

**Confidential**

**PROTOCOL:**

Effects of traumatic brain injury and post traumatic stress disorder on Alzheimer's disease (AD) in Veterans using ADNI (DoD-ADNI)

**Sponsored by**

Department of Defense (DOD)  
Telemedicine and Advanced Technology Research Center (TATRC)

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**PROTOCOL SYNOPSIS**

<b>Title</b>	<b>Effects of traumatic brain injury (TBI) and post traumatic stress disorder (PTSD) on Alzheimer’s disease (AD) in Veterans using (Alzheimer’s Disease Neuroimaging Initiative) ADNI</b>
<b>Overall Objective</b>	<p>The overall long-term goal of this project is to prevent Alzheimer’s disease (AD) in combat Veterans. This project is an important step in that direction because it will identify risk factors for the development of AD in military Veterans and will provide information and a network of sites for design, statistical powering, and performance of clinical treatment and prevention trials in the future.</p>
<b>Primary Objectives</b>	<p>The primary objectives to be tested are:</p> <ol style="list-style-type: none"> <li>1. Veterans without mild cognitive impairment (MCI)/dementia, with a history of moderate to severe TBI during military service (but no PTSD), as well as Veterans without MCI/dementia, with ongoing PTSD (but no TBI) have increased evidence for AD pathophysiological markers, when compared with Veteran controls (without TBI, PTSD, MCI/dementia, and also matched for age, APOE4 status, and accounting for other comorbidities) as measured by: <ol style="list-style-type: none"> <li>a. Greater uptake on Florbetapir F18 amyloid PET scans</li> <li>b. Lower CSF amyloid beta levels</li> <li>c. Increased CSF tau/P tau levels</li> <li>d. Greater brain atrophy in hippocampus, entorhinal cortex, and parietal/temporal cortices</li> <li>e. Greater longitudinal rates of brain atrophy in hippocampus, entorhinal cortex, and parietal/temporal cortices</li> <li>f. Reduced cognitive function, especially delayed memory</li> <li>g. Greater rate of change of cognitive function</li> </ol> </li> <li>2. TBI and/or PTSD reduces brain reserve, causing greater cognitive impairment after accounting for age, educational status, pre-war cognitive function, as assessed with the Armed Forces Qualifying Exam score during basic training, to be measured by: <ol style="list-style-type: none"> <li>a. Brain amyloid load or hippocampal volume.</li> <li>b. Greater cognitive impairments at a given level of brain A<math>\beta</math>, or</li> <li>c. Brain volume in the TBI or PTSD group than controls</li> </ol> </li> </ol>

	<ol style="list-style-type: none"> <li>3. TBI, when compared to controls, is associated with changes in brain regions previously reported to be associated with TBI [37-39].             <ol style="list-style-type: none"> <li>a. White matter regions frequently noted to have reduced microstructural integrity due to TBI on DTI include the anterior corona radiata, uncinate fasciculus, corpus callosum, forceps minor, forceps major, sagittal stratum, corticospinal tract, inferior fronto-occipital fasciculus and cingulum bundle [37-39].</li> <li>b. Reduced hippocampal volume in PTSD compared to controls, [32, 33-36].</li> </ol> </li> <li>4. There will be significant correlations between severity of TBI (from hospital records) and severity of PTSD (CAPS score) on the above-listed outcomes, i.e. a dose response effect.</li> <li>5. Exploratory analyses will also be performed to examine other questions, and compare the patterns (using voxel based methods) of amyloid deposition (from Florbetapir F18 uptake) and brain atrophy among TBI, PTSD, and control subjects, and with the patterns from non-Veteran subjects in ADNI. The results of these studies may provide insight into:             <ol style="list-style-type: none"> <li>a. The question of whether or not TBI and PTSD alter the pattern of amyloid distribution or brain atrophy.</li> <li>b. the relationship between cortical areas with amyloid plaque (from Florbetapir) and,</li> <li>c. Underlying white matter integrity as assessed with DTI, to determine if axonal injury resulting from TBI was associated with greater amyloid accumulation, or whether regions of brain with axonal damage have less amyloid accumulation due to disconnection and reduced brain activity.</li> </ol> </li> </ol>
<p><b>Study Design</b></p>	<p>This is a non-randomized natural history non-treatment study.</p> <ol style="list-style-type: none"> <li>1. Using military and Veterans Affairs (VA) Compensation and Pension records, SFVAMC will identify Vietnam War Veterans with well documented history of moderate/severe Traumatic Brain Injury (TBI) or evidence of ongoing Post Traumatic Stress Disorder (PTSD), and comparable Veteran controls. Subjects meeting criteria for mild cognitive impairment/dementia will be excluded.</li> <li>2. SFVAMC will mail out invitation letter, brochure, and response postcard (a self-addressed stamped envelope will be included for the</li> </ol>

subject to return the response postcard) to large numbers of Veterans who meet above broad criteria, based on diagnostic codes in military and VA Compensation and Pension records, and who live within 150 miles of closest ADNI clinic in subject's area. Selected sites will have the General Electric Diffusion Tensor Imaging / Magnetic Resonance Imaging [GE/DTI MRI] scanner). The mileage distance from the clinics may be extended if the recruitment numbers are low. The timing of the mail out effort to the geographic location of a selected ADNI site will only occur once the specific site has obtained full human subjects approval from both their agency review boards as well as the Department of Defense (DOD).

3. SFVAMC will contact subjects by telephone – contact those that have returned the response post card, as well as those who have not.
  - a. Obtain verbal consent to administer screening and TBI questionnaire over the telephone.
  - b. Administer screening and TBI questionnaires to determine eligibility criteria to be enrolled in the Psychiatric Assessment (Clinical Interview) part of the study, using the Structured Clinical Interview 1 of the Diagnostic and Statistical Manual of Mental Disorders, Version IV, (Axis 1) - Text Revision (SCID 1 of the DSMIV-TR) and the Clinician Administered PTSD Scale (CAPS). The SCID/CAPS will be audio recorded for quality control purposes, essentially to make sure that clinicians are administering the interview in a similar fashion. Subject will be asked to sign a separate consent form for permission to audio-record. Audio-recordings will be stored in a secure and locked file cabinet, in a secure and locked file room. No names will be included on the audio recording. They will be stored with study code only. Audio-recording is OPTIONAL. Subjects who do not wish to be audio-recorded can still participate in the study.
  - c. Determine if subject has a study partner. If subject has a reliable study partner, and is found to be eligible after completing the screening and clinical interviews, the partner will be asked to accompany the subject to the clinic visits. Study partners are helpful in confirming memory problems if they exist. However, because many subjects may not have a regular person in their life who can act as a study partner, a study partner is not required for this study.
  - d. The screening questions will be an adapted version of the AD8 assessment (70, 71) and will also include some of the questions of the Clinical Dementia Rating (CDR). For this study, subjects with mild cognitive impairment (MCI)/dementia may be screened depending on the answers to the screening questions.

	<p>The Study Coordinator will discuss subject responses to the Subject Matter Experts to assess whether or not the memory issues are exclusionary. Questionable items will be discussed among the clinical core investigators to assess who will be screened out.</p> <p>e. At completion of the telephone screener, subjects will be told whether or not they are eligible to be referred to the clinical telephone interview, or if some of their responses need to be discussed with the study doctors. (Some answers to the screening questions will be discussed with the clinical leaders of the study to assess whether there are any exclusionary criteria present, such as MCI/dementia, psychological disorders, alcohol or substance abuse, etc.). After the discussion with study doctors, subject will be called back and invited to continue, or will be thanked and compensated for the time spent in study thus far.</p> <p>f. If after the screening interview, subject is eligible for the SCID/CAPS, SFVAMC staff will mail a written consent form w/ stamped addressed return envelope to the home of the subjects along with two self-report questionnaires on MRI safety and medical history and a consent form for audio-recording. In a few days, Study staff will call the subject to make sure that subject received the consent forms, will go over the consent forms with the subject, answer any questions the subject may have, and assist with the self report questionnaires if needed. Subject will be asked to sign the consent forms and fax or mail them back to SFVAMC in the stamped addressed envelope along with the completed self-report questionnaires. The SCID/CAPS cannot be administered without first receiving the signed consent form for the clinical interview. The SCID/CAPS cannot be audio-recorded without also receiving the signed consent form giving permission to audio-record. If the consent to audio -record the SCID/CAPS is received, SCID/CAPS will be recorded and the tape will be stored and filed by study code number only, in a locked and secure file cabinet in a locked and secure file room. Audio-recording is optional. Subjects who choose not to be audio-recorded can still participate in the study.</p> <p>g. As soon as the signed consent forms and questionnaires are received back at SFVAMC, by mail or fax, the questionnaires will be reviewed and if eligible, subject will be referred to the PTSD core at SFVAMC.</p> <p>h. Because the project is only enrolling subjects without MCI/dementia, a study partner (if available) will NEVER act as</p>
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a surrogate for the subject. All subjects will consent for themselves. A study partner is NOT a requirement for this study.

