Cognitive Rehabilitation for Older Veterans with Mild Cognitive Impairment

NCT03225482

April 13, 2021

Human Protocol (Version 1.17)

General Information

***Please enter the full title of your protocol:**

Cognitive Rehabilitation for Older Veterans with Mild Cognitive Impairment

***Please provide a short name (nickname) to reference this protocol:**

CCT for MCI
* This field allows you to enter an abbreviated version of the Protocol Title to quickly identify this protocol.

Add Site(s)

VA Site (******** DO NOT ADD OR CHANGE, just save and continue **********):**

Primary Dept?	Department Name
◆	**VASDHS** - VASDHS

Identify protocol staff members

***Please add a Principal Investigator for the study:**

Twamley, Elizabeth W., PhD

3.1 Add all other VA research staff personnel (if name is not in the list, please contact Research Staffing to confirm appointment status)

A) Additional Investigators

Jak, Amy J., PhD
Co-Investigator

B) Research Support Staff

Clark, Jillian, PhD
Post-Doc
Contreras, Ingrid
Study Coordinator
Green, Chloe T., PhD
Research Associate
Hernandez, Jeffrey
Research Associate
Jurick Lefler, Sarah, PhD
Research Associate with no PHI access

Keller, Amber Victoria
Study Coordinator
Lykins, Hannah
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Mahmood, Zanjbeel, BA
Research Associate
Maye, Jacqueline, PhD
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Wyckoff, Janae Ruth
Research Associate

***Please select the Research Contact(s)**

Twamley, Elizabeth W., PhD

The Research Contact(s) will receive all important system notifications along with the Principal Investigator. (Research Contacts are typically Study Coordinators or the Principal Investigator themselves).

VASDHS - IRB Protocol

v20150312

Section 1 - Preliminaries

Principal Investigator:

Elizabeth W. Twamley, PhD

Protocol Title:

Cognitive Rehabilitation for Older Veterans with Mild Cognitive Impairment

IRB Protocol Number:

H170016

Protocol Nickname:

CCT for MCI

Form Template Version:

v20150115

Date Prepared:

04/06/2021

1a) Is this study considered human research?

(●) Yes ( ) No

1b) Is this a request for a determination of exemption from IRB review?

( ) Yes (●) No

1c) Is this a request for an expedited IRB review?

( ) Yes (●) No

Section 1.3 New Protocol or Transfer/Renewal of Prior Protocol

1.3) Select the type of protocol application:

1.3a) Is this a new protocol? (if transfer to VA IRB, select **No**)

(●) Yes ( ) No

1.3b) Is this a resubmission of a VASDHS IRB protocol?

( ) Yes (●) No

1.3c) Is this a transfer of a protocol to the VASDHS IRB?

( ) Yes (●) No

Section 2 - Research Subjects

2a) What is the total planned number of VASDHS-consented subjects needed?

(Include even if using a waiver of documented consent, e.g. oral consents)

108

2b) What is the total number of VASDHS subjects needed that WILL NOT be consented (e.g., retrospective reviews) ?

0

Section 2.1 Consented Subject Groups

2.1) For each of the subject categories listed below, indicate whether or not these subjects will be enrolled (consented) in the study: (exclude cases of data or specimens only)

2.1a) Children under age 18

( ) Yes (●) No

2.1b) Women of child-bearing potential

( ) Yes (●) No

2.1c) Pregnant women

( ) Yes (●) No

2.1d) Individuals with cognitive/decisional impairment

(•) Yes ( ) No

2.1e) Non-English speaking individuals

( ) Yes (•) No

2.1f) Prisoners of War [explicitly targeting this group]

( ) Yes (•) No

2.1g) Non-Veterans (Note: A justification will be required below)

( ) Yes (•) No

2.1h) Incarcerated individuals (Note: VA CRADO approval will be required)

( ) Yes (•) No

2.1i) VA employees (or WOCs)

( ) Yes (•) No

2.1j) Students

( ) Yes (•) No

2.1k) Patients with cancer (or high cancer risk) [explicitly targeting this group]

( ) Yes (•) No

Section 3 - Study Features (these items default to "No" for convenience)

3) This section consists of several Yes/No questions addressing protocol characteristics. Click on *Save and Continue*.

Section 3.1 Protocol Basics

Indicate whether or not each of the following applies to this protocol

3.1a) The research **intends to change** the participant

(•) Yes ( ) No

3.1b) **Interactions** with living participants to collect data or specimens with no intent to change them.

( ) Yes (•) No

3.1c) This is a study that **never** has any **subject contact or subject identifiers** (e.g., de-identified tissue only).

( ) Yes (•) No

3.1d) This is a **multi-site** study (multiple IRB's involved) and **VASDHS** is the **main** or a coordinating site

(•) Yes ( ) No

3.1e) This is a **multi-site** study (multiple IRB's involved) and VASDHS is NOT the main or a coordinating site

( ) Yes (•) No

3.1f) There is an **international** component to this research

○ Yes ◉ No

3.1g) Any study activity occurs at **non-VASDHS locations** (not including VHASDC leased space or clinics) under the VASDHS IRB protocol.

○ Yes ◉ No

3.1h) VASDHS subjects **participate** in whole or in part **at other locations** (not including VHASDC leased space or clinics) under this VASDHS IRB protocol.

○ Yes ◉ No

Section 3.2 Specimen Use and Data Repository

Indicate whether or not each of the following applies to this protocol

3.2a) Involves specimens that are left over from pathological or diagnostic testing (**non-research specimens**)

○ Yes ◉ No

3.2b) Involves **specimens collected for research** purposes **only**

○ Yes ◉ No

3.2c) This study includes **specimen banking** (specimens are retained for use outside of the purposes of this protocol)

○ Yes ◉ No

3.2d) The study involves **DNA** genotyping or other **genetic analysis**

○ Yes ◉ No

3.2e) A Biological **Materials Transfer** Agreement is required.

○ Yes ◉ No

3.2f) A **data repository** is maintained (data are retained after completion of the protocol for other uses, IMPORTANT see ? before checking "yes")

○ Yes ◉ No

Section 3.3 Treatment and Clinical Trials

Indicate whether or not each of the following applies to this protocol

3.3a) Includes a **treatment** component (a research treatment)

◉ Yes ○ No

3.3b) Study is a **clinical trial**

◉ Yes ○ No

3.3c) Has a data safety monitoring board (**DSMB)** or data safety monitoring committee

○ Yes ◉ No

3.3d) Has a **data safety monitoring plan** (but not a DSMB) (this is not the data security plan, it is a safety plan)

◉ Yes ○ No

Section 3.4 Drugs and Devices

Indicate whether or not each of the following applies to this protocol

3.4a) **Drugs** that require **FDA** action such as an Investigational New Drug (IND) approval or exemption or 510(k) approval.

○ Yes ◉ No

3.4b) Other drugs that **do not require FDA** action for inclusion in the study

○ Yes ◉ No

3.4c) Medical **devices requiring FDA** IDE approval or waiver

○ Yes ◉ No

3.4d) **Other** medical **devices**

○ Yes ◉ No

Section 3.5 Risk and Hazards

Indicate whether or not each of the following applies to this protocol

3.5a) Study places subjects at **greater than minimal risk** (do not include risks that are due to standard care)

○ Yes ◉ No

3.5b) Human subjects are exposed to **radioisotopes** (do not include standard care)

○ Yes ◉ No

3.5c) Subjects have other **radiation exposure** (e.g., x-rays) (do not include standard clinical use)

○ Yes ◉ No

3.5d) Target population has psychiatric diagnosis or behavioral complaint.

◉ Yes ○ No

Section 3.6 Clinical Facilities and Standard Care

Indicate whether or not each of the following applies to this protocol

3.6a) Study **uses VA clinical services** (e.g., adds required tests run in the VA lab for study purposes)

○ Yes ◉ No

3.6b) Includes procedures or drugs that will be considered **part of standard care**

○ Yes ◉ No

3.6c) Involves **lab tests done for research** purposes

○ Yes ◉ No

Section 3.7 Subject Expenses and Compensation

Indicate whether or not each of the following applies to this protocol

3.7a) There may be expense or added **costs to the subject** or the subject's insurance.

○ Yes ◉ No

3.7b) This is a **qualifying cancer treatment trial** and subjects may be billed for study drugs or procedures.

○ Yes ◉ No

3.7c) This is a cancer treatment trial but **subjects will not be billed** for study drugs or procedures.

○ Yes ◉ No

3.7d) Subjects will be **compensated** (either in cash or other means such as a gift certificate)?

◉ Yes ○ No

Section 3.8 Subject Activities

Indicate whether or not each of the following applies to this protocol

3.8a) Involves **surveys or questionnaires** completed by subjects

◉ Yes ○ No

3.8b) Includes the use of **recruitment materials** such as flyers, advertisements, or letters

◉ Yes ○ No

3.8c) Involves facial **photographs** or audio or video **recordings** of **patients**

◉ Yes ○ No

Section 3.9 Sponsors and Collaboration

Indicate whether or not each of the following applies to this protocol

3.9a) This research has a **commercial (industry) sponsor.**

○ Yes ◉ No

3.9b) Other **commercial (industry) non-financial support** is provided (e.g., drugs or supplies).

○ Yes ◉ No

3.9c) The PI or other study staff member has a financial interest or other **real or potential conflict** related to this study.

○ Yes ◉ No

3.9d) The protocol has **Department of Defense** involvement (e.g., subjects or funding).

○ Yes ◉ No

3.9e) **Non-VASDHS Research collaborators** (either researchers or entities, not VA WOCs, can be VA Other service also) are involved in this VASDHS IRB protocol. (Generally they cannot have access to sensitive information)

○ Yes ◉ No

Section 4 - Estimated Duration

4) What is the estimated duration of the entire study? (From IRB approval to IRB closure)

6 years

Section 5 - Lay Language Summary

5) Provide a summary or synopsis of the proposed study using non-technical language (not more than 1 paragraph)

Due to the aging of the United States population, age-related cognitive problems resulting from Alzheimer's disease and other causes of dementia are increasingly prevalent. Before individuals are diagnosed with dementia, they typically exhibit a period of "mild cognitive impairment" (MCI). Mild cognitive problems associated with MCI frequently impact an individual's ability to perform everyday tasks, including working, independent living, and medication adherence. Veterans are at increased risk of cognitive decline, and the Veterans Healthcare Administration (VA) is now providing health care to surging numbers of older Veterans with MCI who report significant cognitive complaints, difficulties with everyday functioning, and concerns about impending dementia. Despite high patient demand, few cognitive rehabilitation interventions exist that specifically address the needs of older Veterans with MCI that are widely accessible, patient-centered, and evidence-based. To our knowledge, no randomized controlled trials have been conducted that evaluate the efficacy of manualized, brief and inexpensive, yet comprehensive (multi-modal) cognitive rehabilitation interventions for older Veterans with MCI. Hence, the primary objective of this study is to evaluate the efficacy of Motivationally Enhanced Compensatory Cognitive Training (ME-CCT), a manualized cognitive rehabilitation group treatment for older Veterans with MCI. The study's specific aims are to determine whether ME-CCT is effective for: 1) improving objective cognitive performance and functional capacity, 2) improving subjective cognitive complaints, subjective functioning, and collateral measures of everyday function, and 3) increasing modifiable protective factors (e.g., diet, exercise) associated with reduced risk for MCI. We will also explore mediators and moderators of treatment effects. The overall goal is to evaluate a manualized group treatment for the symptoms of MCI that can be readily implemented in VA treatment settings. The study design makes use of the convergent availability of resources at the two participating VA Healthcare Systems in San Diego, California and Portland, Oregon to conduct a randomized controlled trial of ME-CCT. The study will recruit a sample of 216 Veterans (108 at each site) who meet criteria for MCI. Inclusion criteria will be: 1) Veterans 55 years old or older enrolled at one of the participating VAs who are able to provide informed consent, 2) Independently living, 3) Meet criteria for MCI based on previously published criteria (Petersen, 2004; Petersen, 2011), and 4) Willingness to participate in audio-recorded group sessions. Exclusion criteria will be: 1) Current substance use disorder with less than 30 days abstinence, 2) History of schizophrenia, schizoaffective disorder, or other primary psychotic disorder, 3) History of significant head trauma with loss of consciousness >30 minutes, and 4) Auditory or visual impairments that would prevent ability to participate in the cognitive rehabilitation group. Eligible participants will be randomly assigned to either the ME-CCT or an active control group, Goal-focused Supportive Contact (SC). The SC group will provide the same frequency and amount of therapist and peer contact as ME-CCT, but without specific training in cognitive strategies, lifestyle strategies, or motivational enhancement. 8 2-hour long weekly sessions will be delivered in both conditions. Both groups will undergo evaluations at baseline, 4 weeks (midway through the intervention), 8 weeks (immediately following the end of the intervention), and 21 weeks (3 months after completion of the intervention).

