participants will call the study phone number listed on a flyer for additional details regarding the study or if working with a clinician, may request that the clinician contact the study on their behalf using the referral template described above.

3) By Recruitment Letter: A letter from the study, with an opt-out option may be mailed to potential participants identified through administrative VINCI-based data pulls and electronic review of aforementioned VA outpatient clinics, informing Veterans of the project. If study staff have not received the opt-out postcard after 2 weeks, project staff will contact Veterans who were sent letters by telephone to assess eligibility and interest in participation and to arrange an enrollment visit. Study staff will make a total of 3 calls to each listed number before deeming the participant as not interested. We will retain a list of individuals who were deemed not interested (either due to sending the opt-out postcard or non-response to recruitment calls) so that those individuals are not re-contacted in the future. We will contact no more than 500 Veterans using this approach.

4) BNG Repository: We will also screen the VA Puget Sound BNG registry of individuals who have specifically indicated they are interested in hearing about future research opportunities; Veterans identified as being highly likely to be eligible will be sent information about the study by mail. This mailing will include an opt-out mechanism to decline further information described above. If the potential subjects do not return the opt-out form, we may follow up with them over the phone using our telephone script (no more than three times as described above).

If a Veteran is found to be eligible for the study and agrees to participate, the study coordinator will schedule a diagnostic and pre-treatment interview. Potential participants will then meet with a staff-member from the study, who will review study procedures (nature and frequency of assessments, nature of treatments, random assignment to treatments), answer any questions, and obtain written informed consent. During the COVID-19 pandemic, this interaction will take place over telehealth. Primary care providers will follow routine treatment and referral procedures regardless of patient interest in the study.

We expect similar enrollment and recruitment rates at the Portland and VA Puget Sound. There is evidence that a substantial pool of potential participants exists, suggesting that the goal of recruiting 192 participants over the course of the study is feasible. Even allowing for more rigorous diagnostic procedures, exclusionary criteria, and a moderate refusal rate, the sample size should be easily attained. Total enrollment for the study at both sites would be 96 participants per site (48 CABA and 48 TAU), for a total of 192 participants (96 CABA and 96 TAU).

Steps to minimize dropout rate: We had a relatively low non-completer rate 11% among subjects enrolled in

our funded CCT study with OEF/OIF Veterans with mTBI. We partially attribute the low non-completer rate to reminder phone calls and financial incentive. Since compensation and reminder phone calls will once again be used in the proposed study, we expect a low attrition rate. Subjects will be compensated for time involved in the study as described below. We will also call all subjects to remind them of each session and study visit.

Reimbursement for time and travel: Compensating subjects for their participation reduces attrition rates. We plan to compensate participants at each assessment point. They will receive a payment of $50 after each of the first three assessments. For completion of all three assessments, total compensation will be $150.

5.3 Informed Consent Procedures

Informed Consent: This study will make use of a waiver of informed consent for screening purposes only. The waiver will cover the pre-screening period of the study during which, upon provider referral (or participant response to recruitment flyer and/or letter), the study coordinator will conduct a CPRS chart review and telephone pre-screen interview to confirm screening criteria before the pre-treatment assessment is scheduled where informed consent will be obtained and final eligibility will be confirmed. Eligible participants screened for the study will be mailed the study informed consent form, Authorization for Use and Release of Individually Identifiable Health Information Collected for VHA Research form (HIPAA form), and detailed instructions for completing the forms at the time of their consent appointment. A self-addressed, pre-stamped return envelope will be provided to each participant and will be tracked by study staff.

Trained, closely supervised staff will conduct the informed consent procedure and the assessments. Assessors will be the study coordinators or research assistants and will have at least one year of graduate experience. These staff obtaining consent will have completed web-based courses with post-test on Human Research Protections and Good Clinical Practice, and will have received training from the co-PIs in obtaining informed consent. A copy of the signed consent form will be kept with the participant's research materials and a copy will be given to the Veteran (participants who are consenting over the phone will be sent 2 copies of the consent so that they can keep one for their records). Information provided to the potential participant and included in the written consent form will include the following:

- Invitation to participate because of the presence of comorbid mTBI/PTSD
- Duration of the study (4 years)
- The general purpose of the study
- The randomization procedure
- A description of the CABA intervention, including general content of sessions, expectations for between session practice, number of sessions, and the use of audiotaping of sessions
- A description of TAU, including information about the PTSD specialty care clinic and the types of treatments offered by the PTSD specialty care clinic
- A detailed description of the assessment procedures, including estimated time involved, the use of audiotaping (for assessment of reliability and treatment adherence), frequency of assessments
- A description of alternative treatments within the facility, including medications and alternative psychotherapy
- The expectation that additional psychotherapies not be participated in during the active phase of the CABA treatment [with specification that they will not be dropped from treatment if they do initiate additional treatment]

- Description of potential risks, discomfort, and inconveniences
- The potential for loss of privacy and a description of efforts to protect confidentiality and privacy
- Specific circumstances that may require loss of privacy (e.g., acknowledgement of suicidal intent)
- The ability to decline participation or withdraw from the study at any time without jeopardizing treatment at the VA
- Specification of payment for participation
- Contact information for study personnel for questions

Informed Consent Process via Telephone and Postal Mail

A study staff member will arrange a time to conduct the informed consent process via telephone or video-based telehealth platform such as VA Video Connect (VVC). Participants will have received a self-addressed, stamped envelope along with two copies of the approved consent form and a cover letter. The cover letter will specify that research staff will call them to review the consent document, and that although Veterans are encouraged to review the forms in advance, they should not complete the forms until they have reviewed the forms with research staff at the scheduled informed consent session.