4. PTSD core (at the SFVAMC) will call the subject and perform the Structured Diagnostic Interview I for DSM-IV-TR & Clinician Administered PTSD Scale (CAPS) by telephone. If a signed consent for audio recording has been received along with the signed consent for the clinical interview, this interview will be audio recorded for quality control purposes, to ensure that the interview is administered in a consistent manner. The tape will be filed and stored by study code only in a secure locked file system. Audio recording is optional. Subjects who choose not to be audio-recorded can still participate in the study.
5. If after clinical telephone interview, the subject is still eligible, SFVAMC staff will refer subject to local clinic in network of Alzheimer's Disease Neuroimaging Initiative sites (ADNI).
6. SFVAMC staff will mail a packet of self-report questionnaires to subject, with instructions for subject to complete and bring completed packet to his or her first in-person clinic visit.
7. SFVAMC will give the subject the contact information of the clinic in the subject's area, and will call the clinic directly to refer the subject's contact information.
8. The local ADNI site will contact subject and make an appointment for the subject to come to the site. At the ADNI site, trained staff will conduct the procedures listed below with each subject. Completing all of the procedures may take 2-3 days, or so, within a few weeks:
  - a. Explain study and obtain written consent;
  - b. For those subjects who have a reliable person in their lives who can act as a study partner (spouse, friend, or relative), the full CDR will be administered during the clinic visits to confirm that the subject does not have MCI/dementia, or to further rule out the presence of MCI/dementia. If a study partner is available, the study partner will be asked to accompany the subject to all clinic visits and to communicate changes in the subjects' health status over the period of the study. Study partners will be fully informed of the study, and will be asked to read and sign the consent form. There will be a separate signature line on the subject's consent form for study partners (if a study partner is available).
  - c. ADNI staff will also discuss autopsy with subject. An ADNI



clinician will lead a discussion about autopsy with all subjects at their initial assessment (study partners and families are welcomed in the discussion). There are 3 objectives of the discussion:

- To convey information about the value of brain autopsy in confirming the clinical diagnosis and advancing knowledge regarding mild cognitive impairment and Alzheimer's disease;
- To initiate consideration of the individual's wishes concerning an autopsy; and
- To answer questions, misconceptions, or concerns about autopsy. The involvement of the physician in these discussions emphasizes the importance of autopsy.
- There is no pressure on an individual to decide; they are encouraged to involve family members, clergy, physicians, or other appropriate persons in their decision-making. Participants are assured that a decision not to have an autopsy in no way jeopardizes their research participation or any other patient rights. It is important to note that autopsy will not interfere with funerary arrangements nor will it be a financial burden to the participant's family. Subjects will be asked to sign whether or not they are interested in **considering** autopsy at the time of his or her death, and will be told that study personnel will ask permission to autopsy from his or her next of kin; therefore, subjects are encouraged to let their next of kin know their wishes concerning autopsy prior to death.

- d. Collect packet of self-report questionnaires
- e. Collect baseline measurements of cognition and function. (This will confirm that there is no MCI/dementia and/or any other health issues that may make it unsafe for a subject to continue.)
- f. Perform a blood draw by venipuncture
- g. Collect cerebrospinal fluid for analyses (lumbar puncture)
- h. Conduct MRI scans (structural, diffusion tensor, and resting state BOLD fMRI). No contrast agent will be used. T2 FSE and T2\*GRE.
- i. Conduct an amyloid PET imaging scan with Florbetapir F18. The dose of Florbetapir F18 is 10 mCi per procedure.
- j. Because the Florbetapir F18 can affect a fetus, pregnant women may not participate in this study. Women of childbearing age will receive a urine test at the time of the baseline PET scan and at the 12 month follow-up PET scan to ensure that she is not

	<p>pregnant.</p> <p>k. Those subjects who have completed the procedures at the ADNI clinic are eligible for the 12 month (approximate) follow-up screener. At about 6 months, SFVAMC staff will call each subject to remind them of the 12 month (approximate) follow-up screener and to update patient status, with the following questions:</p> <p><i>“We’re calling to remind you that the follow-up telephone interview for the study, Effects of Effects of traumatic brain injury and post traumatic stress disorder on Alzheimer’s disease (AD) in Veterans using ADNI, will begin in about 6 months from now, and to check in on how you are doing.</i></p> <ul style="list-style-type: none"> <li>• <i>Have you had any change in memory or thinking in the past 6 months?</i> <ul style="list-style-type: none"> <li>○ <i>Yes or no; If yes, specify:</i></li> <li>_____</li> </ul> </li> <li>• <i>Have you had any overall change in activity in the past 6 months?</i> <ul style="list-style-type: none"> <li>○ <i>Yes or no; If yes, specify:</i></li> <li>_____</li> </ul> </li> <li>• <i>Is there anything that you cannot do now, that you could do 6 months ago?</i> <ul style="list-style-type: none"> <li>○ <i>Yes or no; If yes, specify:</i></li> <li>_____</li> </ul> </li> <li>• <i>Have you had any changes in medications, illness, surgeries or hospital visits in the last 6 months?</i> <ul style="list-style-type: none"> <li>○ <i>Yes or no; If yes, specify:</i></li> <li>_____</li> </ul> </li> </ul> <p><i>Thank you so much for your help. We’ll be calling you in about 6 months to begin the follow-up interview.</i></p> <p>l. If at the 6 month reminder/check in call, the subject indicates that they do not want to continue the study in the next 6 months, we will ask them whether or not they would be willing to move their one year visit to the time of the 6 month call and make it an exit visit, and complete as many procedures as they are willing.</p> <p>9. The follow-up screener, follow-up clinical telephone interview, and follow-up self administered questionnaires will be identical to the baseline questions, but will only reference the time period since the last baseline clinic visit. The follow-up screener will not be screening anyone out of the study, but will help us determine whether anything has changed since the last clinic visit that may make a particular procedure unsafe, and to determine that the subject is still willing and</p>
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able to participate.

10. Mild Cognitive Impairment/dementia at the time of the follow-up procedures will NOT be exclusionary, unless it would be unsafe for the subject to participate. With the exception of the lumbar puncture and the PET scan, all procedures at the clinic sites will be repeated at the follow-up visit unless there are specific health reasons that may make it unsafe for the subject to participate (for example, new metal implants).
11. Analysis of the data to test the hypotheses as stated, including the exploratory analyses, will begin after the first 12 months or so and will continue until the follow-ups are completed.
12. Deliver final report to the DOD.
13. Should additional funding be obtained, the number of longitudinal follow-up years may be increased.

***Summary of Communication and Data Flow between SFVAMC and Clinic Sites:***

- This study will use much of the existing network of communication that exists for the Alzheimer's Disease Neuroimaging Initiative (ADNI) study, including the ADNI Data and Safety Monitoring Board (DSMB).
- The San Francisco site will manage the initial contacts with subjects by mail and telephone, as well as the collection of telephone screening and clinical interviews and self-report data. All patient data and telephone calls will be logged into a currently existing electronic capture system, modified for the study. All case report forms (CRFS) will be uploaded to the Alzheimer's Disease Cooperative Study (ADCS) database.
- The ADCS was formed in 1991 as a cooperative agreement between the National Institute on Aging (NIA) and the University of California San Diego. The ADCS is a major initiative for Alzheimer's disease (AD) clinical studies in the Federal government, addressing treatments for both cognitive and behavioral symptoms.
- Upon completion of the mail/telephone assessments, eligible subjects will be referred to the ADNI sites, and ADCS will coordinate all data capture. Upon arrival at the ADNI sites, all subjects will have the complete standardized ADNI assessments. The subjects will be asked about the presence of all medical conditions and use of medications.