Section 6 - Specific Aims

6) Provide a statement of specific aims and hypotheses that serve as the basis for this protocol. Emphasize those aspects that justify the use of human subjects.

Due to the aging of the United States population, age-related cognitive problems resulting from Mild Cognitive Impairment (MCI), Alzheimer's disease, and other causes of dementia are increasingly prevalent. Before individuals are diagnosed with dementia, they typically exhibit a period of MCI. Mild cognitive problems associated with MCI frequently impact an individual's ability to optimally perform everyday tasks, including working, tasks of independent living, and medication adherence. Veterans are at increased risk of cognitive decline, and older Veterans diagnosed with posttraumatic stress disorder (PTSD) are twice as likely to have a diagnosis of dementia as individuals without PTSD. Hence, the Veterans Healthcare Administration (VA) is now providing health care to surging numbers of older Veterans with MCI who report significant cognitive complaints, difficulties with everyday functioning, and concerns about impending dementia. Despite high patient demand, few cognitive rehabilitation

interventions exist that specifically address the needs of older adults with MCI and that are widely accessible, patient-centered, and evidence-based. Although several clinical trials are currently evaluating behavioral interventions for MCI, they assess highly focused interventions (e.g., attention training) which are unlikely to effectively address the broader range of impairments (e.g., memory, attention, executive function, everyday functioning) and cognitive risk factors (e.g., low physical and mental activity levels) that adults with MCI commonly report. Alternatively, they evaluate highly intensive and therefore expensive interventions (>100 hours), which are not likely to be feasible for broad numbers of Veterans across typical VA facilities nationally. Accessible (e.g., brief, manualized), holistic/comprehensive, and effective treatments for rising numbers of Veterans with MCI are urgently needed.

Our study team recently completed a randomized controlled trial (RCT) that demonstrates the efficacy of our manualized, group-based, 10-week (two hours per week), Compensatory Cognitive Training (CCT) intervention for OEF/OIF Veterans with mild traumatic brain injury (TBI). CCT is a brief, inexpensive, patient centered, and holistic/comprehensive multi-modal behavioral intervention. Because Veterans with mild TBI have cognitive impairments similar to those seen in older Veterans with MCI, we conducted a small pilot study demonstrating the feasibility and acceptability of Motivationally Enhanced CCT (ME-CCT), which is our 8-week revision of CCT specifically adapted for the needs of older Veterans with MCI. In addition to compensatory cognitive training, ME-CCT includes motivational interviewing tools to boost the adoption of lifestyle strategies (e.g., diet, exercise) that improve cognition. Thus, the proposed RCT will extend our research and allow us to evaluate the efficacy of our intervention in a large sample of older Veterans with MCI. We will compare ME-CCT to Goal-Focused Supportive Contact (SC) for 8 weeks, followed by a 3 month follow-up period.

Aim 1: To determine whether ME-CCT is effective for improving objective cognitive performance and functional capacity (co-primary outcomes) in older Veterans with MCI. Hypothesis 1: Compared to those in SC, participants in ME-CCT will show significant improvements in objective cognitive performance and functional capacity.

Aim 2: To determine whether ME-CCT is effective for improving secondary outcomes in older Veterans with MCI. Hypothesis 2: Compared to those in the SC control group, participants in ME-CCT will show significant improvements on measures of subjective cognitive complaints, subjective functioning, and collateral measures of everyday functioning.

Aim 3: To determine whether ME-CCT is effective for increasing modifiable protective factors (i.e., physical exercise and mental exercise) associated with reduced risk for MCI and dementia. Hypothesis 3: Compared to those in SC, participants in ME-CCT will show increased participation in protective activities, as measured by physical and cognitive activity inventories.

Exploratory Aim 4 (Mediation and Moderation): As a preliminary evaluation of mechanism, we will conduct exploratory analyses to evaluate whether increased use of compensatory cognitive strategies and increased physical and cognitive activity mediate improvements in objective cognitive performance and functional capacity. In order to preliminarily explore for whom this intervention is most effective, we will evaluate whether baseline variables (i.e., demographics, premorbid IQ, baseline health and psychiatric status, medication and substance use) or baseline performance on primary and secondary endpoint measures moderate ME-CCT-associated improvements in objective cognitive performance and functional capacity.

This study addresses the significant gap in services and evidence-based treatments for aging Veterans with MCI. The overall impact of this project is the potential to yield a manualized, empirically-validated, highly feasible, person-centered intervention that meets the needs of surging numbers of older Veterans with MCI across the United States. If found to be efficacious, our study team will work with VA Central Office leaders toward national dissemination and scale-up of the ME-CCT for MCI intervention.

Section 7 - Background and Significance

7) Provide a succinct discussion of relevant background information to justify performing the proposed study.

1) Scope of the problem. Due to the aging of the United States population over the past few decades, cognitive problems such as Mild Cognitive Impairment (MCI), dementia, and Alzheimer's disease are becoming more prevalent among the elderly. Hence, the Department of Veterans Affairs (VA) is faced with providing healthcare for an increasing number of elderly Veterans who are beginning to exhibit signs of cognitive decline. MCI is an intermediate stage between normal aging and dementia [8] and is the prodromal stage for a variety of dementing neurodegenerative disorders [9]. Over 5 million Americans currently have Alzheimer's disease, the most common form of dementia; 35 years from now, that number is expected to more than triple to 16 million [10]. Alzheimer's disease is the costliest disease in the country, at $214 billion per year; 35 years from now, that cost will be $1.2 trillion per year [10]. Given the personal, family, societal, and fiscal costs of dementia, interventions to slow the onset of dementia are urgently needed.

2) There is no single cause of MCI, but risk and protective factors have been identified. MCI is frequently classified into subtypes based on whether cognitive deficits are amnestic versus non-amnestic, and whether deficits affect a single cognitive domain versus multiple domains [9]. MCI has been demonstrated to precede various dementing neurodegenerative disorders. There are numerous risk and protective factors associated with MCI [1] (see **Table 1**). The risk and protective factors for conversion to dementia have been shown to be similar to the risk and protective factors for the development of MCI [11-15].

Table 1. Risk and Protective Factors Associated with Mild Cognitive Impairment (MCI)

Demographic Risk Factors	• Older age • Lower education • African American
Genetic Risk Factors	• Family history, the presence of apolipoprotein E #4 allele (APOE)
Disease Risk Factors	• Cardiovascular disease, high cholesterol, high blood pressure • Metabolic and endocrine diseases, diabetes mellitus, thyroid dysfunction • Chronic renal failure • Psychiatric disorder, depression, psychosis • Sleep disorder • Polypharmacy • Vitamin B12 deficiency
Negative Lifestyle Factors	• Smoking • Heavy alcohol consumption
Positive Lifestyle Factors	• Physical activity, exercise • Cognitively-stimulating activity and mental exercise • Healthy nutrition, Mediterranean diet

Note: See Huckans et al. (2013) [1] for a review and individual references supporting each factor.

3) Individuals with MCI report increased neuropsychiatric symptoms, reduced everyday functioning, and reduced quality of life (QOL), and they are at risk for increasing disability. Although Petersen's [9, 16] widely accepted diagnostic criteria stipulate that individuals with MCI should have no more than minimal functional impairment, research suggests individuals with MCI nevertheless demonstrate changes in their psychological and everyday functioning [17, 18]. Neuropsychiatric symptoms are very common in individuals with MCI, with prevalence rates of at least one symptom ranging from 35-85% [19]. The most common neuropsychiatric issues associated with MCI are depression, anxiety, irritability, agitation, apathy, euphoria, disinhibition, delusions, hallucinations, and sleep disorders [19-22]. Areas of everyday functioning most frequently affected by MCI include appointment scheduling/attendance, transportation, and financial and medication management [23]. Individuals with MCI also report reduced QOL relative to older adults without cognitive impairment; reduced QOL is associated with increased neuropsychiatric symptoms and reduced functioning [24]. Annual conversion rates of MCI to dementia range from 10-15% in clinical samples [25].

4) Medications have shown minimal benefit. Pharmacologic interventions for MCI are based on current treatment guidelines for the management of Alzheimer's disease and have primarily focused on administering acetylcholinesterase inhibitors or other compounds to individuals with MCI in order to lower the rate of conversion to dementia [26]. The majority of findings from these studies indicate that acetylcholinesterase inhibitors, Vitamin E, rofecoxib, and piracetam do not significantly lower the rate of progression to dementia [27-29]. Given the lack of pharmacologic efficacy for MCI, non-pharmacologic interventions have been receiving increased attention over the past decade [12, 30].

5) Evidence supports the effectiveness of behavioral treatments, namely cognitive rehabilitation therapy. Cognitive rehabilitation therapies can improve cognitive functioning to slow the onset of disability and prolong the independence of individuals with prodromal dementia [31]. Cognitive rehabilitation therapies for MCI include behavioral interventions such as cognitive training, psychotherapeutic, and lifestyle techniques. Cognitive rehabilitation therapies for MCI have been associated with improvements in subjective cognitive complaints, objective cognitive performance (e.g., memory and problem-solving), Independent Activities of Daily Living (IADLs), mood, and QOL; mechanisms of these effects have included increases in choline and creatine signals in the hippocampus and increased activation in frontal and parieto-occipital regions of the brain [32-49]. Two studies have examined long-term effects (6 months post-treatment) of cognitive training, finding continued gains in QOL, work performance, objective processing speed, and memory appraisal [42, 45]. Th ese results suggest that individuals with MCI demonstrate learning potential and cognitive plasticity, and can benefit from cognitive interventions [32, 50]. The bulk of the evidence from both randomized controlled trials (RCTs) and epidemiological studies suggests that positive lifestyle factors can also improve cognition and lower risk of dementia in adults with MCI [51]. In particular, cognitively-stimulating activities, physical exercise, and diet can improve objective cognitive performance in adults with MCI [51]. In our own recently published systematic review on this topic [1], we

evaluated the efficacy of cognitive rehabilitation therapies for MCI. The bulk of the evidence suggested that cognitive rehabilitation therapies, including those incorporating cognitive training, psychotherapeutic, and/or lifestyle techniques, can change targeted behaviors in individuals with MCI and that cognitive rehabilitation therapies are associated with improvements in objective cognitive performance. Relatively few studies evaluated other important outcomes such as subjective cognitive complaints, everyday functioning, functional capacity, or neuropsychiatric symptom severity. We concluded that additional well-designed and adequately powered trials are warranted and required before cognitive rehabilitation therapies for MCI can be considered evidence-based. Our proposed trial will, therefore, address this gap and advance the field toward establishment of an evidence-based intervention for a rapidly growing population of older adults with MCI.

6) A comprehensive multimodal cognitive approach, as opposed to a single domain cognitive rehabilitation intervention, will better address the diverse needs of Veterans with MCI. Because individuals with MCI represent a heterogeneous sample and may present with a wide variety of cognitive, functional, and neuropsychiatric problems [19, 22], MCI has been broken into four subtypes in order to improve accuracy of diagnosis and prediction of conversion to dementia [9]. The subtypes are determined by the type of cognitive impairment the individual with MCI is demonstrating: amnestic vs. nonamnestic, and single domain impairment vs. multi-domain impairment [9]. Impairment can be seen in virtually all cognitive domains including memory, language, attention, visuospatial functioning, and executive functions [52]. Because of the heterogeneity of cognitive impairments noted in MCI populations, multi-modal cognitive training techniques, as opposed to single domain cognitive interventions, are needed to fully address their rehabilitation needs. In addition to improving cognitive functioning, rehabilitation interventions should also include healthy lifestyle strategies and techniques to reduce emotional distress, as these can both decrease risk for the development of dementia [53]. We found in our systematic review of cognitive rehabilitation for MCI that improvements in objective cognitive functioning were highly associated with multi-modal as opposed to single-domain cognitive training interventions [1]. Based on these results, we are confident that our decision to make our Motivationally Enhanced Compensatory Cognitive Training (ME-CCT) intervention comprehensive (i.e., includes cognitive training, psychotherapeutic, and lifestyle techniques) and to include multi-modal compensatory cognitive training techniques (i.e., teaches skills to address attention, memory and executive function problems) offers the greatest potential to effectively treat MCI.