5.4 Inclusion/Exclusion Criteria

Inclusion criteria:

1) Veterans ≤ 55 years of age enrolled at participating VA sites able to provide informed consent.

2) Diagnosis of PTSD based on the Clinician Administered PTSD Scale[60.]

3) Positive screen on the Structured Interview for Collecting Head Trauma Event Characteristics as per the VA/DoD Clinical Practice Guideline for Management of Concussion/mTBI; AND endorsed any of the Neurobehavioral Symptom Inventory (NSI)[61] cognitive symptoms items (items 13-17).

4) English speaking, able to travel to the primary care clinics weekly for 10 sessions and for the follow- up assessments, and willing to refrain from additional mental health treatment during the first 3 1/2 months of the active phase of treatment if they are assigned to the CABA condition.

5) Willingness to participate in audio-recorded sessions.

Exclusion criteria: In order to maximize the generalizability and public health relevance of the study, exclusion criteria are minimized and based primarily on the well-being of the participant.

1) Current diagnosis of moderate or severe substance (alcohol) use disorder using DSM-5 within the past 30 days.

2) Current Bipolar or psychotic disorder (requirement to refrain from additional treatments might be harmful).

3) Veterans with a history indicated by medical record review of a diagnosis of moderate, severe,

or penetrating TBI, or self-reported history on the Structured Interview for Collecting Head Trauma Event Characteristics of TBI with PTA greater than 24 hours or LOC greater than 30 minutes.

4) Active suicidal intent indicating significant clinical risk, which would suggest that a treatment specifically targeting this intent was indicated clients who report suicidal ideation without imminent risk will be admitted into the study.

5) Initiated psychotropic medication, including Prazosin, within 4 weeks or changed dosage within 2 weeks prior to the first assessment, as this would make it difficult to determine which treatment contributed to change in the CABA condition; additionally, started or changed dosage of sleep medication or low dosages of tricyclic antidepressant or trazodone for pain or sleep within 1 week prior to the first assessment. Participants could be re-considered for eligibility after stability on medication was achieved. Enrollees will be asked, but not prohibited, to hold the doses of the current medications stable over the course of enrollment (though changes in medications after enrollment will not exclude them from on-going participation).

6) Auditory or visual impairments that would compromise ability to participate cognitive rehabilitation group or benefit from compensatory strategies.

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5.5 Study Evaluations

Visit schedules

Pre-enrollment screening:

1) Medical Record Review: Study personnel will review each participant's medical record, including their neuropsychological assessment records, to document severity and type of current cognitive status, medical and psychiatric history, current treatment, and medications.

2) Clinical Screening Phone Interview: Study personnel will conduct a brief phone screening to ensure subjects meet initial eligibility criteria. Participants interested in the study will be asked to provide an email address for scheduling video telehealth appointments.

Study Enrollment: All eligible participants will complete a consent visit including:

Informed Consent: Study personnel will complete consent procedures. All effort will be made to ensure participants fully comprehend study procedures, risks, and benefits.

Baseline Assessment: All eligible participants will complete a baseline assessment visit including: Baseline Psychological and Cognitive Assessment Battery (see below). This includes assessment of exclusionary diagnoses as well a brief neuropsychological battery, diagnostic interviews, and self-report questionnaires of current emotional and post-concussive symptoms. If an individual is found not be eligible during this assessment, the assessment will be discontinued at that point.

Treatment Visits: All eligible patients will be randomized (CABA or TAU). CABA participants will be assigned to a therapist and receive the 10-session intervention (during COVID-19 this will be completed using telehealth modalities); TAU participants will be referred to PTSD specialty care.

Mid-treatment Assessment: Participants will complete questionnaires at mid-treatment (approximately 7 weeks after initiation of treatment) designed to assess current emotional and post-concussive symptoms.

Post-treatment Assessment: Participants will complete a brief cognitive assessment battery, diagnostic interviews, and questionnaires designed to assess current emotional and post-concussive symptoms (see section B "Data Collection and Assessment" below for a list and description of each battery measure). This will take place approximately 14 weeks after the initiation of treatment.

See Table 3 in section B "Data Collection and Assessment" below for a schedule of administration for each measure. Participants will be sent a response key via postal mail (see documents **Survey Response Key** and **Response Key Cover Lette**r). Staff will read the questions to participants, who will respond to each item with the aid of the response key. If the response key is lost, a new one may be sent to them.

Telephone Reminder Calls (Visits 1-14): The site coordinator or designated study staff member will contact participants by phone to remind them of the initial visit, mid-treatment assessment, and post-treatment assessment. CABA therapists may contact participants 1-2 days prior to treatment session to remind them of upcoming appointment; participants who are using VA Video Connect for the CABA sessions may also receive automated reminders of the appointment via email. Participants assigned to TAU will get standard VA reminder calls.

Visits 2-6 and 8-12: During visits 2-6 and 8-12, subjects will attend weekly 90-minute individual sessions of the CABA intervention via telehealth and TAU (at a minimum, the opportunity to attend 10 90-minute individual sessions).

Documentation in CPRS: A Research Screening/Enrollment/Disenrollment note will be entered into CPRS for all Veterans who consented into the study. An additional note documenting informed consent, completion of intake procedures, eligibility determination, and next steps will also be entered into CPRS following the baseline/intake visit. Disenrollment notes will be entered into CPRS at the completion of each Veteran's participation in the study. Veteran assigned to the CABA condition will have session appointments entered into a research clinic and the study therapist will enter a note into CPRS summarizing the session content for each CABA treatment session.