	<p>When the Site Medical Doctors (MDs) and study coordinators have questions about this, they contact the central ADNI clinical core, and these issues are adjudicated.</p> <ul style="list-style-type: none"> <li>• All de-identified data will be available at the ADCS database, displayed at the Laboratory of Neuroimaging (LONI) website at University of California, Los Angeles without embargo. LONI is a leader in the development of advanced computational algorithms and scientific approaches for the comprehensive and quantitative mapping of brain structure and function.</li> <li>• The San Francisco Veterans Affairs Medical Center (SFVAMC) site will maintain the protocol and consent templates, and any changes to these documents will be distributed to each study site as soon as they are locally approved.</li> <li>• SFVAMC will be responsible for the mail effort, recruitment, and the telephone screeners and clinical interviews, as well as the self-report questionnaires, and maintain the protocol and consent templates, but no subjects will be seen on the SFVAMC campus.</li> <li>• UCSF will be one of the selected ADNI sites. There will be subjects seen at the UCSF ADNI clinic and at the China Basin PET scan facility. The UCSF ADNI site will be submitting their own IRB documents, using this master template for protocol and consent forms, as will each of the selected ADNI sites.</li> </ul>
<p><b>Sample Size</b></p>	<p><b>Overall Sample of Consented/Screened/Eligible and Enrolled all the way to the ADNI site with a full battery of assessments will be 195- 300 eligible subjects.</b></p> <ul style="list-style-type: none"> <li>• 65-100 Vietnam Veterans w/ TBI, but w/o PTSD, MCI/dementia</li> <li>• 65-100 Vietnam Veterans w/ PTSD, but w/o TBI, MCI/dementia</li> <li>• 65-100 Vietnam Veteran controls, w/o TBI or PTSD and comparable in age, gender, and education to above groups</li> </ul> <p>Subjects with mild cognitive impairment (MCI)/dementia will be excluded. Rationale for this approach is that it's already established that 50-60 % of subjects w/MCI have AD pathology in their brain, and it may be difficult to detect added effects of a history of TBI or ongoing PTSD in MCI/demented subjects.</p> <ul style="list-style-type: none"> <li>• The Sample size of 65-100 Vietnam Veterans in each of the study</li> </ul>

	<p>cohorts is the estimate for how many subjects will successfully enroll and complete all study procedures. Our goal is to enroll and complete one year (approximate) follow-up visits on a total of 210 subjects.</p> <ul style="list-style-type: none"> <li>Given expected drop-outs, we plan to enroll and complete all baseline measurements on 230 subjects. Based on our experience we believe that we will need to refer approximately 300 subjects to the ADNI sites (that is about 100/group).</li> <li>To achieve this number of subjects who pass the screening examination and the SCID we plan to send out several thousand brochures and will be making many hundreds, perhaps thousands of telephone contacts. At the current time it is not possible to precisely identify the exact number of brochure mailings which will result in satisfactory responses leading to telephone contacts. Therefore our approach will be to begin with sending 1000 brochure mailings to veterans in the zip codes of the ADNI sites and then observe the response rate. If the response rate is high, then fewer additional mailings will be needed. If the response rate is low, we will increase the number of mailings until we achieve a satisfactory number of responses, so that during our follow-up phone calls we obtain a reasonable number of subjects who pass the screening telephone interview.</li> </ul> <p>We also do not know the fraction of subjects who will fail to pass the SCID CAPS telephone interview. However since we are examining the VA and military records of the subjects prior to mailings, we are hopeful that we are targeting subjects who have histories of TBI or PTSD, or neither, and that we are able to exclude subjects with exclusionary criteria by examination of their records. In summary we approximate that 300 persons will come in for the in person visit, that 500 will undergo the clinical telephone interview, that 1000 subjects will undergo the screening interview, and that it will be required to mail 5000 brochures to obtain this number of interested veteran subjects.</p>
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<p><b>Summary of Key Inclusion/Exclusion Criteria for TBI Subjects</b></p>	<p><b>TBI Subjects: <u>Identification and inclusion criteria</u></b></p> <ul style="list-style-type: none"> <li>Subjects must be Veterans of the Vietnam War, 50-90 years of age. (Subjects 60-80 will be recruited first, but subjects at the lower and upper ages may be added as study progresses). Subjects &lt;60 or &gt;80 will be added if recruitment numbers are too low in the 60-80 age range.</li> <li>Subjects must have a documented history of moderate-severe <b>non-</b></li> </ul>
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	<p><b>penetrating</b> TBI, which occurred during military service in Vietnam (identified from the Department of Defense or VA records).</p> <ul style="list-style-type: none"> <li>• Must live within 150 miles of the closest ADNI clinic in subject’s area.</li> <li>• TBI will be defined as:             <ul style="list-style-type: none"> <li>○ Loss of consciousness,</li> <li>○ Post-traumatic amnesia &gt;24 hours, OR</li> <li>○ Alteration of consciousness or mental state &gt;24 hours</li> </ul> </li> </ul> <p><b>TBI Subjects: <u>Exclusion criteria</u></b></p> <ul style="list-style-type: none"> <li>• Mild Cognitive Impairment/Dementia</li> <li>• Presence of PTSD by SCID-I for DSM-IV-TR criteria, or a CAPS score of &gt;30 (Both current and/or a history of PTSD will be excluded).</li> </ul>
<p><b>Summary of Key Inclusion/Exclusion Criteria for PTSD Subjects</b></p>	<p><b>PTSD Subjects: <u>Identification and inclusion criteria</u></b></p> <ul style="list-style-type: none"> <li>• Subjects must be Veterans of the Vietnam War, 50-90 years of age (Subjects 60-80 years will be selected first). Subjects &lt;60 or &gt;80 will be added if recruitment numbers are too low in the 60-80 age range.</li> <li>• Subjects who meet the SCID-I (for DSM-IV-TR) criteria for current/chronic PTSD (identified by records, and verified by our telephone assessments)</li> <li>• <i>In addition to meeting DSM-IV-TR criteria for current/chronic PTSD, subjects must have a minimum current CAPS score of 50 as determined by telephone assessment.</i></li> <li>• The PTSD symptoms contributing to the PTSD Diagnosis and Current CAPS score must be related to a Vietnam War related trauma.</li> <li>• Must live within 150 miles of the closest ADNI clinic in subject’s area.</li> </ul> <p><b>PTSD Subjects: <u>Exclusion criteria</u></b></p> <ul style="list-style-type: none"> <li>• Mild Cognitive Impairment/Dementia</li> <li>• Documented or self report history of mild/moderate severe TBI</li> <li>• Any history of head trauma associated with injury onset cognitive complaints, or</li> <li>• Loss of consciousness for &gt;5minutes</li> </ul>
<p><b>Summary of Key Inclusion/Exclusion Criteria for Control</b></p>	<p><b>Control Subjects: <u>Identification and inclusion criteria</u></b></p> <ul style="list-style-type: none"> <li>• Subjects must be Veterans of the Vietnam War, 50-90 years of age</li> </ul>

<p><b>Subjects</b></p>	<p>(Subjects 60-80 years will be selected first). Subjects &lt;60 or &gt;80 will be added if recruitment numbers are too low in the 60-80 age range.</p> <ul style="list-style-type: none"> <li>• Comparable in age, gender, and education with TBI and PTSD groups</li> <li>• May be receiving VA disability payments for something other than TBI or PTSD – or no disability at all.</li> <li>• Must live within 150 miles of the closest ADNI clinic in subject’s area</li> </ul> <p><b>Control Subjects: <u>Exclusion criteria</u></b></p> <ul style="list-style-type: none"> <li>• MCI/Dementia</li> <li>• Presence of PTSD by SCID-I for DSM-IV-TR criteria, or a CAPS score of &gt;30 (Both current and/or a history of PTSD will be excluded).</li> <li>• Documented or self report history of mild/moderate severe TBI</li> <li>• Any history of head trauma associated with injury onset cognitive complaints, or</li> <li>• Loss of Consciousness for &gt;5 minutes</li> <li>• History of PTSD or current PTSD</li> <li>• Exclusionary criteria applied to TBI/PTSD will be applied to controls</li> </ul> <p><i>No controls will be enrolled until 25% of the TBI/PTSD enrolled</i></p>
<p><b>Exclusion Criteria for ALL Subjects</b></p>	<p><b>All Subjects: Exclusion Criteria for all subjects:</b></p> <ul style="list-style-type: none"> <li>• MCI/dementia</li> <li>• History of psychosis or bipolar affective disorder;</li> <li>• History of alcohol or substance abuse/dependence within the past 5 years (by DSM IV – TR criteria);</li> <li>• MRI-related exclusions: aneurysm clips, metal implants that are determined to be unsafe for MRI; and/or claustrophobia;</li> <li>• Contraindications for lumbar puncture, PET scan, or other procedures in this study;</li> <li>• Any major medical condition must be stable for at least 4 months prior to enrollment. These include but are not limited to clinically significant hepatic, renal, pulmonary, metabolic or endocrine disease, cancer, HIV infection and AIDS, as well as cardiovascular disease, including:             <ul style="list-style-type: none"> <li>○ cardiac surgery or myocardial infarction within the last 4 weeks;</li> <li>○ unstable angina;</li> <li>○ acute decompensated congestive heart failure or class IV heart failures;</li> <li>○ current significant cardiac arrhythmia or conduction disturbance particularly those resulting in ventricular fibrillation, or causing syncope, or near syncope;</li> </ul> </li> </ul>

- Uncontrolled high blood pressure
- Seizure disorder or any systemic illness affecting brain function during the past 5 years will be exclusionary
- Clinical evidence of stroke.
- Have a history of relevant severe drug allergy or hypersensitivity.
- Subjects with current clinically significant unstable medical comorbidities, as indicated by history or physical exam, that pose a potential safety risk to the subject.