7) Clinical practice guidelines have not been adequately implemented. The VA/Department of Defense (DoD) does not currently have a published practice guideline for the management of MCI, but various professional organizations, panels, and clinicians have published recommendations for the management of MCI [16, 18, 31, 54]. Even though these publications acknowledge the need for treatments to reduce the rate of conversion to dementia, few specific treatment guidelines are provided. Those that were provided included: providing information on maintaining a healthy lifestyle; prevention and management of modifiable risk factors for cognitive impairment; treatment of behavioral and psychiatric symptoms; cognitive training that includes the use of mnemonics, association strategies, and computer-assisted training programs; and lifestyle interventions such as exercise, intellectually-stimulating activities, and leisure activities/socializing. Recommendations to the field include the need for randomized controlled designs using large samples, particularly because of the heterogeneity of the MCI population, as well as use of both cognitive and functional outcome measures and adequate follow-up periods [31].

8) Our ME-CCT intervention is consistent with guideline recommendations, and our preliminary data support the ME-CCT intervention (see Preliminary Data). Our proposed study is consistent with future directions suggested in recent MCI literature as well as the President's national plan to fight Alzheimer's disease, released in 2012. The plan aims to develop effective prevention and treatment approaches for Alzheimer's disease and related dementias by 2025. Consistent with these recommendations, our proposed study intends to conduct a multi-site RCT evaluating the efficacy of a cognitive rehabilitation therapy for individuals with MCI. Because we intend to include participants who meet criteria for each of the four subtypes of MCI, our cognitive training program will address a variety of areas of cognitive impairment including memory, attention, and executive functions. We also intend to recruit a large sample of participants in order to account for the expected heterogeneity of our sample and make findings more generalizable. A 3-month follow-up will be conducted in order to examine the long-term effect of our intervention. In addition to focusing on improving cognitive functioning, the ME-CCT intervention also addresses the healthy lifestyle strategies that are associated with reduced MCI and dementia risk. Finally, our program's efficacy will be determined by the use of multiple outcome measures that not only assess objective cognitive performance, but also functional capacity, subjective everyday functioning, neuropsychiatric symptom severity, and frequency of participation in protective activities including exercise and cognitively-stimulating activities.

9) Working toward a theoretical model and a theoretically driven evidence-based treatment for MCI. In our systematic review of cognitive rehabilitation therapies for MCI [1], we published the first theoretical model of MCI treatment and rehabilitation. In doing so, we aimed to guide the future development and evaluation of evidence-based treatments for MCI, including our own proposed intervention. In this model, MCI is viewed as an intermediate stage between normal cognition and dementia. Individuals with MCI may convert to dementia, return to normal cognition, or have persistent MCI that does not convert to dementia. The etiology of MCI and dementia are viewed as multi-factorial, and a range of risk and protective factors, including those in **Table 1**, contribute toward increased or decreased risk, respectively. In some individuals, the cumulative and interactive impact of these factors on the brain results in the behavioral manifestation known as MCI, which is characterized by three types of symptoms: a) mild cognitive compromise (measured by objective neuropsychological tests), b) mild functional compromise (evaluated by measures of subjective cognitive complaints, everyday functioning, and functional capacity), and c) commonly associated neuropsychiatric symptoms (measured by neuropsychiatric symptom questionnaires). Based on this model, effective cognitive rehabilitation therapies for MCI would therefore directly address and reduce these three types of symptoms. A cognitive rehabilitation therapy may also indirectly reduce these symptoms by targeting modifiable risk and protective factors that are known to increase (depicted as arrows

with plus signs) or decrease (depicted as arrows with negative signs) risk of MCI and dementia. This theoretical model serves as the conceptual framework for the design of our proposed ME-CCT intervention and clinical trial. ME-CCT is designed to target all three types of MCI symptoms – cognitive compromise, functional compromise, and neuropsychiatric symptoms – along with increasing modifiable protective factors associated with reduced risk of MCI and dementia. The ME-CCT intervention is comprehensive and multi-modal and, thus, incorporates the following three elements to target these symptoms and protective factors:

1) Multi-Modal Compensatory Cognitive Training Techniques: Participants learn and practice compensatory cognitive skills designed to improve memory, attention, and executive functioning (i.e., organization, planning, and problem-solving). Compensatory strategies include internal strategies (e.g., visual imagery, chunking or acronyms to compensate for memory difficulties, structured problem-solving and planning methods to compensate for executive dysfunction), external strategies (e.g., calendars and timers), and environmental strategies (e.g., setting up a quiet work space). Participants are given in-class activities and weekly home exercises so they can practice and implement compensatory cognitive skills in their daily lives. Home exercises are discussed at subsequent sessions so that participants can receive feedback and troubleshoot application of new skills to their specific real life problems and activities of daily living. Given this emphasis on everyday functioning, and because previous MCI studies [55, 56] and our own pilot data (see **Preliminary Studies**) suggest that cognitive training interventions can increase daily functioning in adults with cognitive impairments, our primary hypothesis is that ME-CCT will improve everyday functioning in individuals with MCI. Because previous MCI studies [40, 56, 57] and our own pilot data (see **Preliminary Studies**) also suggest that comprehensive multi-modal cognitive interventions can improve objective cognitive performance in adults with cognitive impairments, we additionally hypothesize that ME-CCT will improve objective functional capacity and cognitive performance in adults with MCI.

2) Psychotherapeutic Techniques: Given the high rates of neuropsychiatric symptoms (e.g., depression, anxiety, fatigue, and sleep problems) among individuals with MCI and the likelihood that these symptoms exacerbate problems with cognition and everyday functioning, our ME-CCT intervention incorporates mindfulness-based stress reduction exercises, fatigue and energy management skills, and sleep hygiene skills. In particular, our intervention includes weekly in-class practice of tension reduction exercises such as abdominal breathing and mindfulness meditation, as well as an education module that utilizes brief motivational interviewing techniques [58, 59] to enhance participants' motivation to regularly practice mindfulness-based stress reduction exercises. In a systematic review of the benefits of mindfulness-based stress reduction techniques, empirically supported benefits included reduced stress, depression, anxiety and worrying; improved sleep; and improved cognition, including improved attention, working memory, problem-solving, mental flexibility, and processing speed [60].

3) Lifestyle Techniques: Epidemiological and cross-sectional studies indicate that adults who frequently engage in physical activity (i.e., exercise) and cognitively-stimulating activities (e.g., puzzles, games, reading, social and cultural activities) are at significantly reduced risk for MCI and dementia [51, 61-64]. Moreover, we found in our systematic review of MCI treatments [1] that all 7 RCTs testing interventions to increase physical activity or cognitively-stimulating activities found significant improvements in objective cognitive performance relative to control conditions. Our ME-CCT intervention provides participants with education about the benefits of reducing modifiable risk factors (i.e., smoking and heavy alcohol use) and increasing modifiable protective factors (i.e., physical activity, cognitively-stimulating activity, and a healthy /Mediterranean diet) known to be associated with MCI (**Table 1**). We additionally incorporate education modules that utilize brief motivational interviewing techniques [58, 59] to enhance participants' motivation to increase the frequency of physical activity and cognitively-stimulating activities in their daily life; evidence suggests that motivational interviewing can effectively promote healthy lifestyle changes in adults with a range of conditions [58, 59, 65, 66].

10) Relationship to competing local or national clinical trials. A search of the national clinical trials registry [67] reveals that several trials are underway that evaluate cognitive rehabilitation interventions for MCI. Several of these trials evaluate single modality (i.e., non-comprehensive) memory or attention training techniques for MCI, which are not likely to have as robust of effects as comprehensive multi-modal interventions such as ME-CCT. Additional trials entail highly intensive (e.g., > 100 hours) and therefore expensive interventions for MCI, which are not likely to be feasible for broad numbers of Veterans across typical VA facilities nationally. However, to our knowledge, there are no competing national or local trials underway which specifically evaluate manualized, brief and inexpensive, yet comprehensive multi-modal cognitive rehabilitation interventions for older Veterans with MCI.

11) Relevance of the proposed work to the VA Patient Care Mission. The number of older Veterans with MCI seeking treatment is increasing and is expected to increase more rapidly as Vietnam Veterans and the Baby Boomer population age. The cognitive effects of MCI and subsequent neurodegenerative disorders can adversely affect Veterans' abilities to function independently. The VA currently spends over $19,000 annually per patient to care for Veterans with dementia [68], and delaying the onset of dementia even by one to two years will result in QOL gains for Veterans and substantial financial savings to the VA. Treatments that work are urgently needed. Therefore, an evidence-based cognitive training intervention that optimally addresses the complex needs of older Veterans with MCI is of critical importance to the VA patient care mission. To our knowledge, no RCTs have been conducted to evaluate the efficacy of manualized comprehensive compensatory cognitive training with older Veterans with MCI. Demonstrating that a new treatment for MCI is effective in improving cognition and functioning would be a significant contribution to the quality of care provided by the VA. If the treatment is found to be effective, the ME-CCT manual could be quickly disseminated to all VA facilities. With the program's portability and ready availability, it will immediately be possible to deliver cost-effective, evidence-based compensatory cognitive training to Veterans with MCI.

Section 9 - Design and Methods

9) Describe the research design and the procedures to be used to accomplish the specific aims of the

project. Provide a precise description of the planned data collection, analysis and interpretation. Address sample size, inclusion of women and minorities. Define in clear terms exactly what will be done to the human subjects.

Overview. The planned RCT uses a 2 (ME-CCT vs. SC) x 4 (Weeks 0, 4, 8 and 21) mixed effects experimental design. A total of 216 older participants with MCI will be recruited from the two participating sites, VASDHS and VAPORHCS (108 from each site). By including two geographically distinct sites, we will not only enhance the efficiency of our recruitment and diversity of our sample, but also demonstrate the efficacy of ME-CCT at different geographic areas with different providers. Participants will be randomized to either the ME-CCT or SC group. Participants in the CCT group will receive our ME-CCT intervention during the first 8 weeks of participation in the study, whereas SC participants will receive a robust control intervention, Goal-Focused Supportive Contact. During study participation, all participants will continue to receive their usual medical, psychiatric and psychotherapeutic care. Both groups will undergo study evaluations at baseline, 4 weeks (midway through ME-CCT), 8 weeks (immediately following ME-CCT completion) and 21 weeks (3 months after ME-CCT completion).

Participants and eligibility criteria. Inclusion Criteria: 1) Veterans ≥55 years old enrolled at one of the participating VA sites (VASDHS and VAPORHCS) who are able to provide informed consent. 2) Independently living. 3) Meet criteria for MCI based on previously published criteria [9, 16]. 4) Willingness to participate in audio-recorded sessions. Exclusion Criteria: 1) Current substance use disorder with < 30 days abstinence. 2) History of schizophrenia, schizoaffective disorder, or other primary psychotic disorder. 3) History of significant brain injury with loss of consciousness > 30 minutes. 4) Auditory or visual impairments that would prevent ability to participate in the cognitive rehabilitation group or benefit from compensatory strategies. MCI Criteria: Criteria for MCI will be based on previously published criteria [9, 16]: 1) Concern about a decline in cognitive functioning expressed by a physician, informant, participant or nurse. 2) Cognitive impairment in one or more of the following domains: executive function, memory, attention, language or visuospatial abilities. 3) Normal or minimal impairment in functional activities. 4) Does not meet criteria for dementia. To determine whether individuals meet criteria for MCI, two neuropsychologists (Drs. Twamley, Huckans, Jak, or Storzbach) will separately review each individual's neuropsychological performance on a comprehensive neuropsychological battery (see **Table 6**) to determine study eligibility and classify MCI subtypes. If there are discrepancies, a third neuropsychologist will review the data and the participant will only be included if consensus can be reached. The standard clinical neuropsychological assessment batteries conducted with adults with MCI through the Neuropsychology Clinics at the VASDHS and VAPORHCS sites are typically much longer (often exceeding three hours), and adults with MCI tolerate these batteries well. All subtypes of MCI will be included; however, in order to facilitate exploratory analyses to determine whether ME-CCT is more effective for particular subtypes, participants will be classified as follows, using previously published criteria [9, 16] and procedures similar to those we have used in our previous studies [73]: A) Single domain amnestic MCI will be operationally defined as performance on at least two memory measures falling ≥1 standard deviation (SD) below their age-appropriate norms. B) Single domain non-amnestic MCI will be operationally defined as performance on at least two measures in one domain of the above mentioned cognitive domains falling ≥1 SD below their age-appropriate norms in the absence of memory impairment. C) Multiple domain amnestic MCI will be defined as meeting the above criteria for a memory deficit as well as meeting criteria for a deficit ≥1 SD below their age-appropriate norms on at least two measures within one or more of the additional cognitive domains (attention/processing speed, language, executive functioning). D) Multiple domain non-amnestic MCI will be operationally defined as performance on at least two measures in more than one of the above mentioned non-memory cognitive domains falling ≥1 SD or more below their age-appropriate norms in the absence of memory impairment.