Compliance: Attendance will be recorded. Financial compensation and reminder calls will be used.

Standardization of intervention delivery and testing between sites

Therapists for CABA will be PhD-level psychologists or Master's level or greater mental health practitioners. Two therapists (one from each site) are experts in BA (Amy Wagner, PhD and Matthew Jakupcak, PhD). Several therapists from the Portland VA and VA Puget Sound were involved in writing the CCT and CABA manuals and have experience conducting these interventions. Remaining therapists will have competence in cognitive-behavioral approaches to PTSD and/or cognitive training. All therapists will be required to complete an initial training which will involve reading the treatment manual, research protocol, and treatment related materials, reviewing therapy tapes, and, when possible, attending a half-day training with Drs. Wagner, Jakupcak, or Storzbach. If therapists have significant experience/expertise in behavioral activation and/or cognitive

rehabilitation, the half day training requirement may be waived at the discretion of the study PIs. Dr. Wagner will review the session recordings of the first patient for each new therapist to ensure adherence to the treatment protocol and to provide clinical feedback when needed. Therapists are invited to participated in biweekly study phone calls to discuss clinical concerns, with more immediate consultation/supervision available with study PIs on an as needed basis.

To assure treatment fidelity, audio recordings of sessions will be used to rate therapists on CABA treatment manual compliance. Sessions from both participating VA study sites will be digitally audio-recorded, and 20% of sessions will be randomly selected by Dr. Golshan, the study statistician, throughout the course of the proposed study for quality adherence and fidelity ratings. A member of the study team from the main study site (Portland VA), who will be selected and trained by the co-PIs, will serve as the adherence and fidelity rater. This rater will not be involved in delivering the treatment intervention and will be trained in adherence/fidelity coding. The rater and the Principal Investigator (Storzbach) will individually rate several practice tapes and any discrepancies in the practice coding will be discussed and reconciled. An adherence and fidelity instrument will be developed for use with the CABA manual (see Appendix 3 for the CCT fidelity instrument). Only when reliability has been demonstrated at 90% agreement will the rater begin independently coding treatment tapes from the proposed study. Adherence rate will be calculated as percentage of goals achieved by Dr. Golshan. Audio recordings will be examined on a monthly basis. The co-PIs will meet with the therapists and other study team members on a monthly basis to discuss any discrepancies, to review any adherence/fidelity rates below 80%, and to develop a plan for ensuring that all session goals are met. If adherence and fidelity monitoring reveals that any treatment goals have not been addressed, then the therapist will be retrained on the corresponding material to properly address those inefficiencies. The therapist will be recertified prior to returning to study. If it is not possible to provide the missing information (for example, because the treatment has ended), then those subjects will be excluded from the project's dataset and statistical analyses.

Project monitoring and oversight

Routine communication and coordination between the study sites will primarily occur through joint teleconferenced team meetings. These meetings will be scheduled bi-weekly the first 6 months of the study and monthly the latter part of the first year, and then quarterly during years two and three. Additional meetings may occur on an as-needed basis. Some funding will be budgeted toward travel for site visits.

Data Collection and Instruments

1) Demographics and disorder/disease-related assessments. At the assessment visit, demographic information including age, gender, ethnicity, and education will be collected. We will document severity and type of current cognitive status, PTSD symptom severity, medical and psychiatric history, current treatment, and medications. We will also collect information about any new medication changes and/or changes in additional mental health treatment at the initial and follow-up treatment visits in an effort to track any changes in the initial eligibility criteria.

2) Measures. The RR&D TBI RFA requires use of National Institute of Neurological Disorders and Stroke (NINDS) core Common Data Elements (CDEs) for TBI. All current (version 1) core CDE measures are included except the Cognition Subscale of the Functional Independence Measure (Cog-FIM) as the NINDS CDE website indicates that this measure is "Not sufficiently sensitive for mild TBI." Assessment measures are not limited to TBI CDEs because of the need for measures of symptoms/functional effects of

PTSD or mTBI/PTSD.

Select measures of the full testing battery will be used for telehealth administration. See below for more details:

- Clinician Administered PTSD Scale (CAPS-V)[60,66]. A widely used diagnostic interview, provides an overall severity score and subscale scores for symptom clusters.
- Posttraumatic Stress Disorder Checklist-Fifth Version (PCL-5)[57,67]. A widely used self-report measure of PTSD symptom severity.

Global Outcome

- Glasgow Outcome Scale Extended (GOS-E)[96] A revision of the GOS, a commonly used global outcome measure in TBI studies; a core NINDS CDE. This test will not be administered during telehealth visits.

Cognitive and TBI Symptom Severity

- Rivermead Post Concussive Symptom Questionnaire (RPQ)[95] will be used to measure postconcussive symptoms (PCS); a core NINDS CDE. This test will not be administered during telehealth visits.
- Structured Interview for Collecting Head Trauma Event Characteristics (DoD HTEC) [62], head trauma history and to assess eligibility.
- The Neurobehavioral Symptom Inventory (NSI)[61] a PCS measure mandated for use in the VA, and is a NINDS TBI supplemental CDE recommended for use in Military studies.

Cognitive Compensation

- Memory Compensation Questionnaire (MCQ)[70]. Rates the extent to which patients use various strategies to improve memory performance. This test will not be administered during telehealth visits.