***For Florbetapir Scans:***

- Subjects who have received an investigational medication within the last 30 days; additionally, the time between the last dose of the previous experimental medication and enrollment (completion of screening assessments) must be at least equal to 5 times the terminal half-life of the previous experimental medication.
- Subjects who have received a radiopharmaceutical for imaging or therapy within the past 24 hours prior to the imaging session for this study.
- Current or recent participation in any procedures involving radioactive agents such that the total radiation dose exposure to the subject in any given year would exceed the limits of annual and total dose commitment set forth in the US Code of Federal Regulations (CFR) Title 21 Section 361.1.
- Prohibited medications: Subjects who have ever participated in an experimental study with an amyloid targeting therapy (e.g., immunotherapy, secretase inhibitor, selective amyloid lowering agents) may not be enrolled without prior sponsor/AVID approval unless it can be demonstrated that the patient received only placebo in the course of the trial.
- Women of childbearing potential who are not surgically sterile, not refraining from sexual activity or not using reliable methods of contraception. Women of childbearing potential must not be pregnant or breastfeeding at screening. Women must avoid becoming pregnant and must agree to refrain from sexual activity or to use reliable contraceptive methods for 24 hours following administration of Florbetapir F18 injection
  - *Because the drugs in this study can affect a fetus, pregnant women may not participate. Women of childbearing age will receive a urine test for pregnancy on the date of the Florbetapir F18 scan. Given that the selected age of subjects will be 50-90, it is unlikely that many pregnancy tests will be needed.*
- Subjects, who in the opinion of the investigator are otherwise unsuitable



	<p>for a study of this type, are also excluded.</p>
<p><b>Procedures</b></p>	<ul style="list-style-type: none"> <li>• After initial mail contact and telephone screening, all eligible subjects will undergo a clinical psychological interview using the Structured Diagnostic Interview SCID-I for DSM IV-TR, and the Clinician Administered PTSD Scale (CAPS) by telephone, conducted by the PTSD Core at the San Francisco VA Medical Center to determine eligibility. The SCID/CAPS will be audio-recorded for quality control purposes. Subject will be asked to sign a separate consent form for audio recording. All audio recordings will be stored by study code only in a locked filed cabinet in a locked file room. Audio-recording is optional. Subjects who choose not to be audio recorded can still participate in the study.</li> <li>• Those subjects, who are still eligible and live within 150 miles of the closest ADNI clinic, will be referred to their local site for a full battery of clinical/cognitive assessments, biomarker and genetic sample collection (Blood and cerebrospinal fluid), and imaging (MRI and PET scans).             <ul style="list-style-type: none"> <li>○ <i>Again, because the drugs in this study can affect a fetus, pregnant women may not participate. Women of childbearing age will receive a urine test for pregnancy on the date of the Florbetapir F18 scan. Given that the selected age of subjects will be 50-90, it is unlikely that many pregnancy tests will be needed.</i></li> </ul> </li> <li>• All MRI and PET scans will be rapidly assessed for quality so that subjects may be rescanned if necessary. In the event that the scan fails the quality control procedure and cannot be used, we will repeat the Florbetapir scan. In ADNI to date, less than .5% of scans require repeat. Because of this, we include the total dose in the case of the necessity for repeating the scan once. See dosimetry table on page 62.</li> <li>• All clinical data will be collected, monitored, and stored by the Coordinating Center at University of California, San Diego. The University of Pennsylvania will collect biomarker samples and, and NCRAD will collect genetic samples. All raw and processed image data will be archived at LONI.</li> <li>• SFVAMC will be responsible for the mail effort, recruitment, and the telephone screeners and clinical interviews. There will be NO subjects seen on the SFVAMC campus. UCSF will be one of the ADNI sites. There will be subjects seen at the UCSF ADNI clinic and at the China Basin PET scan facility. The UCSF ADNI site will submit their own</li> </ul>

	<p>IRB documents, using this master template for protocol and consent forms, as will each of the selected ADNI sites.</p>
<p><b>Outcome Measures</b></p>	<ol style="list-style-type: none"> <li>1. Level of early cognitive functioning as measured by Armed Forces Qualifying Exam Score.</li> <li>2. Level of current cognitive function as measured by Cognitive tests.</li> <li>3. Prevalence of brain AD pathology (measured by amyloid PET, CSF A<math>\beta</math> and tau, medial temporal lobe atrophy, (after accounting for effects of age and APOE).</li> <li>4. Prevalence of AD pathology and other co-morbid diseases/pathology identified at autopsy.</li> <li>5. Examine group differences for each imaging and biomarker measurements:             <ol style="list-style-type: none"> <li>a. Brain uptake –Florbetapir F18 amyloid PET scans</li> <li>b. Levels of CSF Amyloid beta, tau/P tau</li> <li>c. Rate of brain atrophy in hippocampus, entorhinal cortex, and parietal/temporal cortices (both current and longitudinally)</li> </ol> </li> <li>6. Hippocampal atrophy while accounting for brain amyloid.</li> </ol>
<p><b>Sponsor</b></p>	<p>Department of Defense</p>

### Schedule of Events

Completed by SFVAMC Recruiters and PTSD Core								
Stage of Project	Baseline				12 Month (approximate) Follow-up			
Who is responsible?	SFVAMC Recruiters	PTSD Core	Self Reports	Local ADNI SITE	SFVAMC Recruiters	PTSD Core	Self Report	Local ADNI SITE
Invitation letter, brochure, & response postcards mailed to subjects	X				X			
6 month (approximate) contact call	X							
Birthday cards/holiday cards	X			X	X			X
Thank you cards	X			X	X			X
Subjects contacted by telephone; Explain Study	X				X			
Verbal Consent obtained for Screening/TBI interview /Self Report Questionnaires (SRQ's)	X				X			
Structured interview for TBI history and screening	X				X			
If Eligible, mail MRI safety/Medical history SRQ's w/written consents for Clinical Interview and Consent for audio recording (w/stamped/ addressed envelope)	X				X			
Call subject, review consents. Answer questions. If interested, instruct subject to return consents /SRQ's in								

prepared envelope.	X				X			
Once written consent/SRQ's received and reviewed at SFVAMC, refer eligible subjects to clinical core for SCID/CAPS,	X				X			
If eligible after SCID/CAPS; Mail SRQ's	X				X			

Completed Over the Telephone by PTSD CORE								
Stage of Project	Baseline				12 Month (approximate) Follow-up			
Who is responsible?	SFVAMC Recruiters	PTSD Core	Self Reports	Local ADNI SITE	SFVAMC Recruiters	PTSD Core	Self Report	Local ADNI SITE
Structured Clinical Interview for SCID-I for DSM-IV TR		X				X		
Clinician Administered PTSD Scale		X				X		
Life Stressor Checklist - Revised		X				X		

SELF REPORT QUESTIONNAIRES (SRQ):								
	Baseline				12 Month (approximate) Follow-Up			
Who is responsible?	SFVAMC Recruiters	PTSD Core	Self Reports	Local ADNI SITE	SFVAMC Recruiters	PTSD Core	Self Report	Local ADNI SITE
MRI Safety			X				X	
Medical History			X				X	

Symptom Check-List-90 Rev.			X				X	
Pittsburgh Sleep Quality Index			X				X	
Smoking Questionnaires			X				X	
Addiction Severity Index Lite			X				X	
SF-12 Health Survey			X				X	
Combat Exposure Scale			X				X	

PROCEDURES DONE AT CLOSEST ADNI CLINIC to Subject								
Who is responsible?	Baseline				12 Month (approximate) Follow-Up			
	SFVAMC Recruiters	PTSD Core	Self Reports	Local ADNI SITE	SFVAMC Recruiters	PTSD Core	Self Report	Local ADNI SITE
Explain study at ADNI Site to both subject and (subject's study partner (SP) - if available				X				X
Consent Subject & SP				X				X
Demographics, Family History, Inclusion and Exclusion Criteria				X				X
Height & Weight				X				X
Screening Labs				X				X
DNA Sample Collection for APOE Genotyping and GWAS				X				
Cell Immortalization Sample Collection				X				