Recruitment and feasibility. Total enrollment for the study will be 108 participants per site (54 ME-CCT and 54 SC per site), for a total of 216 participants (108 ME-CCT and 108 SC). Participants will be primarily recruited through clinic referrals and medical record review followed by recruitment letters sent to patients who meet the requisite pre-screening criteria. The recruitment letter will state that the individual may opt out by calling the research team indicating that they do not wish to be contacted, or they may indicate they are interested in learning more about the study by calling the study team. The letter will state that if the individual has not responded to the letter within two weeks, research personnel will contact them by phone. Participants will also be recruited through other research study referrals and contacted by letter /phone (see Section 11: Recruitment for more recruitment methods). We will recruit a sample composed of at least 25% of individuals from ethnic/racial minority groups, including African Americans, consistent with the 2013 US Census. This will provide us with enough subjects to explore minority status as a moderator of treatment outcome, although we do not expect differential effects. By having two sites, we will be better able to ensure adequate ethnic/racial diversity in our sample. We will recruit women and men. At the VASDHS, over the past year approximately one third of the 500+ total referrals to the Neuropsychological Assessment Unit were diagnosed with MCI and likely would have been eligible for the proposed study. At VAPORHCS, 2,472 Veterans with a diagnosis of MCI were treated over the past two years; moreover, within the past year, of the 336 neuropsychological assessments conducted through the VAPORHCS Neuropsychology Clinic, 129 of those (59%) resulted in a diagnosis of MCI and likely would have been eligible to participate in the proposed study. At the VAPORHCS, since January 2015, 125 patients have been referred for the waiting list for the ME-CCT intervention; all referrals came from clinicians who had heard about the groups through word of mouth. We did not implement any intensive research recruitment efforts such as those proposed in this study (e.g., advertisements, letters to eligible patients, study compensation, study coordinators with protected time to seek out referrals). This demonstrates not only recruitment feasibility but also genuine interest in the groups, both by patients and the clinicians who refer them. Based on these data, we estimate that over 250 adults per year will be eligible to participate in the proposed study between the two sites, indicating that the goal of recruiting 216 participants over the course of the five-year study is very feasible. Nevertheless, should our VA recruitment efforts prove less successful than we anticipate,

we will recruit additional participants from the academic institutions affiliated with each participating VA, namely University of California, San Diego (UCSD) and Oregon Health & Science University (OHSU), where Drs. Twamley and Huckans have joint appointments, respectively. UCSD programs that can refer participants include Senior Behavioral Health and the Memory and Resilience Center (see letter of support from Dr. Daniel Sewell, Medical Director and Co-Director of these two outpatient programs). At UCSD, the Senior Behavioral Health Program and the Memory, Aging, and Resilience Center evaluate and treat about 75 patients per year with MCI. OHSU programs that can refer participants include the National Institute on Aging (NIA)-funded Layton Aging & Alzheimer's Disease Center (Directed by Co-Investigator Kaye) and the OHSU Division of General Internal Medicine and Geriatrics (Directed by Co-Investigator Eckstrom) (see letters of support from Drs. Kaye and Eckstrom). At OHSU, the Layton Center longitudinally follows about 450 research volunteers at risk for MCI or dementia, and enrolls 60 new volunteers per year.

Retention and reimbursement. We had a relatively low non-completer rate (11%) among subjects enrolled in our funded CCT study with OEF/OIF Veterans with mild TBI; moreover, all of the non-completers dropped out prior to the start of the group, while those who attended the first session of the group completed the 10-week CCT intervention. The five ME-CCT for MCI groups that we have run at VAPORHCS have had a similar drop-out rate of ~10%. We have, therefore, conservatively assumed a 20% drop-out rate and will recruit 216 participants to yield a final sample size of 180. Our power analyses were calculated assuming 20% attrition, yielding a total final sample of n=180 (see power analyses for each hypothesis). We will use subject compensation and reminder phone calls to reduce our attrition rate. Participants will be compensated $50 after each of the first three assessments, and $75 after the fourth and final follow-up assessment. If participants complete all four assessments, their total compensation will be $225. VASDHS participants who elect to use the Fitbit during the study will be able to keep the Fitbit device at the conclusion of their study participation.

Experimental intervention (ME-CCT). ME-CCT was developed, authored, and piloted by the PIs, Drs. Twamley and Huckans (see **Pilot Study 1**). ME-CCT is a manualized group-based behavioral intervention (8 weeks, 2 hours per week, 16 hours total) designed to improve cognitive and everyday functioning in patients with MCI. See **Table 2** for a description of the ME-CCT intervention and **Appendix 6** for the treatment manual.

Control intervention (SC). We propose to use a robust control condition, Goal-focused Supportive Contact (SC), a group therapy intervention that provides the same frequency and amount of therapist and other group member contact as ME-CCT, but does not provide training in cognitive strategies, lifestyle strategies, or motivational enhancement. The SC intervention will have a primary focus on setting and achieving short or long-term goals. Focusing on goals is intended to provide "face validity" to potential participants and to enhance treatment attendance and reduce drop-out in this population. Sessions will be semi-structured and consist of check-in about the week prior, current symptoms or concerns, followed by a flexible discussion about setting and working toward goals. Sessions will typically include components of empathy and non-directive reinforcement of health, coping, and symptom management behaviors that grow out of group discussions, with only minimal therapist guidance. Participants will be asked to think about how the discussions had bearing on their individual goals, and will be encouraged to ask for the advice of other participants in achieving specific goals, but no specific training will be provided. Study therapists will not provide advice on reaching goals, but will encourage feedback from other group members. The SC control condition is being used in one of Dr. Twamley's currently-funded cognitive training studies (NIMH R34) and has been used in published studies by her colleague, Dr. Granholm [6, 7].

Procedures. Potential subjects will be identified through the specific recruitment methods described in the below section 11. Prior to enrollment, interested Veterans will be **pre-screened**. Study personnel will conduct a medical record review, including neuropsychological assessment records, to ensure study eligibility. As described in the following sections related to recruitment (Section 9: "Recruitment and Feasibility" and Section 11: "Recruitment"), study personnel will then contact individuals by phone or letter, depending on the specific recruitment method, to answer questions about the study, confirm interest in participation, and to schedule an initial study visit. All eligible participants will then complete an **initial study visit** which will include informed consent and baseline measures (see **Table 5**); all participants will be carefully screened to ensure their ability to comprehend study procedures, risks and benefits. Participants at the VASDHS site will be offered the opportunity to use a Fitbit to track their physical activity and sleep during the study. (The Fitbit Charge 2 is a non-invasive, water-resistant, wrist-worn device that measures steps taken, distance traveled, heart rate, and sleep quality and stages.) Upon enrollment, we will create a unique login ID and password for each participant to enable us to track their data on the Fitbit website each week of the 8-week intervention; we will upload these data during the weekly group session. When connected to a compatible device (i.e., study computer), data are automatically uploaded to the users' Fitbit accounts. The researchers will bring a study laptop to the groups each week, at which time the researchers will upload participants' data for adherence and assessment purposes. These data will then be "dumped" into and stored on a secure study server. We will also upload their data during their last assessment at 21 weeks; however, participants will be given the option of coming to the VA between the 8 week and 21 week assessment to upload their data so they can get continued summary of their progress each week. The participants will be allowed to keep the device when the study ends and guided through the procedure for establishing a new username and password, thereby terminating the research staff's access to their account. All eligible participants will then be **randomized** to either the ME-CCT or SC group. Randomization tables will be prepared by Dr. Golshan, the study statistician, at the beginning of the study. For each site, groups will be randomly assigned to ME-CCT or SC based on the site's randomization table. New study participants will be allocated to the current group awaiting randomization. Once group membership reaches the minimum of 6, the group will be randomized by Dr. Golshan, who will be blind to membership of each group. Randomization procedures and enrollment for each site will be monitored by Dr. Golshan, and if imbalance occurs at any site, he will recommend the necessary adjustment. Following randomization, participants will receive the **intervention (ME-CCT or SC)** for 8 weeks. To reduce the risk of treatment

contamination, groups will be held at times and locations where Veterans in different groups will not have the opportunity to meet in a waiting room. We will also ask Veterans not to discuss their treatment with other Veterans until after completion of the protocol. Both groups will complete outcome measures (see **Table 5**) at baseline, 4 weeks (midway through ME-CCT), 8 weeks (immediately following ME-CCT), and at 21 weeks (3 months after ME-CCT is completed); assessors will be blind to randomization status. None of the study procedures are part of standard care. Both groups are experimental.

COVID Procedures: Assessments and group intervention sessions: All assessment and intervention procedures will be completed using social distancing whenever possible, and requiring medical-grade procedure masks at all times. *Study has required follow up visits, but if restrictions were re-imposed, we would instead gather the information by phone or home-based video telemedicine so subjects would not need to return to the VA. We cannot do baseline assessments remotely, but if need be, we can collect partial follow-up data remotely.

Treatment Adherence. Attendance of each participant at each session will be recorded. Individual make-up sessions will be offered to participants who miss a session, and attendance at make-ups will be recorded.

Treatment Fidelity. In addition to extensive therapist training and weekly supervision to ensure treatment fidelity, treatment fidelity will be closely monitored by Drs. Twamley and Huckans, using procedures similar to those used in our CCT for TBI study. ME-CCT sessions will be audio-recorded with an Olympus digital voice recorder (VN-4100PC or similar), and 20% of sessions randomly selected by Dr. Golshan will be rated by Drs. Twamley or Huckans using the ME-CCT fidelity monitoring tool (see **Appendix 7**). Scores < 90% will trigger a review and plan for improving fidelity. SC sessions will also be audiotaped and 20% of sessions randomly selected by Dr. Golshan will be rated by Drs. Twamley or Huckans using the ME-CCT fidelity monitoring tool to ensure that no ME-CCT content is present in SC sessions. Scores > 0% will trigger a review and plan for improving fidelity. Specific plans have been developed for responding to sub-threshold adherence, ranging from extra training to statistically controlling for adherence to replacing therapists (in the extreme).

Assessment Methodology. Participants will complete the assessment battery at weeks 0, 4, 8 and 21, consisting of self-report questionnaires and performance-based tests of cognition and functioning. Performance-based tests will not be administered at week 4, however, to avoid practice effects. Collateral informants (e.g., spouse, adult child, relative), when available, will complete questionnaires at weeks 0, 4, 8, and 21. Study measures and the rationale for including them are listed in **Table 5**. Measures will take < 3.5 hours to complete at week 0 (baseline), < 1 hour at week 5, and approximately 3 hours at weeks 8 and 21 (follow up). We have selected measures based on 4 criteria: 1) importance for assessing constructs evaluated in our aims, 2) brevity (to reduce subject burden), 3) reliability, and 4) demonstrated validity. The rationale for including each study measure is listed in **Table 5** and further described below. Data collected at the second site, VAPORHCS, will be transferred to VASDHS via drive behind the VA firewall, as we have done in a previous study. Fitbit data will be collected at the VASDHS site only.

Fitbit Charge 2 (https://www.fitbit.com/charge2): This non-invasive, water resistant device, which is worn around the wrist, will be used to measure participants' activity levels, heart rate, and sleep quality. The Fitbit uses a three-dimensional accelerometer to sense movement. It measures steps taken, distance walked, calories burned, active/inactive minutes, stationary time, heart rate, hours and quality of sleep, as well as stages of sleep. The Fitbit's measurement of self-paced and prescribed intensity exercise has been validated against the Omron HJ-720IT accelerometer and direct observation.