Cognitive Functioning (all tests were selected because of their excellent validity and reliability, and the availability of large normative databases)

- The Wide Range Achievement Test-4 (WRAT-4)[71] Baseline ability, a NINDS supplemental TBI CDE.
- Hopkins Verbal Memory Test–Revised (HVLT-R)[72] A measure of verbal list learning and delayed recall.
- Wechsler Adult Intelligence Scale–4th Edition, Digit Span Subtest (WAIS-IV)[73] A WAIS-IV subtest that measures attention and working memory, and is a NINDS supplemental TBI CDE.
- Wechsler Adult Intelligence Scale–3rd Edition, Symbol Search Subtest (WAIS-III)[74] WAIS-III subtest measuring processing speed; component of WAIS PSI, a core NINDS TBI CDE. This test will not be administered during telehealth visits.
- Trail Making Test (TMT)[75] DKEFS- trails subtest is a visual-motor task used to measure flexibility in thinking (executive function) and processing speed, a core NINDS TBI CDE. This test will not be administered during telehealth visits.
- Controlled Oral Word Association Test (COWAT)[76] Verbal fluency, a supplemental NINDS TBI CDE.

Depression:

- Beck Depression Inventory-II (BDI-II)[67] A widely used 21-item measure of current levels of depression.

Psychiatric Disorders:

- Mini-international Neuropsychiatric Interview – Depression, Substance Use Disorders, Manic Episode, Hypomanic Episode, and Psychotic Disorders subtests (MINI)[77] Brief structured interview for the major Axis I psychiatric [DSM-V version will be substituted if available at the time of funding].

- Brief Symptom Inventory 18 (BSI 18)[78] Psychological symptom complaints; a core NINDS CDE. This test will not be administered during telehealth visits.

Cognitive Related Functional Impairment:

- Neuro-QOL[79]. Health-related quality of life assessment tool; a NINDS supplemental TBI CDE. This test will not be administered during telehealth visits.

Social Role Participation:

- Craig Handicap Assessment Reporting Technique - Short Form (CHART-SF)[80] Consisting of 6 subscales; a NINDS core TBI CDE. This test will not be administered during telehealth visits.

General Functioning:

- Sheehan Disability Scale (ShDS)[81]. A brief self-report measure of functional impairment. This test will not be administered during telehealth visits.

Quality of Life:

- Satisfaction with Life Scale (SLS)[69] A 5-item measure assessing global life satisfaction or quality of life.

Participant Satisfaction:

- The Client Satisfaction Questionnaire (CSQ-8)[82] A questionnaire used routinely in the Seattle Post Deployment Health Services and PTSD Clinic to assess satisfaction with care.

Other Measures:

- Severity of Dependence Scale (SDS)[83]A 5-item measure assessing severity of substance dependence. This test will not be administered during telehealth visits.
- Scale for Suicide Ideation (SSI)[97], a 21-item interviewer-administered rating scale that measures the frequency and severity of suicidal ideation. This test will not be administered during telehealth visits.
- Functional Outcomes of Sleep Questionnaire (FOSQ-10)[98] A 10-item measure of sleep function.
- Insomnia Severity Index (ISI)[99] A 7-item measure of insomnia severity. This test will not be administered during telehealth visits.

Scheduling of Assessment Measures: Assessment measures are administered at times indicated in Table 3.

Table 3: Visit and Assessment Schedule (updated for telehealth visits)

	Visit 1,Wk. 0	Visits 2-6	Visit 7,Wk. 7	Visits 8-12	Visit 13,Wk. 14
Duration	180 mins	90 mins	60 mins	90 mins	180 mins
Purpose	screen + baseline	intervention	mid-assessment	intervention	post-assessment
Informed Consent	x				
Demographic	x				
CAPS-V	x				x
PCL-5	x		x		x
DoD HTEC	x				
NSI	x		x		x
BDI-II	x		x		x
MINI – M,H,&P	x				
MINI – MDD & SUD	x				
SLS	x		x		x
CSQ					x
NP Battery	x				x

5.6 Data Analysis

Statistical Analysis of Data

Data integrity. Data will be collected at both participating sites: Portland VA and VA Puget Sound. The co-PIs and multi-site project coordinator will be located at the Portland VA. Trained study personnel will conduct the structured clinical screening interview. Similarly, a paper questionnaire will be used to guide the medical record review to ensure that the same historical information is gathered and coded for all subjects. The self-report questionnaires/surveys and psychological and cognitive assessment battery consists of standardized protocols with specific/scripted questions and scoring systems that quantify answers. All study personnel from all study sites who will be gathering data from these sources will be trained by the co-PIs regarding the collection of data and will have professional education and training as required for these instruments.

Data will be labeled with a code unique to each patient. All hard copy data will be stored in locked filing cabinets in locked rooms, while electronic data will be stored in password-protected files in a limited access folder on the secure VA network drive. Each study site will maintain a key code that links that site's patients with their coded identifier with key code stored separately from all other study data. Only the multisite and site PI's and the multisite and site study coordinators and research assistants will have access to the key code linking document. Materials with protected health information will be stored in separate locked file cabinets from coded materials to ensure privacy. Special multilevel data security programs have been written into the network operating system to ensure that only authorized research personnel have access to the Center Network. Backups of daily changes are done regularly and all other data are backed up on a rotating schedule. An electronic archive of all data is kept offsite to insure against loss by fire, theft, etc. All statistical transfer routines are inherently secure via operating platform and contain no patient names or personal data.