Plasma, Serum, Buffy coat, Biomarker Collection				X				X
RNA Sample Collection				X				X
American National Adult Reading Test				X				X
Medical History, Physical Exam, Neurological Exam, Hachinski				X				X
Vital Signs				X				X
Mini Mental State Examination				X				X
Logical Memory I and II				X				X
Everyday Cognition (ECog)				X				X
Montreal Cognitive Assessment (MoCA)				X				X
Category Fluency (Animals)				X				X
Trails A & B				X				X
Boston Naming Test (30-item)				X				X
Auditory Verbal Learning Test				X				X
Geriatric Depression Scale				X				X
Clock drawing				X				X
Neuropsychiatric Inventory				X				X

ADAS-Cog 13 (with Delayed Word Recall and Number Cancellation)				X				X
Clinical Dementia Rating Scale				X				X
Activities of Daily Living (FAQ)				X				X
AFQT				X				X
ACT				X				X
Concomitant Medications				X				X
Adverse Events				X				X
Diagnostic Summary				X				X
Neuropathological Diagnosis (autopsy) discussion				X				X
3T MRI with DTI Imaging				X				X
Florbetapir F 18 Injection Amyloid Imaging with PET				X				
CSF Collection by Lumbar Puncture (LP)				X				

## Study Glossary

18F-AV-45	Florbetapir F 18 (under IND with Avid Radiopharmaceuticals, Inc.)
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive
ADC	Alzheimer's Disease Center
ADC's	Alzheimer's Disease Centers (under NIA)
ADCS	Alzheimer's Disease Cooperative Study
ADEAR	Alzheimer's Disease Education & Referral Center, under the NIA
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADNI-CC	Alzheimer's Disease Neuroimaging Initiative Coordinating Center
ADRDA	Alzheimer's Disease and Related Disorders Association
AE	Adverse Event
ANART	American National Adult Reading Test
ANOVA	Analysis of Variance
APOE/APOE4	Apolipoprotein (APOE) epsilon 4 (APOE4)
AVLT	Auditory Verbal Learning Test
A $\beta$	Beta Amyloid
BNT	Boston Naming Test
CDR	Clinical Dementia Rating
CN	Cognitively Normal
CSF	Cerebral Spinal Fluid
CT	Computerized Tomography
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DTI	Diffusion Tensor Imaging
ECG	Electrocardiogram
ECog	Everyday Cognition
eCRF	Electronic Case Report Form
FAQ	Functional Activities Questionnaire (Activities of Daily Living)
FLAIR	Fluid Attenuation Inversion Recovery
FDG	Fluorodeoxyglucose
fMRI	Functional Magnetic Resonance Imaging
GDS	Geriatric Depression Scale
GWAS	Genome Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IRB	Institutional Review Board
LONI	Laboratory of Neuroimaging



LP	Lumbar Puncture
MCI	Mild Cognitive Impairment
MMSE	Mini Mental State Examination
MoCA	Montreal Cognitive Assessment
MPRAGE	Magnetization Prepared Rapid Gradient Echo
MR/MRI	Magnetic Resonance / Magnetic Resonance Imaging
NCRAD	National Cell Repository for Alzheimer's Disease
NINCDS	National Institute of Neurological and Communicative Diseases and Stroke
NPIQ	Neuropsychiatric Inventory Questionnaire
PET	Positron-Emission Tomography
PI	Principal Investigator
PTSD	Post Traumatic Stress Disorder
QA	Quality Assurance
QC	Quality Control
RARC	Resource Allocation Review Committee
REB	Research Ethics Board
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SD	Standard Deviation
SFVAMC	San Francisco Veterans Affairs Medical Center
T	Tesla
T2* GRE	T2 Star-Weighted Gradient-Echo
TBI	Traumatic Brain Injury
TFT's	Thyroid Function Tests
VIQ	Premorbid Verbal Intelligence
WML	White Matter Lesions
WMS-R	Wechsler Memory Scale – Revised

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## 1. Introduction

The overall long-term goal of this project is to prevent Alzheimer's disease (AD), which affects almost 50% of the US population over 85 years of age, and is the most common cause of dementia. Clinical signs and symptoms of AD include cognitive impairments, especially memory and emotional disturbances. In order to accomplish this goal of prevention, a population at risk must be identified. Evidence suggests that both traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) increase risk for cognitive decline, AD, and dementia.

TBI and PTSD are common problems resulting from military service. Thus far, there have been no prospective studies using imaging and biomarkers, which directly measure changes in the brain and AD pathology to study the effects of TBI and PTSD. This proposed study will provide novel data to test these hypotheses. The results will have major implications for identifying, subjects at increased risk for AD, a possible need for early detection of AD in military Veterans with histories of TBI and PTSD, and a possible need to employ prevention and treatment measures to avoid accelerated development of AD in US military Veterans. This study is a first step toward a larger, more comprehensive study of dementia risk factors in Veterans. The results will lead to a design and statistical powering of a prevention trial. Therefore, this project could be the first step toward the prevention of AD in Veterans, and in the general population.

## 2. Background: AD, TBI, & PTSD

**Alzheimer's disease (AD)** is characterized by brain pathology consisting of extracellular plaques containing amyloid  $\beta$  ( $A\beta$ ), tangles of phosphorylated tau protein inside neurons, synapse loss (which begins in the entorhinal cortex and hippocampus in the medial temporal lobe) and neuronal loss, leading to dementia. It is generally recognized that age and family history are the major risk factors for the development of AD. Evidence also exists that several factors including occupation, education, and intellectual/social activity affect cognitive decline and incidence of AD, leading to the concept of "cognitive reserve" [1]. Although acetylcholine-esterase inhibitors and memantine are approved for treatment of AD, these produce modest symptomatic improvement, but do not slow the progression of AD. Currently a large number of treatment trials are underway. Most use immunotherapy (vaccines or monoclonal antibodies) or secretase inhibitors (to reduce synthesis of  $A\beta$ ), but none have been successful. Most treatment trials are conducted using patients with dementia due to AD, although an increasing number are enrolling subjects with mild cognitive impairment (MCI) who have evidence of AD pathology (using imaging/biomarkers). A long-term goal of the field will be to prevent the development of cognitive impairment or dementia by treatment of normal subjects. Previous attempts at prevention trials with Ginkgo Biloba [2] or non-steroidal anti-inflammatory drugs [3,4] have failed.

**Traumatic Brain Injury (TBI)** is defined as traumatically induced physiological disruption of brain function, as manifested by either loss of consciousness, memory impairment, alteration of mental state, and/or focal neurological deficits. TBI has many effects on the brain including focal injuries such as cerebral contusions, lacerations and epidural, subdural, intracerebral or intraventricular hemorrhage. Diffuse injuries include hypoxia/ischemia, vascular damage, and diffuse macro/microstructural axonal injury.

**Posttraumatic stress disorder (PTSD)** is an anxiety disorder that develops in some individuals following exposure to traumatic stress [26]. Diagnostic symptoms include flashbacks or nightmares, avoidance of stimuli, increased arousal, anger, and hypervigilance. In addition to experiencing symptoms of intrusion, avoidance, and hyperarousal following exposure to trauma, individuals with PTSD are at increased risk of co-morbid psychiatric disorders including depression, alcohol and drug abuse, panic disorder, and agoraphobia [27-31].

### 3. Imaging and Biomarkers

Although the diagnosis of AD dementia and MCI are made by clinical information and neuropsychological tests, there has been increasing use of magnetic resonance imaging (MRI) and positron emission tomography (PET), as well as analysis of proteins in cerebrospinal fluid (CSF) obtained by lumbar puncture (LP) for diagnosis, early detection, and monitoring of the progression of AD. The literature in this field is vast, but in brief: AD is associated with 1) low CSF A $\beta$ , and elevated tau; 2) high uptake of the A $\beta$  [5] imaging agent C-11PIB (Pittsburgh compound B), a ligand which sticks to A $\beta$  neuritic plaques, and other more recently developed Florbetapir F18 labeled amyloid PET ligands, including Florbetapir F18 which will be used in this study; and 3) reduced volume of entorhinal cortex, hippocampus and cortical thinning of the temporal and parietal cortices. Furthermore, many subjects with MCI show similar patterns, and these biomarkers predict more rapid decline and conversion to AD. About 20-30% of normal subjects in their early 70s also appear to have imaging/biomarker evidence of AD, consistent with previous pathological studies. The recognition of the importance of biomarkers in the AD field, and the need for standardization and validation, led to the Alzheimer's disease Neuroimaging Initiative (ADNI).