Table 5. Study Measures

Measure	Purpose /Specific Aim: Hypothesis	Construct Assessed	Weeks Administered	Time (min)
Patient Health Questionnaire-9 (PHQ-9) [74].	Subject characterization; Exploratory Aim 4.	Depression symptom severity.	0	2
General Anxiety Disorder-7 Scale (GAD-7) [75].	Subject characterization; Exploratory Aim 4.	Anxiety symptom severity.	0	2
PTSD Checklist (PCL)	Subject characterization; Exploratory Aim 4.	PTSD symptom severity.	0	2
Wide Range Achievement Test-4-Reading (WRAT-4) [76].	Subject characterization; Exploratory Aim 4.	Reading ability (premorbid IQ estimate).	0	5

Neurocognitive Composite Score (Average z Score of tests in **Table 6** targeted by ME-CCT).	Aim 1: H1 (co-primary outcome).	Neurocognitive functioning (see cognitive domains in **Table 6** targeted by ME-CCT).	0, 8, 21	90
Functional Capacity Composite Score (Average z Score of tests in **Table 7**).	Aim 1: H1 (co-primary outcome).	Functional capacity (i.e., performance based measures of everyday functioning; see **Table 7**).	0, 8, 21	45
Subjective Everyday Functioning Composite Score (Average total score across two Neuro-QOL scales, Applied Cognition Executive Function and Applied Cognition General Concerns [77]).	Aim 2: H2 (secondary outcome).	Subjective cognitive complaints and everyday functioning.	0, 4, 8, 21	5
Everyday Cognition Scale (ECog) [78].	Aim 2: H2 (secondary outcome).	Collateral measure of cognitive and everyday functioning.	0, 4, 8, 21	10
Cognitive Activity Inventory [63, 79].	Aim 3: H3; Exploratory Aim 4.	Recent frequency of engagement in activities requiring mental exercise, a protective factor known to reduce risk of MCI and dementia.	0, 4, 8, 21	3
CHAMPS Physical Activity Questionnaire for Older Adults [80].	Aim 3: H3; Exploratory Aim 4.	Recent frequency of engagement in activities requiring physical exercise, a protective factor known to reduce risk of MCI and dementia.	0, 4, 8, 21	6
Portland Cognitive Strategies Scale (PCSS) [69].	Exploratory Aim 4.	Recent frequency of use of cognitive strategies taught in the ME-CCT class.	0, 4, 8, 21	5

Additional Measures Added to the Study or Required by eScreening:

Motivation/Efficacy items -- added to the study to track participant motivation for lifestyle changes addressed in the intervention. These are the same items that are used in the ME-CCT intervention. Example item: On a scale of 0-10, based on your current life and goals, how confident are you that, if you decided to exercise more regularly than you do now, you could do it? (rated 0-10)
Measures Required by eScreening: basic demographics and military history, Basic Pain, PROMIS Pain Intensity and Interference, Alcohol Use Disorders Identification Test-C, Insomnia Severity Index, Brief TBI Screen, Patient Health Questionnaire 15, and WHO Disability Assessment Schedule-2. All are brief, standard measures required by eScreening. They are brief enough to not increase subject burden significantly.

Co-Primary Outcomes (Aim 1: H1). **Objective cognitive performance** will be a composite z score derived by averaging the scores across tests in our battery (see **Table 6**) except for language measures, which are only used in the diagnostic evaluation. ME-CCT teaches strategies that participants can use to improve their performance on real-world tasks as well as traditional objective neuropsychological tests. The neurocognitive battery was also designed to confirm accurate diagnosis of MCI using published [9, 16] criteria and therefore confirm eligibility criteria. When possible, we have selected measures with equivalent forms which will be alternated to reduce practice effects. We found significant CCT-associated improvements on several of these measures, namely WAIS-IV Digit Span, HVLT-R, and D-KEFS Verbal Fluency, following CCT for TBI (see **Pilot Study 2**). **Objective, performance-based functional capacity** will be a co-primary outcome, measured with a battery of performance-based (role play) measures (see **Table 7**) that ask participants to apply everyday living skills on tasks that are highly congruent with analogous real-world activities (e.g., medication management, financial skills). Performance-based tests of everyday living skills are the most objective way to capture improvements in functional abilities. We will use a composite z score derived by averaging scores across tests in the battery. We found near-significant (p=.059) improvements on one of these measures, the UPSA, following CCT for TBI (see **Pilot Study 2**).

Secondary Outcomes (Aim 2: H2). Subjective cognitive complaints and subjective everyday functioning will be a composite score derived by averaging the total scores across two Neuro-QOL scales, the Applied Cognition Executive Functions Scale and the Applied Cognition General Concerns Scale [77]. The Neuro-QOL scales were developed as part of the NIH Measurement Initiative to promote aggregation and cross-comparability of results across studies nationally, and they are specifically designed for use in clinical trials for the evaluation of interventions for neurological conditions [77]. Neuro-QOL measures are brief (8-items), psychometrically robust, and highly patient-centered in that they are sensitive to the symptoms, concerns and issues that neurological patients most commonly report and deem relevant to their well-being. We found significant improvements on these Neuro-QOL scales following ME-CCT for MCI in our pilot study (see **Pilot Study 1**). We also found significant improvements on two other measures of cognitive complaints and everyday functioning following CCT for TBI (see **Pilot Study 2**). We will also include the ECog, a collateral (e.g., spouse, close relative) measure of cognitive and everyday functioning [78]. The ECog has demonstrated sensitivity to detecting varying levels of impairment across clinical groups and can differentiate between the four subtypes of MCI [78]. We found significant improvements on the ECog in adults with MCI following the CogSMART intervention in our pilot study (see **Pilot Study 3**). We will focus analyses on the general factor (i.e., single summary score) derived from the ECog.

Table 6. Neurocognitive Battery

Domain	Test	Description
Memory (targeted in ME-CCT)	Hopkins Verbal Learning Test-Revised (HVLT-R) [81] Brief Visuospatial Memory Test-Revised (BVMT-R) [82]	Oral list-learning task requiring acquisition of a list of 12 words from 3 categories over 3 trials. A test that involves learning and reproducing six geometric figures from memory.
Attention (targeted in ME-CCT)	Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) Digit Span [83] WAIS-IV Coding [83] Delis-Kaplan Executive Function System (D-KEFS) Trails, Number and Letter Sequencing [84]	Participant recalls sequences of numbers in the same order (Digits Forward), in reverse order (Digits Backwards), and in ascending order (Digit Span Sequencing). Participant uses a key to draw symbols corresponding to numbers. Participant quickly draws a line connecting numbers in order (Number Sequencing) and then letters in order (Letter Sequencing).
Executive Function (targeted in ME-CCT)	D-KEFS Trails, Number-Letter Switching [84] D-KEFS Color-Word Interference Test, Inhibition and Inhibition-Switching [84] NAB Categories [88]	Participant switches back and forth between connecting letters and numbers in order (i.e., 1, A, 2, B, 3, C, etc.) A Stroop task in which participants name the color words are printed in rather than reading the color word (Inhibition), and then switches between naming the color or reading the word (Inhibition-Switching). An ecologically valid measure in which the participant is asked to generate as many different two-group categories as they can based on photographs and verbal information.
Language (needed for diagnostic evaluation, but not targeted in ME-CCT or included in composite z score)	Boston Naming Test [85] D-KEFS Verbal Fluency [84]	Participant names pictures of familiar objects. Participant names animals for 1 minute (Category Fluency), and then words that start with a particular letter for 1 minute (Letter Fluency).

Table 7. Performance Based Functional Capacity Battery

Domain	Test	Description
Communication and financial management skills	UCSD Performance-Based Skills Assessment-Brief (UPSA-B) [86]	A role-play-based test that measures ability to communicate efficiently and accurately and apply financial skills to simple (counting change) and more complex (paying a bill by check) situations.
Medication management skills	Medication Management Ability Assessment (MMAA) [87]	A performance-based measure of ability to manage a simulated, complex medication regimen similar in complexity to one that an older person is likely to be prescribed.
Memory skills relevant to everyday functioning	NAB Daily Living Memory [88]	An ecologically valid measure in which the participant is asked to recall, both immediately and following a delay, information encountered in daily life, including medication instructions and a name, address and phone number.
Problem-solving skills relevant to everyday functioning	NAB Judgment [88]	An ecologically valid measure in which the participant is asked to respond to questions about how they would address various everyday problems related to home safety, health and medical issues.
Driving/attention skills	NAB Driving Scenes [88]	An ecologically valid measure in which the participant is asked to attend to and identify changes across simulated driving scene relevant to driving safety.

Additional Outcomes (Aim 3: H3). ME-CCT uses motivational interviewing techniques designed to increase participant engagement in healthy lifestyle behaviors known to reduce risk for dementia, namely physical exercise and mental exercise [1, 51]. Increased participation in these modifiable protective factors will be evaluated using physical and cognitive activity inventories. The CHAMPS Physical Activity Questionnaire for Older Adults has previously demonstrated adequate short-term stability and construct validity in older adults, and is sensitive to changes in physical activity [80]. The Cognitive Activity Inventory (Current Cognitive Activity Subscale) has demonstrated adequate short term temporal stability, internal consistency and validity in older adults [79], and higher scores on this measure are associated with reduced risk for cognitive decline in healthy older adults and for developing MCI and Alzheimer's disease [62-64].

Mediators (Exploratory Analyses). As a preliminary evaluation of mechanism, we will conduct exploratory analyses to determine if increased use of the compensatory cognitive strategies taught through the intervention mediates

improvements in objective cognitive performance and functional capacity. The frequency with which participants use these strategies will be evaluated with the Portland Cognitive Strategies Scale (PCSS) [69]. Our pilot data demonstrate significant increases in cognitive strategy use on the PCSS in Veterans with MCI following ME-CCT (see **Pilot Study 1**). We also found significantly increased strategy use on the PCSS in combat Veterans following CCT for TBI (see **Pilot Study 2**). Using the CHAMPS Physical Activity Questionnaire, the Fitbit data, and the Cognitive Activity Inventory, we will also evaluate whether increases in physical activity and mental activity mediate improvements in objective cognitive performance and functional capacity.

Baseline Characterization and Moderators (Exploratory Analyses). Baseline measures were selected to ensure that baseline rates of demographics, medical conditions, BMI, medication and substance use, psychiatric disorders, premorbid IQ, and significant other involvement are equivalent across groups. If between group analyses reveal any differences across groups in terms of these factors, they will be controlled for in subsequent analyses. In order to preliminarily explore for whom this intervention is most effective, we will evaluate whether these baseline variables (see **Table 5**) or baseline performance on primary and secondary endpoint measures moderate ME-CCT associated improvements in objective cognitive performance and functional capacity.

HYPOTHESIS-SPECIFIC DATA ANALYSIS PLAN AND POWER ANALYSES

Data analyses will proceed in stages: 1) First, descriptive statistics and exploratory analyses will be used to assess the normality of the data and homogeneity of variance. The continuous outcome data will be transformed if necessary by using an appropriate transformation such as the log transform for skewed long tailed data. Similarly, potential covariates will be summarized with descriptive statistics and graphs to determine the most appropriate way to treat these variables. In addition, the results will be inspected for bias due to dropouts or missing data. 2) Although we don't anticipate any baseline differences, we will compare any differences among groups and sites on baseline measures. Any statistically and clinically significant differences will be controlled for in subsequent analyses by adding the target variables as covariates to the model. 3) We propose to use mixed effects modeling to account for clustering structure of the data (i.e., repeated assessments within an individual, groups, therapists and sites) for main hypotheses testing. The mixed effects approach is more powerful than traditional methods and allows the 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 models of random regression models (RRM), also known as hierarchical linear models (HLM) or multilevel models, and mixed model analysis of variance (MMANOVA) will be considered. Each outcome variable will be graphed versus time for each subject to evaluate what function of time best describes the data. If the change is linear we will proceed with the HLM structure. If the time pattern is not immediately apparent we will proceed with the MMANOVA. 4) We will use the extension of the Pattern-Mixture models [89] which allow subject-to-subject heterogeneity, to assess if there is bias due to drop out or missing data. Furthermore, the randomness of missing data will be examined according to recommended procedures [90], which includes comparing group differences in the primary outcomes of subjects with versus without missing data. Specific plans for testing each hypothesis are below.

H1: Compared to those in SC, participants in ME-CCT will show significant improvements in objective cognitive performance and functional capacity.