A database will be developed using Microsoft Access or Excel by the multi-site study team located at the Portland VA, and adapted from the current Merit study. The database will be tested and the final version will be distributed to participating study sites by the Portland VA data manager. Two study support persons located at each site will enter data from the hard copy forms into the database to ensure accuracy of data entry. All data entry discrepancies will be solved by the site study coordinator. Hard copy source documents will be kept and stored at the VA site location (Portland or VA Puget Sound) at which they were gathered; data collected at the American Lake Division will be transported securely to the Seattle Division for storage. For adherence monitoring, digital audio-recordings of sessions will be kept in limited access drive on the VA network. The recording will be coded, password- protected and encrypted. Following completion of the planned analyses, the statistician's files will be sent back to the VA site to be stored with all other data and subject to all IRB-approved storage and deletion procedures. The statistician will be able to retain a data dictionary and all associated syntax and output files, provided that these files do not contain any identifiable data. Throughout the entire course of the study, the off-site statistician will only ever have access to coded data. Additionally, the off-site statistician holds a VA appointment with the San Diego VA and will only analyze and maintain databases from within the VA network.

DATA ENTRY FLOW: The following sequence of events will be followed: 1) Assessment forms completed by clinical rater; 2) Forms reviewed by rater and data manager for completeness; 3) Assessment forms entered into database; 4) Data entry procedures verify key items, out of range and unacceptable values; 5) Data

added to database; 6) Programs run to check for missing data and for logic errors; 7) Data reviewed by investigators, clinical staff, and key data management personnel at regular protocol review meeting for final validity.

DATA SAFETY MONITORING: Safety monitoring analyses will occur every six months from study inception through completion. The unblinded data manager will provide the blinded study statistician with a limited data set containing blinded group membership data, i.e., group membership that is numerically labeled but unidentifiable as treatment vs. control group. This dataset will also contain in-progress data safety variables including CAPS scores and any serious adverse events including 1) the onset of imminent risk of harm to self or others such as active thoughts of suicide or violence with expressed plan and intent to act; 2) the onset of psychotic and or manic symptoms; 3) a decline in global daily functioning indicating that inpatient mental health services are required for stabilization; 4) the onset or exacerbation of major medical illness that interferes with participation in regular outpatient mental health services. Differences between the treatment and control groups will be analyzed using t-test comparisons.. We will consult with the CIRB and consider the appropriateness of study suspension if, at the set data monitoring time periods every six months, we find that either group of participants is experiencing, on average, an increase in CAPS scores of 12 or more points and/or is experiencing, on average significantly more SAE's including those defined above. For serious adverse events, significance is defined as a statistically significant difference of $p < .01$ and/or a large effect size equivalent to a Cohen's d value of .8 or greater. The two study PIs will be responsible for notifying and consulting the CIRB of any conditions meeting criteria for possible study suspension within one business day of discovery.

Randomization procedures as well as overall multisite study interim, data safety monitoring and final data analyses will be conducted by our contracted statistician, Shah Golshan, Ph.D who is affiliated with University of California, San Diego. Dr. Golshan will receive a limited data set copied in encrypted format onto CD's sent via secure FedEx with tracking services. This data set will be considered a limited data set due to inclusion of patient assessment dates and otherwise is de-identified. A Data Use Agreement will be pursued between the VAPORHCS and Dr. Golshan recognizing the agreement of the terms for use of this data which shall be transmitted and accessed strictly for data analysis purposes pursuant to the goals of this study.

Sample size and power. Power analyses are performed for primary hypotheses *1a, 1b and 2a*, incorporating the longitudinal nature of the design. We propose a Random Regression model (also known as Multilevel or Growth Curve Models) as a basis of the analysis. In this approach, the repeated measures over time for each individual subject form a trajectory that can be described by a relatively simple model with a few parameters, here a linear model described by intercept (baseline value) and slope (rate of change). With random assignment to groups, there should be no group differences in baseline values, and slopes differences reflect treatment effects. With repeated measures, repeated observations within subjects are potentially correlated, impacting tests of significance[84]. When within subject correlation is properly incorporated, the repeated measures analysis takes full advantage of all information obtained from each subject, thereby greatly increasing statistical power over cross-sectional methods[85].This approach can model differential patterns over repeated assessments instead of totals at one point and therefore increases the reliability of the measurement of response (since the slope combines repeated measures which cancel much of the error of measurement), and increases the protection against the major effects of missing data (since one can impute from the non- missing data for that subject as well as for other similar subjects). These result in increased power to detect effects and precision of effect size estimation without increased sample size.

Power calculations can be made for repeated measures designs under specified assumptions[86]. Hedeker et al[86] extend Diggle et al.'s[87] method for various covariance structures. Procedures described by Hedeker et al[86] for Random Regression Models were used for the proposed study to estimate needed sample size using RMASS (see Hedeker http://tigger.uic.edu/~hedeker/ml.html). Data from our previous studies were used to calculate effect sizes. The design consists of a 2 (sites) X 2 (CABA vs TAU) X 4 (baseline, 7, and 14 weeks) where the slope is the dependent measure. Site and Treatment by Site interaction were included as "nuisance parameters", that is, included to account for possible overall site effects (Site) or possible site differences in treatment effects (Treatments X Site). With a balanced design (equal numbers at each site in each group), ignoring these would not increase the probability of Type I error, but would increase the Error Sum of Squares (SS) and probability of Type II error. The main effect of treatment represents the common effect size across sites if there is one, or the average site effect, if there is heterogeneity across sites. This is true because sample sizes will be balanced across treatment groups and sites. In any case, the analysis procedures will include site and site interaction effects to avoid allowing site effects to bias treatment comparisons. However, if we detect imbalances between the treatment groups within each site, we will follow the primary analyses with subsequent analyses considering the imbalances to verify that conclusions are not affected by imbalances.