### 4. The Alzheimer's Disease Neuroimaging Initiative (ADNI)

ADNI is a large multisite project funded by the National Institute on Aging (NIA) of the National Institutes of Health (NIH), the Alzheimer's Association and other nonprofit groups, and private industry (more than 20 corporate partners) through the Foundation for NIH (FNIH). The overall goal of ADNI is validation of imaging and biomarkers for AD clinical trials. ADNI was initially funded for \$60 million for 5 years, enrolled more than 800 subjects (200 controls, 400 MCI, and 200 AD subjects) in 57 sites throughout the US and Canada, and performed standardized longitudinal, clinical and cognitive [6,7], MRI [8], Fluorodeoxyglucose (FDG)-PET and PIB-PET [9], blood/cerebrospinal fluid biomarker [10], and genetics measurements [11,12]. All data is centrally data-based and has been available to the scientific community without embargo at Laboratory of Neuroimaging (LONI) website at University of California, Los Angeles. More than 200 peer-reviewed publications have sprung from ADNI including special journal issues [13]. ADNI methods are used in many AD trials, and ADNI results were used to define the newly proposed research criteria for AD [14]. ADNI sparked similar studies in Australia [15, 16], Japan [17, 18], Europe [19], Taiwan, Korea, and China (known as World Wide ADNI [20]). ADNI subsequently received \$24 million in American Reinvestment and Recovery ACT (ARRA) funds (for additional data analysis and to enroll 200 subjects with early MCI), and has recently been refunded by NIA and its partners for an additional \$69 million for the next 5 years in order to follow those subjects originally enrolled and to enroll an additional 550 subjects. The current ADNI uses clinical/cognitive

tests, lumbar Puncture (LP) for cerebral spinal fluid (CSF), 3T MRI, Florbetapir F18 PET [21-24] and FDG PET on all subjects.

This project will use many of the ADNI sites, ADNI methods, and the ADNI data collection and analysis infrastructure for this project concerning TBI and PTSD as risk factors for AD.

## 5. Hypotheses

### Primary Hypothesis

The primary hypothesis to be tested (all data analyses will be covaried for age, gender, and Apolipoprotein E (APOE) 4 genotype) are that Veterans without MCI/dementia with a history of moderate to severe TBI during military service, as well as Veterans with ongoing PTSD, have increased evidence for AD pathophysiological markers, when compared with Veteran controls (without TBI or PTSD and matched for age, APOE4 status and accounting for other comorbidities) manifested as the following dependent variables:

- Greater uptake on Florbetapir F18 amyloid PET scans;
- Lower CSF amyloid beta levels;
- Increased CSF tau/P tau levels;
- Greater brain atrophy in hippocampus, entorhinal cortex, and parietal/temporal cortices;
- Greater longitudinal rates of brain atrophy in hippocampus, entorhinal cortex and parietal/temporal cortices;
- Reduced cognitive function, especially delayed memory; and
- Greater rate of change of cognitive function.

### Second Hypothesis

The second major hypothesis to be tested is that TBI and/or PTSD reduce brain reserve, causing greater cognitive impairment after accounting for age, educational status, and pre-war cognitive function as assessed with the Armed Forces Qualifying Exam score during basic training, brain amyloid load or hippocampal volume. Greater cognitive impairments at a given level of brain A $\beta$  or brain volume in the TBI or PTSD group compared with controls would support the hypothesis of reduced cognitive reserve.

### Third Hypothesis

The third hypothesis will be that TBI, when compared to controls, is associated with changes in brain regions previously reported to be associated with TBI [37-39]. White matter regions frequently noted to have reduced microstructural integrity due to TBI on DTI include the anterior corona radiata, uncinate fasciculus, corpus callosum, forceps minor, forceps major, sagittal stratum, corticospinal tract, inferior fronto-occipital fasciculus and cingulum bundle [37-39]. Previous findings of reduced hippocampal volume in PTSD compared to controls will also be replicated [32-36].



## Fourth Hypothesis

The fourth hypothesis is that there will be significant correlations between severity of TBI (from hospital records) and severity of PTSD (CAPS score) on the above-listed outcomes, i.e. a dose response effect.

## Exploratory Analyses

Exploratory analyses will be performed to examine other questions and to compare the patterns (using voxel based methods) of amyloid deposition (from Florbetapir F 18 uptake) and brain atrophy among TBI, PTSD, and control subjects, and with the patterns from non-Veteran subjects in ADNI. These results of these studies may provide insight into the question of whether or not TBI and PTSD alter the pattern of amyloid distribution or brain atrophy. The relationship between cortical areas with amyloid plaque (from Florbetapir) and underlying white matter integrity as assessed with DTI will also be studied to determine if axonal injury resulting from TBI was associated with greater amyloid accumulation, or whether regions of brain with axonal damage have less amyloid accumulation due to disconnection and reduced brain activity.

## 6. Study Design

This is a non-randomized natural history non-treatment study.

1. Using military and VA Compensation and Pension records identify Vietnam War Veterans with well documented history of moderate/severe TBI or evidence of ongoing PTSD, and comparable Veteran controls. Subjects meeting criteria for mild cognitive impairment/dementia will be excluded.
2. SFVAMC will mail out invitation letter, brochure, and response postcard (a self addressed stamped envelope will be included, so that the subject can return the postcard) to large numbers of Veterans who meet above broad criteria (based on diagnostic codes in military and VA Compensation and Pension records), and who live within 150 miles of closest ADNI clinic in subject's area. Selected sites will have the General Electric Diffusion Tensor Imaging / Magnetic Resonance Imaging [GE/DTI MRI] scanner). The mileage distance from the clinics may be extended if the recruitment numbers are low. The timing of the mail out effort to the geographic location of a selected ADNI site will only occur once the specific site has obtained full human subjects approval from both their agency review boards as well as the Department of Defense (DOD).
3. SFVAMC will contact subjects by telephone for those that have returned the response post card, as well as those who have not.

SFVAMC staff will:

- a. Obtain verbal consent to administer screening and TBI questionnaires over the telephone.
- b. Administer screening and TBI questionnaires to determine eligibility criteria to be enrolled in the Psychiatric Assessment, using the SCID-I for DSMIV-TR (will be audio recorded for quality control purposes – subject will be asked to sign a separate consent form for audio-recording). Audio recording is optional. Subjects who choose not to be audio-recorded can still be in the study.

- c. Determine if subject has a study partner. If subject has a reliable study partner, and is found to be eligible after completing the screening and clinical interviews, the partner will be asked to accompany the subject to the clinic visits. Study partners are helpful in confirming memory problems if they exist. However, because many subjects may not have a regular person in their life who can act as a study partner, a study partner is not required for this study.
  - d. The screening questions will be an adapted version of the AD8 assessment (70, 71) and will also include some of the questions of the Clinical Dementia Rating (CDR). For this study, subjects with mild cognitive impairment (MCI)/dementia may be screened depending on the answers to the screening questions. The Study Coordinator will discuss subject responses to the Subject Matter Experts to assess whether or not the memory issues are exclusionary. Questionable items will be discussed among the clinical core investigators to assess who will be screened out.
  - e. At completion of the telephone screener, subjects will be told whether or not they are eligible to be referred to the clinical telephone interview, or if some of their responses need to be discussed with the study doctors. (Some answers to the screening questions will be discussed with the clinical leaders of the study to assess whether there are any exclusionary criteria present, such as possible MCI/dementia, psychological disorders, alcohol or substance abuse, etc.). After the discussion with study doctors, subject will be called back and invited to continue, or will be thanked and compensated for the time spent in study thus far.
  - f. If after the screening interview, subject is eligible for the SCID/CAPS, SFVAMC staff will mail a written consent form w/ stamped addressed return envelope to the home of the subjects along with two self-report questionnaires on MRI safety and medical history and the consent for audio-recording. In a few days, study staff will call the subject to make sure that subject received the consent form, will go over the consent form with the subject, answer any questions the subject may have, and assist with the self report questionnaires if needed. Subject will be asked to sign the consent forms and fax or mail it back to SFVAMC in the stamped addressed envelope along with the completed self-report questionnaires.
  - g. As soon as the signed consent forms are received back at SFVAMC, by mail or fax, the questionnaires will be reviewed and if eligible, subject will be referred to the PTSD core at SFVAMC.
  - h. Because the project is only enrolling subjects without MCI/dementia, a study partner if available will never act as a surrogate for the subject. All subjects will consent for themselves. A study partner is NOT a requirement for this study.
4. PTSD core (at the SFVAMC) will call the subject and perform the Structured Diagnostic Interview I for DSM-IV-TR & Clinician Administered PTSD Scale (CAPS) by telephone. If a signed consent for audio recording has been received along with the signed consent for the clinical interview, this interview will be audio recorded for quality control purposes, to ensure that the interview is administered in a consistent manner. This audio tape will be filed and stored by study code and will be locked and secured at all times. Audio-recording is optional. Subjects who choose not to be audio-recorded can still be in the study.
  5. If after the clinical interview, subject is still eligible, SFVAMC will refer subject to a local clinic in the network of Alzheimer's Disease Neuroimaging Initiative sites (ADNI).
  6. SFVAMC staff will mail a packet of self-report questionnaires to subject, with instructions for subject to complete and bring completed packet to first in-person clinic visit.