Dependent variables: Neurocognitive composite score (Average z score across subtests in the Neurocognitive Battery detailed in **Table 6**); Functional capacity composite score (Average z score across subtests in the Functional Capacity Battery detailed in **Table 7**). Independent variables: Treatment group (2 levels, ME-CCT and SC), and Time (4 levels, Weeks 0, 4, 8, 21). Statistical Analysis: We will analyze data on all randomized subjects for whom we have a baseline assessment and at least one post-baseline evaluation. Data will be analyzed by mixed effects model methods [91-93] for linear or non-linear trends based on earlier inspection of data. 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 X time model will be utilized for inference. Covariance structure will be chosen based on Akaike's Information Criterion (AIC). Random group level treatment effects will also be evaluated for importance based on the model AIC. Denominator degrees of freedom will be calculated using the Kenward-Roger small sample correction. The effects of site, therapist and their interaction with treatment will be included and tested. However, we do not anticipate any significant interactions or main effects of these factors given our balanced study design (equal numbers at each site in each group), our standard training and operating procedures at both sites and with all therapists, and our previous analyses from our similarly-designed study (our CCT for TBI study). In any case, the analysis procedures will include these factors and their interaction effects to avoid allowing site or therapist effects to bias treatment comparisons. If we detect any imbalances between the treatment groups, we will follow the primary analyses above with subsequent analyses considering the imbalances to verify that the conclusions are not affected by the 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. In addition, any treatment group comparison will be adjusted for subject-specific characteristics, and adjustments for changes in these characteristics over the course of the study can be incorporated into the single-subject analyses. Power Analysis: In addition to the procedures described by Hedeker and colleagues [94] for Random Regression Models (the RMASS program provided by Hedeker), we used several standard other methods for power calculation and estimation of needed sample size. We selected the sample size that would provide us with a minimum of 80% power across all hypotheses and their expected effect sizes. We used this method with the following assumptions to estimate required sample size: the mixed design of two groups (ME-CCT and SC) and time (4 levels, weeks 0, 4, 8, 21) where the slope is the dependent measure; alpha-level of .02, nature of the hypothesis (two-sided), dropout rate (up to 20%), autoregressive covariance structure (with correlation between sequential assessments set at .45) of the longitudinal data, medium effect size as a between-group difference increasing linearly from 0 at baseline to .5 SD units at the last time point, various correlations (.2, .5, and .8) between the repeated measures, and various effect sizes from medium to large. We estimated that with a final sample size of 180 participants (216, with a drop-out rate of 20%), the study will have

minimum 85% power to yield a statistically significant result for a medium effect size. As is noted in the previous sections, we have found medium to large post-treatment effect sizes for several outcome measures in our previous studies.

H2: Compared to those in SC, participants in ME-CCT will show significant improvements on measures of subjective cognitive complaints, subjective functioning, and collateral measures of everyday functioning.
Dependent variables: Subjective Everyday Functioning Composite Score (average total score across the two Neuro-QOL scales, namely the Applied Cognition Executive Function Scale, and the Applied Cognition General Concern Scale); ECog. Independent variables: Treatment group (2 levels, ME-CCT and SC), and Time (4 levels, Weeks 0, 4, 8, 21). Statistical Analyses: Data will be analyzed similar to the method described for H1. Power Analyses: Power analyses were conducted similarly to H1, and the study will have 87% power to yield a statistically significant result for a medium effect size for H2. We have found large effects on subjective cognitive/functional complaints in previous studies.

H3: Compared to those in SC, participants in ME-CCT will show increased participation in protective activities, as measured by physical and cognitive activity inventories.
Dependent variables: Cognitive Activity Inventory, CHAMPS Physical Activity Inventory for Older Adults. Independent variables: Treatment group (2 levels, ME-CCT and SC), and Time (4 levels, Weeks 0, 4, 8, 21). Statistical Analyses: Data will be analyzed similar to the method described for H1. Power Analyses: Power analyses were conducted similarly to H1, except the alpha level was set at .01; the study will have 80% power to yield a statistically significant result for a medium effect size for each dependent measure evaluated through H3.

Exploratory Analyses. We will conduct exploratory analyses to evaluate whether increased use of compensatory cognitive strategies and increased physical and cognitive activity (PCSS, Cognitive Activity Inventory, CHAMPS Physical Activity Inventory for Older Adults, Fitbit data) mediate improvements in objective cognitive performance and functional capacity. Furthermore, we will explore for whom this intervention is most effective by evaluating whether baseline variables (e.g., demographics, medications, and substance use measured through the clinical interview; premorbid IQ measured by the WRAT-4; baseline health and psychiatric status measured through the clinical interview, PHQ-9, and GAD-7), baseline performance on primary and secondary endpoint measures, or involvement of significant others in treatment will moderate ME-CCT-associated improvements in objective cognitive performance and functional capacity. Statistical Analyses: The effect of moderator and mediator variables will be examined following the procedures recommended by statistical experts Kraemer, Cohen and Cohen, and Busemeyer and Jones [95-97]. The effects of moderator and mediator variables will be explored using similar models as ones described in H1.

Section 9.8 Questionnaires & Surveys

9.8) Provide the name and a reference for questionnaires/surveys that are standard or identify them here and attach a copy of the questionnaire/survey.

Please see Tables 5, 6, and 7 of Section 9. All are standard measures.

Section 9.9 Data Safety Monitoring Board or Plan

9.9) Provide a Data Safety Monitoring Plan (DSMP) or the details of a Data Safety Monitoring Board.

Safety Monitoring will be performed by the study staff who conduct the interviews, administer the assessment questionnaires, conduct the psychological and cognitive assessments, and facilitate the group interventions. Any adverse events will be reported immediately to the PIs, who will examine the patient and determine if any additional evaluation or treatment is needed. The PIs will recommend termination of participation, provide appropriate referrals, and engage in follow-up if substantial decline in functioning is observed. Referrals will also be offered to non-responders and any participant who requests further treatment. The PIs will ensure that adverse events are properly reported to the IRB. Study personnel will examine all cumulative adverse events quarterly to determine if there are any systematic problems.

Data will be monitored for accuracy and integrity across the duration of the study. Study personnel at each site will be adequately trained by the respective PI to conduct screenings, medical record reviews, clinical interviews, standardized neuropsychological assessments, and the ME-CCT and SC interventions prior to engaging in any data collection. Study personnel will also have professional education and training as required to conduct the study assessments and interventions. A paper questionnaire will be used to guide medical record reviews to ensure that the same historical information is gathered and coded for all study participants. The self-report questionnaires, collateral informant measure, functional capacity battery, and neuropsychological battery all consist of standardized protocols with scripted questions and standard scoring systems that quantify answers. Fidelity to the ME-CCT treatment and SC group will be closely monitored by the PIs. All ME-CCT and SC sessions will be audio-recorded, and 20% of group sessions will be randomly selected by Dr. Golshan (the study's biostatistician), and will be rated by Drs. Huckans or Twamley using the ME-CCT fidelity monitoring tool. Scores with <90% fidelity will trigger a review and a plan for improving fidelity.

With regard to safety and security of electronic data, multilevel data security programs have been written into the sites' network operating systems to ensure that only authorized research personnel have access to the Center Network. Backups are conducted regularly, and an electronic archive of all data is kept offsite to ensure 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 by the study biostatistician. The database will be tested and the final version will be distributed to the participating study sites. 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 at which they were gathered. For adherence monitoring, digital audio-recordings of sessions will be kept. The recording will be de-identified, password-protected, and encrypted.

Upon enrollment, we will create a unique login ID (subject number to avoid entering identifiable information) and password for each participant to enable us to track their data on the Fitbit website each week of the 8-week intervention; we will upload these data during the weekly group session. When connected to a compatible device (i.e., study computer), data are automatically uploaded to the users' Fitbit accounts. The researchers will bring a study laptop to the groups each week, at which time the researchers will upload participants' data for adherence and assessment purposes. These data will then be "dumped" into and stored on a secure study server. We will also upload their data during their last assessment at 21 weeks; however, participants will be given the option of coming to the VA between the 8 week and 21 week assessment to upload their data so they can get continued summary of their progress each week. The participants will be allowed to keep the device when the study ends and guided through the procedure for establishing a new username and password, thereby terminating the research staff's access to their account.

Every effort will be made to prevent missing data. Veterans who miss a group session will be encouraged to attend an individual make-up session. Attendance at all group and individual sessions will be recorded and this will be used as a covariate (if appropriate) in final analyses. Veterans will be given every opportunity to reschedule missed study assessment visits (i.e., baseline, week 4, week 8, week 21) and study personnel will closely monitor participants' completion of all study elements. Reminder calls will be conducted prior to scheduled study visit appointments, to increase the likelihood of attendance. In the event of unavoidable missing data (including participant drop-out prior to completion of all study elements), the missing data will be handled in the data analysis stage. Specifically, the proposed mixed effects modeling approach is more powerful than traditional methods and allows for inclusion of subjects with missing data or those who were terminated early on in the study, without relying on data imputation techniques. The randomness of missing data will also be assessed, by comparing group differences on primary outcome variables for subjects with missing data and those without missing data.

The VA Centralized Data Monitoring Committee will assist with data safety monitoring.

Section 9.11 Pictures and Audio/Video Recordings of Patients

9.11) Describe the purpose and of photographs (facial) or audio or video recordings of patients

Audio recordings are necessary for the purpose of assessing therapist fidelity to the intervention.

Section 10 - Human Subjects

10) Describe the characteristics of the proposed subject population. Include age, gender, ethnicity, and health status as appropriate. Provide inclusion and exclusion criteria as appropriate. Indicate the number of VASDHS participants to be studied. For multisite studies, also provide the total number of subjects from all sites. Indicate the estimated number of consented subjects that will fail the screening process, if any.

Inclusion Criteria: 1) Veterans >55 years old enrolled at one of the participating VA sites (VASDHS and VAPORHCS) who are able to provide informed consent. 2) Independently living. 3) Meet criteria for MCI based on previously published criteria [9, 16]. 4) Willingness to participate in audio-recorded sessions. Exclusion Criteria: 1) Current substance use disorder with < 30 days abstinence. 2) History of schizophrenia, schizoaffective disorder, or other primary psychotic disorder. 3) History of significant brain injury with loss of consciousness > 30 minutes. 4) Auditory or visual impairments that would prevent ability to participate in the cognitive rehabilitation group or benefit from compensatory strategies. MCI Criteria: Criteria for MCI will be based on previously published criteria [9, 16]: 1) Concern about a decline in cognitive functioning expressed by a physician, informant, participant or nurse. 2) Cognitive

impairment in one or more of the following domains: executive function, memory, attention, language or visuospatial abilities. 3) Normal or minimal impairment in functional activities. 4) Does not meet criteria for dementia. To determine whether individuals meet criteria for MCI, two neuropsychologists (Drs. Twamley, Huckans, Jak, or Storzbach) will separately review each individual's neuropsychological performance on a comprehensive neuropsychological battery (see Table 6) to determine study eligibility and classify MCI subtypes. If there are discrepancies, a third neuropsychologist will review the data and the participant will only be included if consensus can be reached. The standard clinical neuropsychological assessment batteries conducted with adults with MCI through the Neuropsychology Clinics at the VASDHS and VAPORHCS sites are typically much longer (often exceeding three hours), and adults with MCI tolerate these batteries well.

Total enrollment for the study will be 108 participants per site (54 ME-CCT and 54 SC per site), for a total of 216 participants (108 ME-CCT and 108 SC).

We do not anticipate a large number of consented subjects that will fail to meet MCI criteria, because we expect most referrals to the study to come from the Neuropsychological Assessment Unit, which will have already determined a diagnosis of MCI.

Section 10.5 Individuals with Cognitive/Decisional Impairment

10.5) Provide the rationale and additional study procedures that will be required for including individuals with known cognitive impairment or institutionalized individuals. (Address Decisional Capacity Assessment and Surrogate Consent Sections 12.5 and 12.6).

This is a study of people with known cognitive impairment -- MCI. Decisional capacity assessment will be used to ensure capacity to consent to the research.

Section 11 - Recruitment

11) Describe the plans for recruitment of subjects (or selection of subjects as in record review). This description must include how, when, and where potential subjects are approached as well as procedures such as data mining, physician referral, etc. Include how selection is equitable. Indicate if vulnerability to coercion may be present and if so plans to ensure voluntary participation.

Our primary recruitment method will be from clinic referrals and medical record review (see below for more details). In addition, participants will also be recruited through research study referrals (see below for more details).

For eligible individuals identified by study staff through clinic referrals/medical record review, the study staff will send a recruitment letter (or contact by phone if the Veteran gave their verbal permission to being contacted by phone). The letter will state that the individual may opt out by calling the research team indicating that they do not wish to be contacted, or they may indicate they are interested in learning more about the study by calling the study team. The letter will state that if the individual has not responded to the letter within two weeks, research personnel will contact them by phone. Study Personnel will respond to calls from individuals who are interested in the study to answer any questions they might have about the study and to schedule an Initial Study Visit if they remain interested. If no response to the letter is received within two weeks, the research team will contact the individual by phone but with limited interaction. During this follow-up phone call, the researcher will identify themselves, explain why they are calling, and ask if the individual received the letter. If they did, the researcher will ask if they have reviewed the letter and whether or not they are interested in hearing more about the study. If the individual has received, but not reviewed, the letter, the researcher may ask if they are interested in hearing more about the study or receiving more information. After answering their questions, the researcher will schedule an Initial Study Visit for those who state they are interested in participating. If the Veteran has not received the letter, the researcher will only ask permission to send a second letter and confirm the individual's address; no other information will be requested at that time.