Other assumptions needed are number of repeated measures, alpha-level, nature of the hypothesis (one- or two-sided), drop-out rate, and variance-covariance matrix of the longitudinal data. We assume an overall Type-I error levels alpha *of .01 to .02, drop-out rate of 15%,* and autoregressive covariance structure, with correlation between sequential assessments set at 0.45. Autoregressive covariance structures assume points closer together in time are more correlated than points further in time, which is more plausible compared to the equal correlation between all pair of assessments regardless of time separation assumed by the compound symmetry design. *When multiple analyses are conducted for a given hypothesis, Type I error rates will be controlled*

by a Westfall-Young procedure, we would include an alpha level of .04 for Hypothesis 1a, .03 for Hypothesis 1b and 2a, and .05 for Hypothesis 2b. We estimate that with the proposed sample size of *192* (15% drop-out) patients (*96* for each of the two groups), the study will have minimum power of 80% to yield a statistically significant result for a medium effect size. Hedker et al.[86] defined medium effect size in this model as a between-group difference increasing linearly from 0 at baseline to .5 SD units at the last time point. Hypothesis 2b is a cross-sectional hypothesis using data collected only in the week 14 of the study. The proposed sample size will provided us with a minimum power of 90% to detect a medium to large effect size. The former and foundational Behavioral Activation for PTSD study by Wagner and Jakupcak yielded the following rates which also informed our proposed sample size determination: 192 screened, 81 enrolled, 10 dropped (12.3% dropout rate), 101 screen failures.

Outcome analyses: Data analyses will proceed in stages. Descriptive statistics and exploratory graphing such as frequencies, means, standard deviations, stem and leaf diagrams, and scatterplots will be used to assess normality of data in terms of presence of skew and/or outliers. Continuous outcome data will be transformed if necessary using an appropriate transformation such as the log transform for skewed long tailed data. Prior experience with this kind of data leads us to expect that for all variables, the distributions will be skewed and the variances not homogeneous. Similarly, potential covariates will be summarized with descriptive statistics and graphs to determine the most appropriate way to treat these variables (e.g., continuous, categorical, or interval representation). For outcome measures acquired at baseline, 7, and 14 weeks, the analytical approach will address the nature of the outcome, as well as accommodate the within

individual variability due to the repeated assessments. Results from will be inspected for bias due to drop-outs or missing data.

For major analyses of central hypotheses (1a-1b and 2a), we propose to use Mixed Effects modeling to account for clustered data (i.e., repeated assessments within individuals, treatment groups, and sites). The mixed effects approach provides more information and more power compared to cross-sectional analyses which focus on analysis of one summary index or time-until event methods and traditional analytic approaches such as a change score, end-point or repeated measures analysis of variance (ANOVA). This method allows inclusion of subjects with missing data or those who were terminated early in the study, without relying on data imputation procedures. Two specific forms of the Mixed effects model strategy are commonly implemented: random regression models, or hierarchical models (HLM) or multilevel models; and mixed model analysis of variance (MMANOVA). Each outcome variable will be graphed versus time for each subject to evaluate what function of time best describes the data. The mixed effects framework is robust with respect to drop-out and missing data, unless the drop-out mechanism or cause of missing is informative. We will use pattern-mixture models to assess if there is bias due to drop out or missing data. As described by Hedeker and Gibbons[88], these mixed models allow us to assess whether important estimates are dependent on missing data patterns and provide overall estimates of effects by averaging over the various missing-data patterns. In addition, we will consider the extension of the Pattern-Mixture models as described by Guo et al[89] which includes the incorporation of random effects in the Pattern mixture model, allowing subject-to-subject heterogeneity.

Missing data values will be minimized by intensive training of interviewers in techniques of clarifying answers and checking questionnaires while participants are on-site. When missing values are identified, we will employ several approaches. If possible, participants will be rescheduled for missed assessments. Missing data will be examined to assess randomness. The pattern of missing data will be examined according to the procedure recommended by Little and Rubin[90] which includes comparing group differences in the primary outcomes of subjects with versus without missing data. The Mixed effects model allows inclusion of subjects with missing data or those who terminated the study early, without relying on data imputation procedures.

Hypothesis 1a) PTSD symptom severity. Dependent variables: CAPS-V and PCL-5.

Hypothesis 1b) Functional impairment. Dependent variables: HVLT-R, WAIS-IV (Digit Span subtest), DKEFS (Trails subtest), and COWAT (Verbal Fluency).