7. SFVAMC will give the subject the contact information of the clinic in the subject's area, and will call the clinic directly to refer the subject's contact information
8. The local ADNI site will contact subject and make an appointment for the subject to come to the site. At the ADNI site, trained staff will conduct the procedures listed below with each subject. Completing all of the procedures may take 2-3 days, or so, within a few weeks:
  - a. Explain study and obtain written consent;
  - b. For those subjects who have a reliable person in their lives who can act as a study partner (spouse, friend, or relative), the full CDR will be administered during the clinic visits to confirm that the subject does not have MCI/dementia, or to further rule out the presence of MCI/dementia. If a study partner is available, the study partner will be asked to accompany the subject to all clinic visits and to communicate changes in the subjects' health status over the period of the study. Study partners will be fully informed of the study, and will be asked to read and sign the consent form. There will be a separate signature line on the subject's consent form for study partners (if available).
  - c. ADNI staff will also discuss autopsy with subject. An ADNI clinician will lead a discussion about autopsy with all subjects at their initial assessment (study partners and families are welcomed in the discussion). There are 3 objectives of the discussion:
    - To convey information about the value of brain autopsy in confirming the clinical diagnosis and advancing knowledge regarding mild cognitive impairment and Alzheimer's disease;
    - To initiate consideration of the individual's wishes concerning an autopsy; and
    - To answer questions, misconceptions, or concerns about autopsy. The involvement of the physician in these discussions emphasizes the importance of autopsy. There is no pressure on an individual to decide; they are encouraged to involve family members, clergy, physicians, or other appropriate persons in their decision-making. Participants are assured that a decision not to have an autopsy in no way jeopardizes their research participation or any other patient rights. It is important to note that autopsy will not interfere with funerary arrangements nor will it be a financial burden to the participant's family. Subjects will be asked to sign whether or not they are interested in considering autopsy at the time of death, and will be told that study personnel will ask permission from the next of kin. Therefore, subjects are encouraged to let their next of kin know their wishes.
  - d. Collect packet of self-report questionnaires
  - e. Collect baseline measurements of cognition and function. (This will confirm that there is no MCI/dementia and/or any other health issues that may make it unsafe for a subject to continue.)
  - f. Perform a blood draw by venipuncture
  - g. Collect cerebrospinal fluid for analyses (lumbar puncture)
  - h. Conduct MRI scans (structural, diffusion tensor, and resting state BOLD fMRI). No contrast agent will be used. T2 FSE and T2\* GRE scans as well.
    - A fast spin-echo T2 (FSE) is included to determine the boundary of the outer edge of the cerebral spinal fluid (CSF) from the surrounding dura, meninges and skull. With this sequence it will be possible to calculate the intracranial volume (ICV) for each subject. A T2-weighted SE sequence is standard on all MRI manufacturers and will be acquired using fat saturation for added contrast between CSF and non-brain tissue. This T2 image will also be available for use

in combination with the DWI data to guide distortion correction. This T2 will have similar contrast to the B0 image acquired with the DWI, yet be free from EPI distortions.

- A T2\* gradient echo (T2\*GRE) is included to capture evidence of hemosiderin deposition which could be due to remote cortical contusion, shearing injury, or prior subarachnoid hemorrhage (superficial siderosis). We included resting state task free fMRI in the protocol because of the increasing interest in functional network analysis as a possible precursor of future dementia.
  - T2\*GRE: This sequence will be used to capture evidence of traumatic hemosiderin deposition. We will use a T2\*GRE rather than susceptibility weighted imaging sequence (SWI) because the latter requires an SWI software license. It is unlikely that every site will have purchased the SWI license. Therefore, in order to acquire data on remote hemorrhagic TBI in a uniform manner across all sites, a standard sequence (T2\*GRE) that is available on any scanner will be used.
- i. Conduct an amyloid PET imaging scan with Florbetapir F18. The dose of Florbetapir F18 is 10 mCi per procedure.
  - j. Because the drugs in this study can affect a fetus, pregnant women may not participate. Women of childbearing age will receive a urine test for pregnancy on the date of the Florbetapir F18 scan. Given that the selected age of subjects will be 50-90, it is unlikely that many pregnancy tests will be needed.
  - k. Those subjects who have completed the procedures at the ADNI clinic are eligible for the 12 month (approximate) follow-up screener. At about 6 months, SFVAMC staff will call each subject to remind them of the 12 month (approximate) follow-up screener and to update patient status, with the following questions:

*“We’re calling to remind you that the follow-up telephone interview for the study, Effects of Effects of traumatic brain injury and post traumatic stress disorder on Alzheimer’s disease (AD) in Veterans using ADNI, will begin in about 6 months from now, and to check in on how you are doing.*

- *Have you had any change in memory or thinking in the past 6 months?*
  - *Yes or no; If yes, specify: \_\_\_\_\_*
- *Have you had any overall change in activity in the past 6 months?*
  - *Yes or no; If yes, specify: \_\_\_\_\_*
- *Is there anything that you cannot do now, that you could do 6 months ago?*
  - *Yes or no; If yes, specify: \_\_\_\_\_*
- *Have you had any changes in medications, illness, surgeries or hospital visits in the last 6 months?*
  - *Yes or no; If yes, specify: \_\_\_\_\_*

*Thank you so much for your help. We’ll be calling you in about 6 months to begin the follow-up interview.*

- l. If at the 6 month reminder/check in call, the subject indicates that they do not want to continue the study in 6 months, we will ask them whether or not they would be willing to move their one year visit to now and make it an exit visit, and to complete as much as they are willing.

9. The follow-up screener, follow-up clinical telephone interview, and follow-up self administered questionnaires will be identical to the baseline questions, but will only reference the time period since the last baseline clinic visit. The follow-up screener will not be screening anyone out of the study, but will help us determine whether anything has changed since the last clinic visit that may make a particular procedure unsafe, and to determine that the subject is still willing and able to participate.
10. Mild Cognitive Impairment/dementia at the time of the follow-up procedures will NOT be exclusionary, unless it would be unsafe for the subject to participate. With the exception of the lumbar puncture and the PET scan, all procedures at the clinic sites will be repeated at the follow-up visit unless there are specific health reasons that may make it unsafe for the subject to participate (for example, new metal implants).
11. Analysis of the data to test the hypotheses as stated, including the exploratory analyses, will begin after the first 12 months, or so and will continue until the follow-ups are completed.
12. Deliver final report to the DOD.
13. Should additional funding be obtained, the number of longitudinal follow-up years may be increased.

## 7. Overall Study Timetable

This study is funded for three years which involves about 6 months of start-up time, about 12 months of enrollment and about 12 months of follow-up. The first 6 months, or so, will be consumed by submission of protocol to local IRBs and verification of approval.

### Year One:

- Hiring of necessary staff to perform this work.
- Write research protocols and informed consent documents for all performance sites, including documents for local IRB, VA, and the Office of Research Protections (ORP), a Headquarters' Level Regulatory Oversight Office at the Department of Defense (DOD)."
- Successfully establish contacts with individuals in DOD, and VA Compensation and Pension program who can provide names, medical records, Armed Forces Qualifying Exam scores, medical records and other information concerning Vietnam era Veterans with documented traumatic brain injury, PTSD, and other Veteran control subjects.
- Obtain approval from all relevant IRBs and VA Privacy Office, so that recruitment and enrollment can begin.
- Prepare recruitment letter, brochure, response post card
- During the second half of the year, send mailings to large numbers of Veterans age 50-90 currently receiving compensation for TBI and PTSD occurred during Vietnam War and Veteran

controls who are neuropsychiatrically healthy. The first group of subjects to be enrolled will be those between 60-80 years of age. Those subjects between 50-59 years of age, as well as those over 80 years of age may be recruited later in the project if enrollment numbers are too low in the 60-80 age range.