Individuals referred from other VA IRB-approved research studies (who gave their consent to be contacted about additional research opportunities), will also be sent a recruitment letter via mail prior to being contacted by phone, unless they have specifically consented to phone contact. If no response to the letter is received within two weeks, research personnel will follow the same follow-up phone call procedures as stated in the previous paragraph. Studies we will recruit from include protocol numbers: H170028, H160090, H140057, H130022, and H160022, and other applicable VA studies with older Veterans with MCI.

For all individuals who express interest in the study, research staff will provide information about the study and its procedures via phone. For those individuals who remain interested, study staff will confirm their eligibility via phone before proceeding to schedule their baseline visit: consent and initial assessment. Individuals not interested in participating will not be contacted again.

Section 11.1 Recruitment Materials

11.1) Identify all recruitment materials (flyers, advertisements, letters, etc.) that will be used. The text of all communications with prospective participants must be reviewed and approved by the IRB before it can be used. You will be reminded to attach copies of recruitment materials to the initial submission packet.

Recruitment letters and recruitment flyers. Research flyers will be given to other appropriate research studies that include Veterans with MCI, appropriate VA clinics, and VA medical providers, such as geropsychiatrists and neurologists, who may also be able to refer Veterans with MCI.

Section 12 - Informed Consent

12) Indicate whether or not each category of consent is involved in this study:

12a) **Signed** informed consent

(•) Yes ( ) No

12b) Signed consent for **picture/voice recording** (VA form 10-3203) [NO LONGER REQUIRED]

(•) Yes ( ) No

12c) Waiver of documented consent (e.g., **oral** consent)

( ) Yes (•) No

12d) Request for a **waiver** of consent (i.e., a "full" waiver, not just for screening)

( ) Yes (•) No

12e) Alteration of **other required elements** of consent.

( ) Yes (•) No

12f) **Child** assent to participate (Director approval will be required)

( ) Yes (•) No

12g) Will any language **other than English** be used by those obtaining consent and understood by the prospective participant or the legally authorized representative?

( ) Yes (•) No

12h) **Decisional Capacity Assessment** to determine if participants have the capacity to consent for themselves.

(•) Yes ( ) No

12i) **Surrogate** consent (legally authorized representative)

( ) Yes (•) No

Section 12.1 Informed Consent Process

12.1a) Will consent be obtained before any study procedures are performed (including screening procedures except screening procedures with Consent/HIPAA waiver approval)?

(•) Yes ( ) No

12.1b) Will the information being communicated to the participant or legally authorized representative during the consent process include exculpatory language through which the participant or legally authorized representative is made to waive or appear to waive any of the participant's legal rights or release or appear to release the Researcher, Sponsor, the VA or its agents from liability for negligence.

( ) Yes (•) No

12.1c) A master list of all VA subjects consented (written or not) under this protocol number will be maintained. (If a waiver of the master list entry requirement is requested below and will be approved, indicate Agree).

(•) Agree ( ) Disagree

12.1d) Identify the circumstances under which consent will be obtained including where the process will take place; any waiting period between describing the research and obtaining consent including sufficient time for the prospective participant to consider participation, and any steps taken to minimize the possibility of coercion or undue influence.

Written informed consent will be obtained in person by the PI, co-investigator Jak, or a trained member of the research staff, in a private office. Decisional capacity assessment will be administered to all individuals who express a desire to participate. Potential participants will be asked to confirm that all of their questions have been answered prior to providing consent. Any potential participant who would like to take the consent document home for further consideration will be invited to do so.

Section 12.6 Decisional Capacity Assessment

12.6a) Describe the method(s) for determination of decisional capacity: (see ? for guidance)

A post-consent questionnaire will be administered to ensure that individuals understand the purpose of the study, the study procedures, the potential risks, and the voluntary nature of research participation.

12.6b) If subjects with limited decisional capacity will be enrolled, describe methods for obtaining subject assent or why they are not indicated:

Individuals who cannot pass the decisional capacity assessment will not be enrolled.

12.6c) If subjects with limited decisional capacity will be enrolled, describe procedures for respecting subject dissent and any additional safeguards or why these features are not needed:

N/A

12.6d) If subjects with limited decisional capacity will be enrolled, describe the risk and, if greater than minimal, the relation to potential benefits:

N/A

12.6e) If subjects with limited decisional capacity will be enrolled, describe the justification for the inclusion of any incompetent persons or persons with impaired decision-making capacity:

N/A

Section 12.9 HIPAA Authorization

For each category below, indicate whether or not this study involves the indicated process:

12.9a) **Signed** HIPAA Authorization

(•) Yes ( ) No

12.9b) HIPAA/consent waiver or alteration for **screening** purposes only

(•) Yes ( ) No

12.9c) Full HIPAA **waiver** or alteration

( ) Yes (•) No

12.9d) HIPAA **Authorization** or waiver is **not required** for some or all of the study subjects (e.g. no health data)

( ) Yes (•) No

Section 12.10 HIPAA Waivers and Alterations

12.10a) Describe the purpose/nature of the HIPAA waiver or alteration and list specifically, what identifiers and health information are being requested under the waiver/alteration and identify whether the waiver is for access, use, and/or collection of this information.

HIPAA waiver is requested for screening purposes. Veterans with a diagnosis of MCI are sought for this study, and the VASDHS Neuropsychological Assessment Unit diagnoses many such Veterans with MCI every year. Neuropsychological Assessment Unit records of Veterans diagnosed with MCI will be used to identify potential participants. The CPRS records of these potential participants will then be used to determine whether they meet the screening criteria for the study. Individuals meeting study criteria will be sent a letter inviting them to participate in the study.

12.10b) The use or disclosure of PHI involves no more than a minimal risk to the privacy of individuals.

(•) Agree ( ) Disagree

12.10c) The plan to protect the identifiers from improper use and disclosure is adequate.

(•) Agree ( ) Disagree

Describe the plan

The name and last 4 digits of the Social Security Number of each Veteran who meets screening criteria and the date of the letter will be kept in a document stored securely on the R drive. These data will be stored to ensure that duplicate letters are not sent.

12.10d) An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law (VA Records Control Schedule does not currently permit destruction)

(•) Agree ( ) Disagree

12.10d2) Describe the plan

Data will only be destroyed according to RCS-10 under Records Control Manager guidance.

12.10e) By signing this protocol for submission, the PI is providing written assurance that the PHI will not be reused or disclosed to any other person or entity, except as required by law, for authorized

oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by the Privacy Rule. 38 U.S.C. 7332 Information: If the waiver of HIPAA authorization is for the use of 38 USC 7332 information (applicable to drug abuse, alcohol abuse, HIV infection, and sickle cell anemia records), by signing this protocol for submission the PI is providing written assurance that the purpose of the data is to conduct scientific research and that no personnel involved may identify, directly or indirectly, any individual patient or subject in any report of such research or otherwise disclose patient or subject identities in any manner. (Ref: 38 U.S.C. 7332(b)(2)(B))

(•) Agree ( ) Disagree

12.10f) The research could not practicably be conducted without the waiver or alteration

(•) Agree ( ) Disagree

12.10f2) Describe how the waiver/alteration enables the research to be conducted

We do not have the resources to provide testing to every Veteran with a cognitive complaint, and to do so would be replicating clinical services already offered.

12.10g) The research could not practicably be conducted without access to and use of the PHI

(•) Agree ( ) Disagree

12.10g2) Describe why it would be impracticable to conduct this research without the PHI described 12.10 a. (v3/8/18)

We will need to ensure that potential participants have a diagnosis of MCI, and we will need their addresses to be able to send a letter about the study.

Section 13 - Alternatives to Participation

13) Describe the alternatives to participation in this research study (see ? for guidance)

The alternative to participation is not to participate.

Section 14 - Potential Risks

14) Describe any potential or known risks or discomforts and assess their likelihood and seriousness. (see ? for guidance)

Minimal risk is anticipated with the current investigation. Regarding research risks, participants may experience fatigue and/or boredom while completing the interviews, questionnaires, and cognitive tests. Some participants may also experience mild anxiety, frustration, and/or stress while reporting on their psychiatric symptoms, during assessment procedures if a cognitive test proves difficult for them, and/or during the course of group treatment. It is possible that some participants might not experience symptomatic relief from the intervention. Participants may experience mild discomfort as a result of being audio-recorded during the group sessions. Skin irritation is a possible risk of using the Fitbit.

Section 15 - Risk Management

15) Describe the procedures for protecting against or minimizing any potential risks/discomforts, and the adequacy of resources for conducting the study and resources participants may need as a consequence of the research. See ? for further requirements.

If participants experience fatigue, boredom, anxiety, frustration, or stress while completing the interviews, questionnaires, and cognitive tests, they will be invited to take a break or return another day to complete the assessments.

Study participants will be informed that they may choose to discontinue the study without risk to their medical care.

The Fitbit can be taken off if the participant experiences skin irritation.

COVID Procedures: Participants will be informed that participation in research may increase risk for COVID infection and that we will take necessary safety precautions for their safety.

Section 16 - Privacy and Confidentiality

16a) Provide a brief description of how participant privacy and confidentiality will be protected in this study.

All research records will be labeled with a code number, rather than the name of the participant. A master list matching participant names with the code number will be kept in a locked file in the research team's office. Any research records that identify participants will be kept only as paper records in a secure VASDHS location, or as files behind the secure VASDHS computer firewall. Any presentations or publications from this information will not identify participants by name. Audio recordings of treatment sessions will be stored on a VA secure server and will be accessed by Dr. Twamley or her staff for the purposes of rating the psychologist's adherence to the treatment manuals.

16a2) See Privacy and Data Security Plan for further details.

(●) Yes ( ) No

16b) Is SSN used for any purpose other than scanning Consent/HIPAA into the medical record? (e.g., subject payments, use of clinical record)

(●) Yes ( ) No

16b2) If YES, indicate purpose and justification:

SSN is needed for subject payments and last 4 digits are needed to ensure access only to appropriate patients in CPRS.

Section 16.1 Entry of CPRS Notes

16.1) Entry of a CPRS Research Informed Consent Note is required if any of the following apply:

- **The subject is admitted as an inpatient or treated as an outpatient for research**
- **The study involves research medical care or may affect medical care.**
- **The Informed Consent and HIPAA Authorization indicate notes will be entered**

Notes: Scanning the Consent and HIPAA Authorization into CPRS is no longer required. Linking the Consent to the Research Informed Consent Note is permitted (Unless the study has a Certificate of Confidentiality) and may be especially useful for trials involving the Research Pharmacy. · For Non-Veterans, if Research Informed Consent Notes are entered then the NOPP Acknowledgement must be scanned in. · A Research Progress Note should also be entered for each procedure or intervention. · **Address the CPRS note requirement:**

16.1a) Is entry of CPRS notes required based on the above criteria?

(●) Yes ( ) No

16.1b) Are CPRS notes entered?

(●) Yes ( ) No

16.1c) Is a CPRS waiver is requested instead?

○ Yes ◉ No

Section 17 - Potential Benefits

17) Discuss benefits that may be gained by the subject as well as potential benefits to society in general. (see ? for guidance)

This research may provide participants with information about their psychological and cognitive functioning. Participants may experience a reduction in their complaints regarding cognitive impairment and may experience an improvement in their cognitive ability, usage of cognitive strategies, self-efficacy, adaptive functioning, and ability to reliably manage personal affairs. They will receive information about their activity levels and sleep that they may find helpful. The knowledge gained from this study could lead to effective treatments that otherwise might not have been made available. Additionally, study results will help expand knowledge of treatments appropriate for Veterans with Mild Cognitive Impairment.

Section 18 - Risk/Benefit Ratio

18) Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to subjects and in relation to the importance of the knowledge that may reasonably be expected to result.

The risk of increased distress during the assessment, skin irritation due to Fitbit use, or distress associated with the treatment components of the study is balanced by the potential benefit of reduced distress over time for study participants. The knowledge gained from this study could lead to effective treatments that otherwise might not have been made available. Additionally, study results will help expand knowledge of treatments appropriate for Veterans with Mild Cognitive Impairment.