Independent variables: Treatment group (2 levels, CABA and TAU), & Time (3 levels, Weeks 0, 7, and 14). Statistical Analysis: We will analyze data on all randomized subjects in whom we have a baseline assessment and at least one post-baseline evaluation by Mixed effects model methods[84, 91]. Preliminary inspection of data will determine whether the outcome is nearly normal, or whether an appropriate transformation is required, or whether a generalized linear mixed model should be considered. The mixed effects model method provides an estimate of the individual variability around the population trend, the variability of the individual intercepts (baseline values) and slopes (changes across time), and the correlation between them. A fully saturated treatment by time model will be utilized for inference. Co-variance structure will be chosen based on Akaikes Information Criterion (AIC). Random group level treatment effects will also be evaluated for importance based on the model AIC. This allows for any group level effects to be incorporated into the model. Denominator degrees of freedom will be calculated using the Kenward-Roger small sample correction. The design is a 2 (sites) X 2 (CABA vs TAU) X 3 (baseline, 7, and 14 weeks). The interaction of Site and Treatment X Site will be included and tested as

"nuisance parameters". However, we do not anticipate any Treatment by Site or Site effects with the balanced design (equal numbers at each site in each group), our standard training procedure of both sites and standard operating procedure used by both sites. In any case, the analysis procedures will include site and site interaction effects to avoid allowing site effects to bias treatment comparisons. If we detect any imbalances between the treatment groups within each site, we will follow the primary analyses above with subsequent analyses considering the imbalances to verify that the conclusions are not affected by imbalances. Analyses will be conducted within and across nested levels of the study design; this will involve within-subject analyses (comparison of occasions of measurement nested within an individual), as well as between-subject analyses (comparison of the CABA and TAU groups, comparison of groups within a site, comparison of sites, etc). Any treatment group comparison can be adjusted for subject-specific characteristics and adjustments for changes in these characteristics over the course of the study can be incorporated into single-subject analyses. All comparisons described in this section can be effectively analyzed using PROC MIXED in SAS statistical software. Based on our ongoing studies, we expect a drop-out rate of <15% after baseline assessment but prior to first post-baseline evaluation. The drop-out rate is taken into account in power analyses, see above.

Hypothesis 2a) Patient-centered outcomes. Dependent variables: BDI-II, NSI, and SLS. Independent variables: Treatment group (2 levels, CABA and TAU), and Time (3 levels, Weeks 0,7,14). Statistical Analysis: Data will be analyzed similar to hypotheses 1a and 1b.

Hypothesis 2b) Treatment satisfaction. Dependent variables: CSQ. Independent variables: Treatment group (*2 levels, CABA and TAU*). Statistical Analysis: Hypothesis 2b will be tested using Analysis of Variance, comparing the two groups on the treatment credibility and satisfaction (CSQ).

Exploratory Investigation to Provide Guidance for Future Research Directions:
Guidance for future research will be obtained through exploratory analyses including possible mediator and moderator variables in addition to secondary outcome variables, including measures of neuropsychological test performance and general functioning. We will also investigate whether CABA-associated treatment gains are maintained over a 6 month follow-up period. The effect of moderator and mediator variables will be explored following the procedures recommended by Kraemer[92,] Cohen and Cohen[93] and Busemeyer and Jones[94].

Anticipated time table: Table 4 depicts a four-year study plan with 6 months for start-up and 6 months termination; 156 weeks for enrollment and 6 month follow up assessments. The study will be fully enrolled within 39 months of the start of funding of the trial. The last group of subjects will exit by month 42.

Table 4. Anticipated Time Table

	Year One				Year Two				Year Three				Year Four			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4

Start-Up Phase: Establish infrastructure; staff hiring & training; IRB approval; complete manual; fidelity monitoring implementation; & set up data management systems.																
Data Acquisition: *CABA*: assessments + CABA; *TAU*: assessments; Tx fidelity																
Analysis and Dissemination: Data analysis; manuscript; manual dissemination																

Dissemination plan: We will present preliminary and final results at relevant national conferences. Our co- investigators are well-versed in conducting large-scale cyber-seminars for VA and DoD audiences. Drs.
Storzbach and O'Neil have worked with the VA's Center for Information Dissemination and Education Resources and Quality Enhancement Research Initiative to conduct multiple cyber-seminars for large, national audiences of over 500 participants at low- to no-cost, and plan do conduct such seminars on the findings from this trial. Multiple VA and DoD research reports and academic articles are planned for dissemination of findings. A website will be established and the treatment manual will be made available online. This trial would provide critical data on feasibility of providing PTSD treatment to Veterans with mTBI, which is a key issue for the VA and DoD. We expect to disseminate findings in multiple research reports throughout the course of the trial as well as at least 4 peer reviewed academic journal articles following trial completion.

5.7 Withdrawal of Subjects

Should any findings arise during assessment study visits which might affect the participant's health or welfare, the study team will address those findings directly with participants during the assessment study visit within which the issues are discovered. The study team will use CPRS to identify the participant's health care providers as well as communicate the findings with those providers and follow-up via telephone as needed.

The co-PIs will recommend termination of participation, provide appropriate referrals, and engage in follow-up if substantial decline in functioning is observed at any assessment study visit for all participants and/or treatment visits for those assigned to the CABA treatment intervention. Participation in this study therefore, will be terminated at the discretion of study personnel (with final determination by co-PI's), based upon clinical observations and judgments regarding the safety of continued participation to the patient's physical and/or psychological health and well-being. Additionally, if participants fail to comply with important instructions that are part of the approved study protocol, such as actively abusing substances, participation will be terminated without consent.

Although the proposed study poses no serious risks to participants, participants may notify research personnel about pre-existing mental health issues that have not been previously identified by other VA providers. Therefore, participants will be referred to the VA's Mental Health Division for further

assessment and/or treatment if a previously undiagnosed psychiatric disorder is identified. We will inform participants of this procedure as part of the informed consent process and participants must agree to this procedure to be eligible to participate in the study. This ensures that we can adequately manage any pre-existing clinical issues that become apparent through subject evaluation.