Section 20 - Compensation for Participation

20) Provide all details and justifications of the compensation plan. See ? for detailed requirements.

Participants will be compensated $50 after each of the first three assessments, and $75 after the fourth and final follow-up assessment. If participants complete all four assessments, their total compensation will be $225. This compensation is provided in consideration of the participants' time and travel. Participants who elect to use the Fitbit will be given the device at the end of their study participation.

Section 21 - Responsibilities and Qualifications

Here are the identified study staff members

Elizabeth W. Twamley, PhD

Amy J. Jak, PhD, Amber Victoria Keller, Hannah Lykins, Ingrid Contreras, Paula Michelle Seewald, MA, Chantal Muller-Cohn, BA, Chloe T. Green, PhD, Delaney Q. Pickell, Janae Ruth Wyckoff, Jeffrey Hernandez, Matthew R. Morgan, Mili Parikh, PhD, Zanjbeel Mahmood, BA, Jacqueline Maye, PhD, Jillian Clark, PhD, Ryan Van Patten, Sarah Jurick Lefler, PhD

21) Identify here by name those staff working on this protocol, unless they have no contact with subjects or identifiable data. Indicate their role and qualifications. Also indicate which of the study staff are authorized to obtain consent for subjects of VA research.

Dr. Twamley -- PI
Dr. Jak -- Co-Investigator

The above-named study staff are neuropsychologists who will be authorized to obtain consent and deliver intervention.

Amber Keller

Chantal Muller-Cohn
Chloe Green
Delaney Pickell
Hannah Lykins
Ingrid Contreras
Jacqueline Maye
Janae Wyckoff
Jillian Clark
Matthew Morgan
Michelle Seewald
Mili Parikh
Ryan Van Patten
Zanjbeel Mahmood

The above-named study staff and trainees will be authorized to obtain consent and to administer assessments and deliver intervention.

Jeffrey Hernandez is a research associate who will manage the eScreening program, but will not have contact with participants. Sarah Jurick Lefler may run analyses on coded research databases but will not have access to PHI and will not have any contact with participants.

Section 22 - Bibliography

22) List relevant articles that the IRB can use to provide necessary background for the protocol. Do not include an extensive NIH-grant-style bibliography. **(Up to 5 recommended, but use more if needed to support the protocol or citations above.)**

Huckans, M., et al., Efficacy of cognitive rehabilitation therapies for mild cognitive impairment (MCI) in older adults: working toward a theoretical model and evidence-based interventions. Neuropsychol Rev, 2013. 23(1): p. 63-80.

Li, H., et al., Cognitive intervention for persons with mild cognitive impairment: A meta-analysis. Ageing Res Rev, 2011. 10(2): p. 285-96.

Jak, A.J., The impact of physical and mental activity on cognitive aging. Curr Top Behav Neurosci, 2012. 10: p. 273-91.

Storzbach, D., Twamley, E.W. (co first authors), et al., Compensatory Cognitive Training for Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn veterans with mild traumatic brain injury. J Head Trauma Rehabil, in press.

Jak, A.J., et al., Quantification of five neuropsychological approaches to defining mild cognitive impairment. American Journal of Geriatric Psychiatry., in press.

Section 27 - Protocol Attachments

If there is any material, such as tables or figures, that are referenced in the protocol text above but not pasted into the protocol application these can be attached in the Submission form along with other documents such as Consents and HIPAA Authorizations. press Save and Continue

Section 28 - Protocol Association to New or Existing Project

28) Is this a new R&D Project?. Before you go on to complete the *Initial Review Submission Form* (which is used for attachments), please address the association of this Protocol to an R&D Committee Project. This Protocol may represent a new R&D Project, or it may be an additional Protocol under an existing R&D Project (such as when a single grant supports multiple Protocols). Will this Protocol be submitted to the R&D Committee as a new Project?

○ Yes ◉ No

Section 29 - Existing Project Association

29) The associated R&D Project should already exist in the database. Identify the R&D Project(s) that correspond to this protocol.

Project Status	Proposal Number	Project Title	Principal Investigator
Approved	1195749	1195749	Elizabeth W. Twamley, PhD
		Cognitive Rehabilitation for Older Veterans with Mild Cognitive Impairment	

The Protocol Application is now complete for a Protocol attached to an existing Project.

Next you will go on to the Initial Review Submission Form. This form is used to collect the Application and any other needed attachments for submission to the IRB for review.

Press *Save and Continue*

Title of Study: Cognitive Rehabilitation for Older Veterans with Mild Cognitive Impairment	
Principal Investigator: Elizabeth W. Twamley, PhD	**VAMC:** VA San Diego Healthcare System
Subject Name:	**Date:**

1) Purpose of this research study

Elizabeth W. Twamley, PhD is conducting a research study to find out more about treatments for Mild Cognitive Impairment. You have been asked to participate because you have been diagnosed with Mild Cognitive Impairment. There will be approximately 108 participants at this VA site and 108 participants at the Portland VA site. There will be a total of 216 participants at both sites.

2) How long the study will take

Your participation will take approximately 1-3 hours each time you come to the VA hospital, and you will be expected to come to the hospital 12 times over a 6-month period (4 times for assessments and 8 times for treatment groups). The entire study will take about 5 years.

3) What will happen to you in this study

If you agree to be in the study, the following will happen to you:

A. At your first visit you will receive information regarding this study and have an opportunity to ask questions regarding study participation. If you agree to participate in the study, you will sign this informed consent document. You will then take part in an assessment of your cognition, symptoms, and functioning, which will take approximately 3 hours.

B. You will be randomly assigned (like the flip of a coin) to receive Goal-Focused Treatment or Compensatory Cognitive Training. Both treatments will involve weekly groups with a psychologist for approximately 2 hours per week for 8 weeks. Goal-Focused Treatment includes setting and achieving short-term and long-term goals for improving cognition and functioning. Compensatory Cognitive Training includes training in strategies to improve cognition, stress management, and improving nutrition and exercise. Treatment sessions will be audiotaped to ensure that the psychologist is following the treatment manual.

C. You will also complete repeat assessments of your cognition, symptoms, and functioning at 4 weeks, 8 weeks, and 21 weeks after you begin treatment. The 4-week assessment session will take about 1 hour and the 8-week and 21-week assessment sessions will take about 3 hours each.

COVID-19 Safety Procedures: All assessment and intervention procedures will be completed using social distancing whenever possible. All group members and facilitators will be required to wear a medical grade procedure mask for the entire duration of the intervention sessions.

4) Which procedure(s) or treatment(s) are done for research only

All assessments are done for research only. The treatments provided in this study include approaches to address cognitive and functioning problems. Neither treatment is part of standard care; both treatments are experimental. In this study, we will be comparing the two treatments to see which works best.

Title of Study: Cognitive Rehabilitation for Older Veterans with Mild Cognitive Impairment	
Principal Investigator: Elizabeth W. Twamley, PhD	**VAMC:** VA San Diego Healthcare System

5) RISKS <u>reasonably</u> to be expected

Participation in this study may involve some added discomforts. The procedures used may cause:

A. Fatigue, boredom, or stress while completing the assessments.
B. Discomfort as a result of the audiotaping of treatment groups.
C. As with any research study, the possibility of breach of confidentiality exists.
D. Participation in research may increase your risk for COVID infection.

Unforeseeable RISKS

Because this is an investigational study there may be some unknown risks that are currently unforeseeable. You will be informed if the researchers learn of any change in the amount of risk to you.

6) BENEFITS <u>reasonably</u> to be expected.

There may or may not be a direct benefit to you from these procedures. The investigator, however, may learn more about treatments for Mild Cognitive Impairment.

7) Voluntary nature of participation and right to withdraw without penalty.

Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without jeopardy to the medical care you will receive at this institution or loss of benefits to which you are entitled.

8) Alternatives to the research procedure or treatment

The alternative to participation is not to participate.

9) Procedure for the orderly termination of a volunteer's participation

If you decide that you no longer wish to participate in this study please call Dr. Twamley at 858-642-3848. Your participation in this study may be stopped if the investigator decides that stopping is in your best interest or if you do not participate in assessments or treatment.

10) Information learned from the study will be shared with you

While you are a participant in this study you will be told if any important new information is found that may affect your wanting to continue. If the results of this research might influence your medical care after you have completed your participation, the investigators will contact you to let you know these results.

11) Care provided if you are injured as a result of this study

The VA will provide necessary medical treatment should you be injured as a result of participating in this study and following study procedures. You will be treated for the injury by the VA at no cost to you or your insurance but no additional compensation is available.

12) Privacy and confidentiality

Title of Study:
Cognitive Rehabilitation for Older Veterans with Mild Cognitive Impairment

Principal Investigator:	**VAMC:**
Elizabeth W. Twamley, PhD	VA San Diego Healthcare System

Participation in this study may involve a loss of privacy, but information about you will be handled as confidentially as possible. Your participation in study assessments and any study-related treatment will be documented in your electronic medical record.

Your research records will be labeled with a code number. The list that matches your name with the code number will be kept in a locked file in the research team's office. Any research records that identify you will be kept only as paper records in a secure VASDHS location, or as files behind the secure VASDHS computer firewall. Any presentations or publications from this information will not identify you. Audio recordings of treatment sessions will be stored on a VA secure server and will be accessed by Dr. Twamley or her staff for the purposes of rating the psychologist's adherence to the treatment manuals.

This study includes collection of your social security number for the purpose of providing you compensation.

We will keep confidential all research and medical records that identify you to the extent allowed by law. However, you should know that there are some circumstances in which we may have to show your information to other people. For example, the Federal Office of Human Research Protections, the General Accounting Office, the VASDHS R&D Committee, the VASDHS Institutional Review Board, VA Clinical Science Research and Development, and federal compliance officers may look at or copy portions of records that identify you.

13) Payment

Costs to you or your insurance

There will be no costs to you or your insurance for any procedures or testing done only as part of this research study. If you receive a bill for services that you think could be related to your participation in this study, you should contact Dr. Twamley.

Medical care and services provided by the VA that are not part of this study (e.g., normal hospital and prescription expenses which are not part of the research study) may require co-payments if your VA-eligibility category requires co-payment for VA services.

Payment for participating

In consideration of your time, you will receive a payment of $50 for each of the first three assessments you complete in this study, and $75 after the fourth and final follow-up assessment. The maximum compensation for participating in the study is $225. Payments will be made directly to your bank account using electronic funds transfer. If you currently have a debt to the Federal Government, your debt may be subtracted from your funds transfer payment for study participation.

14) Additional Information

The VA San Diego Healthcare System provides oversight and resources for this study. Financial support for this study is provided by VA Clinical Science Research and Development.

Title of Study:
Cognitive Rehabilitation for Older Veterans with Mild Cognitive Impairment

Principal Investigator:	**VAMC:**
Elizabeth W. Twamley, PhD	VA San Diego Healthcare System

A description of this clinical trial will be available on http:\\www.ClinicalTrials.gov, as required by US law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Re-contact.

☐ (initial here) I consent to being contacted by phone for possible participation in future studies.

Disclosure of Results. During your final study visit, Dr. Twamley and/or the study coordinator will provide verbal feedback and/or answer questions you may have about the results obtained in the course of your study participation.

15) RESEARCH SUBJECTS' RIGHTS: You have read or have had read to you all of the above. **You have been informed that you do not have to take part in this study, and your refusal to participate will involve no penalty or loss of rights to which you are entitled. You may withdraw from this study at any time without penalty or loss of VA or other benefits to which you are entitled.**

In the event of illness or injury that you believe to be related to the study, or have questions about this research, you can call Dr. Twamley at 858-642-3848. If you have any questions or concerns about your rights as a research subject, the validity of a research study, or research personnel you can contact the Research Compliance Officer at 858-642-3817, VA Research Service at 858-642-3657, VA Regional Counsel at 858-642-1540, or the VASDHS Human Research Protection Program at 858-642-6320.

_____ has explained the study to you and answered all of your questions. You have been told of the risks or discomforts and possible benefits of the study. You have been told of other choices of treatment available to you. You will receive a copy of this consent form and a copy of the Health Insurance Portability and Accountability Act (HIPAA) Authorization that you signed. You will also receive a copy of the California Experimental Subject's Bill of Rights.

By signing this form you indicate that you have been informed of your rights as a research subject, and that you voluntarily consent to participate in this study. You have been informed what the study is about and how and why it is being done.

_____ _____
Subject's Signature Date

_____ _____ _____
Signature of Researcher obtaining consent Name (print) Date