If a participant chooses to withdraw from the study, study personnel or Drs. Dan Storzbach or Amy Wagner will refer the patient back to their providers in Primary Care for further assessment of treatment needs. The reason for withdraw will be documented. Participants who choose to withdraw early will still be allowed to continue participation in follow-up assessments and would continue to receive financial reimbursement for doing so, but this would be completely voluntary. A possible consequence of a participant choosing to withdraw early from the study is that he/she will likely continue to experience cognitive and/or PTSD symptoms. Without treatment, these symptoms may worsen over time.

6.0 Reporting

All SAE's, UAP's, and protocol deviations occurring at either site will be communicated to the Co-PI's immediately and necessary documentation will be submitted to the CIRB within stipulated timeframes and via designated channels in accordance with the VA Central IRB Table of Reporting Requirements.

7.0 Privacy and Confidentiality

This study will involve the use and collection of Protected Health Information (PHI). Multiple steps will be taken in the current investigation to protect the privacy and confidentiality of research participants. All study personnel will have current training in GCP procedures for the proper use, collection, and disclosure of PHI for research purposes. Study personnel will no longer have access to study data upon termination of employment. Per VA protocol, in the event of improper use and/or disclosure, the local ISO and Privacy Officer will be notified within one hour. A code number will be assigned to each participant and his/her information. Only the multi-site co-PI's, the local site PI's, the multi-site project coordinator, and the site coordinator will be authorized to link the code number to the participant. A Master List will be retained by the study coordinator that will allow us to match each participant's code with their information; however, this Master List will be an electronic database that is password protected, and Informed Consent Forms will be stored in a double-locked cabinet apart from participant information. We will keep participant information in a separate electronic database that is password protected.

Participants who are assigned to the CABA condition will have their therapy sessions audio-recorded using a hand held digital audio recorder. However, these digital audio files will be identified by a number assigned to the participant and will not be marked with the participant's name or other identifying information. These audio- recordings will be listened to by a member of the research staff to determine if the interventions are conducted accurately ("adherence checks"). The audio files will be uploaded into a secure, password-protected folder on the VA network. These files will not contain identifying information audio recordings of sessions will be removed directly from the audio recorders immediately following the session to encrypted,

password protected, limited access drives on the VA network. Audio recorders with session content will not leave the session room before transfer.

Adequacy of Privacy Protection. We will take multiple steps to protect participants' privacy and confidentiality. All data will be labeled with a code number that is unique to each patient in the study, and maintained in a Subject Data File. We will NOT include any protected health information (PHI) in the Subject Data Files. Instead, we will code each Subject Data File with a unique numerical code, which will consist of the VA station number + 3 digits consecutively numbered in order of enrollment (e.g., 648-001, 648-002, etc.). All hard copy subject data will be stored in locked filing cabinets in locked rooms, while all electronic data will be stored in password-protected files in a limited access folder on the secure VA network drive. Each study site will maintain a Master List key code that links that site's subjects with their coded identifier. This key code will be stored separately from all other study data. Only the multi-site co-PI's, the local site PI's, the multi-site project coordinator, and the site coordinator will have access to the Master List key code, and only IRB-approved study personnel will have access to Subject Data Files or Informed Consent Forms. We will analyze and report subject data in aggregate form and no PHI will be entered into these analyses or reports.

8.0 Communication Plan

Routine communication and coordination between the study sites will primarily occur through joint teleconferenced team meetings. These meetings will be scheduled bi-weekly the first 6 months of the study and monthly the latter part of the first year, and then quarterly during years two and three. Additional meetings may occur on an as-needed basis. Local site approvals will be sought after confirmation of multi-site approval is received. As per VA protocol, local site facility directors will be notified of local site research via the standard mechanism of the required PPQ (proposed project questionnaire) paperwork for local R&D approval, concurrent with CIRB local site applications.

We will utilize the CIRB sharepoint site designated for our study as well as email to coordinate local site submissions. Once Multi-site approvals have been acquired, local sites will be informed of changes to the protocol, informed consent, and HIPAA authorization via email. Templates with the necessary changes tracked will be emailed to local site coordinators and uploaded onto the CIRB sharepoint site for this study.

All SAE's, UAP's, and protocol deviations occurring at either site will be communicated to the Co-PI's immediately and necessary documentation will be submitted to the CIRB within stipulated timeframes and via designated channels in accordance with the VA Central IRB Table of Reporting Requirements. Any SAE's, UAP's, and/or protocol deviations which will affect local site operations will be communicated immediately to local site PI's and coordinators via email followed up by telephone confirmation. Templates of forms with tracked changes regarding SAE/UAP/PD information will be emailed to site coordinators to be edited for local site submission whenever applicable.

All local sites will be required to strictly adhere to the most recently IRB-approved protocol of this study. Thorough review of the protocol will be a mandatory component of training for all study personnel and we will maintain both electronic and hard copy records with tracking logs of each dated version of the protocol. All study staff will be directed to refer to the protocol when operational questions arise.

Given the nature of this multisite study, in that the Portland site is both the multi-site study headquarters and a local site with the same staff members in place for the duties of both, a plan for notifying all local facility directors of termination of engagement at the local site level is not necessary. The Portland and Seattle sites will continue to recruit participants and operate normally until recruitment goals are met and/or until the timeframes of the study necessitate termination. At that point, local sites will submit applicable termination paperwork to the local R&D committees and the CIRB and the Portland site will continue to remain open for data analysis at the multi-site level.

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