- Between 6-12 months, or so after funding, the recruitment and enrollment of subjects will begin. All subjects will be identified by DOD and VA records, or will have responded to an advertisement in a media that caters to Vietnam Veterans, then contacted by mail, followed –up by telephone contact to explain the study. After the study explanation, verbal consent for the screening questions and the structured traumatic brain injury questionnaire will be obtained, and then the screening and TBI questions will be administered. If eligible, a written consent form for a telephone clinical interview, as well as a consent to audio-record the clinical telephone interview, and two self-report questionnaires on MRI safety and medical history, will be mailed to subjects.
- Study staff will call a few days after mailing to review the consent forms, answer any questions the subject has, and assist with the self-report questionnaires as necessary. If subject is interested in the study, staff will ask subject to sign the consent form(s) and return them along with the completed self-report questionnaires by fax or mail (in the stamped addressed envelope).
- After self-report questionnaires and written/consent form is received and reviewed, subjects will be called and told of their eligibility status. Eligible subjects will be referred to PTSD core for comprehensive psychiatric assessment, which involves a telephone administration of the SCID I for DSM-IV TR and Clinician Administered PTSD scale (CAPS). If the signed consent form to audio-record the clinical telephone interview is also received, the interview will be audio recorded. The recording will be stored by study code only in a locked file cabinet in a locked file room. Audio-recording is optional. Subjects who choose not to be audio recorded can still be in the study.
- Once the SCID/CAPS is received and reviewed for eligibility criteria, SFVAMC staff will call subject to let him/her know of the eligibility status. Those that are not eligible to continue to the in-person clinic visits will be thanked and compensated by SFVAMC for the time spent completing the telephone interviews and self report questionnaires.
- All eligible subjects will be thanked and SFVAMC will compensate for the time spent completing the interviews and self-report questionnaires, and will be subsequently referred to a nearby ADNI site. SFVAMC staff will give the subject the contact information of the selected clinic, and will call the clinic give the clinic site the subject contact information.
- Upon arrival at the ADNI sites, all subjects will have the complete standardized ADNI assessments, including medical/cognitive evaluation, lumbar puncture, blood testing, MRI, and amyloid PET Florbetapir F18 scanning. The subjects will be asked about the presence of all medical conditions and use of medications before MRI, lumbar puncture, or PET scan.

- This study will use much of the existing network of communication that exists for the Alzheimer's Disease Neuroimaging Initiative (ADNI) study, including the ADNI Data and Safety Monitoring Board (DSMB). If/when the Site Medical Doctors (MDs) and study coordinators have questions about any health related issues, they contact the central ADNI clinical core, and these issues are adjudicated.
- All patient data and telephone calls will be logged into a currently existing electronic capture system, modified for the study. All case report forms (CRFS) will be uploaded to the Alzheimer's Disease Cooperative Study (ADCS) database. The ACDS was formed in 1991 as a cooperative agreement between the National Institute on Aging (NIA) and the University of California San Diego. The ADCS is a major initiative for Alzheimer's disease (AD) clinical studies in the Federal government, addressing treatments for both cognitive and behavioral symptoms.
- All de-identified data will be available at the ADCS database, displayed at the Laboratory of Neuroimaging (LONI) website at UCLA without embargo. LONI is a leader in the development of advanced computational algorithms and scientific approaches for the comprehensive and quantitative mapping of brain structure and function.
- The San Francisco Veterans Affairs Medical Center (SFVAMC) site will maintain the protocol and consent templates, and any changes to these documents will be distributed to each study site as soon as they are locally approved.
- SFVAMC will be responsible for the mail effort, recruitment, and the telephone screeners and clinical interviews. There will be NO subjects seen on the SFVAMC campus. UCSF will be one of the ADNI sites. There will be subjects seen at the UCSF ADNI clinic and at the China Basin PET scan facility. The UCSF ADNI will be submitting their own IRB documents, using this master template for protocol and consent forms, as will the other participating ADNI sites.

**Year Two:**

- Continue and complete enrollment for baseline and begin 1 year (approximate) follow-up examination.
- For follow-up, all subjects will have repeat psychiatric assessment by telephone and return to the ADNI sites for repeat medical/cognitive evaluation, blood testing, and MRI. Due to budget restrictions there will be no follow-up Florbetapir F18 scans and no repeat of the lumbar puncture.
- All raw and analyzed data will be uploaded to the ADNI data center.
- The biostatistical core will begin data analyses on cross sectional results.

**Year Three:**

- Complete the 1 yr follow-up.
- Complete analysis of all data
- Data analysis/hypothesis testing by the biostatistical core continues and uses 1 yr longitudinal data.
- The biostatistical core together with the PI and study investigators completes analysis of data leading to abstracts and publications.

- ADNI publications committee monitors all proposed publication submissions from the grant investigators and outside investigators, to insure that the funding organizations and ADNI are properly credited.
- Final report submitted to DOD

## 8. Resources in Place to Conduct the Study:

This study will use much of the existing network of communication that exists for the Alzheimer's Disease Neuroimaging Initiative (ADNI) study, including the ADNI Data and Safety Monitoring Board (DSMB).

ADNI is a large multisite project funded by the National Institute on Aging (NIA) of the National Institutes of Health (NIH), the Alzheimer's Association and other nonprofit groups, and private industry (more than 20 corporate partners) through the Foundation for NIH (FNIH). The overall goal of ADNI is validation of imaging and biomarkers for AD clinical trials. ADNI was initially funded for \$60 million for 5 years, enrolled more than 800 subjects (200 controls, 400 MCI, and 200 AD subjects) in 57 sites throughout the US and Canada, and performed standardized longitudinal, clinical and cognitive [6,7], MRI [8], FDG-PET and PIB-PET [9], blood/cerebrospinal fluid biomarker [10], and genetics measurements [11,12].

More than 200 peer-reviewed publications have sprung from ADNI including special journal issues [13]. ADNI methods are used in many AD trials, and ADNI results were used to define the newly proposed research criteria for AD [14]. ADNI sparked similar studies in Australia [15, 16], Japan [17, 18], Europe [19], Taiwan, Korea, and China (known as World Wide ADNI [20]). ADNI subsequently received \$24 million in ARRA funds (for additional data analysis and to enroll 200 subjects with early MCI), and has recently been refunded by NIA and its partners for an additional \$69 million for the next 5 years in order to follow those subjects originally enrolled and to enroll an additional 550 subjects. The current ADNI uses clinical/cognitive tests, LP for CSF, 3T MRI, and Florbetapir PET [21-24] on all subjects.

This project will use the ADNI sites, ADNI methods, and the ADNI data collection and analysis infrastructure for this project concerning TBI and PTSD as risk factors for AD. Upon completion of the mail/telephone assessments, eligible subjects will be referred to the ADNI sites, and ADCS will coordinate all data capture. Upon arrival at the ADNI sites, all subjects will have the complete standardized ADNI assessments. The subjects will be asked about the presence of all medical conditions and use of medications. When the Site Medical Doctors (MDs) and study coordinators have questions about this, they contact the central ADNI clinical core, and these issues are adjudicated.

All de-identified data will be available at the ADCS database, displayed at the Laboratory of Neuroimaging (LONI) website at University of California, Los Angeles without embargo. LONI is a leader in the development of advanced computational algorithms and scientific approaches for the comprehensive and quantitative mapping of brain structure and function. The ADCS was formed in 1991 as a cooperative agreement between the National Institute on Aging (NIA) and the University of California San Diego. The ADCS is a major initiative for Alzheimer's disease (AD) clinical studies in the Federal government, addressing treatments for both cognitive and behavioral symptoms.

The San Francisco Veterans Affairs Medical Center (SFVAMC) site will maintain the protocol and consent templates, and any changes to these documents will be distributed to each study site as soon as they are locally approved.



**Study Personnel:**

For each of the ADNI clinic sites, as well as all activities at SFVAMC, there are essentially three staff functions – a clinician, a study coordinator, and a psychometrist that will be required to conduct this protocol. At most sites, this will require three persons. At some sites, two persons may suffice.

**Site Principal Investigator:** This person is responsible for ensuring that the local IRB approves the protocol and oversees all site activity for the study and ensures enrollment and protocol adherence. This person may also serve as the study physician.

**Site Study Physician:** This person is responsible for conducting or supervising the clinical evaluation of all participants, including physical and neurological examinations, reviewing adverse events, and interpreting laboratory results. The study physician will supervise project personnel and ensure that interviewers, psychometricians maintain a high level of skill and accuracy in conducting assessments.

**Site Study Coordinator:** This person will be responsible for managing the day-to-day conduct of the study, ensuring accurate administration of all instruments, maintaining online data and scheduling study procedures, processing laboratory samples, serving as liaison with the clinical monitor, and coordinating clinic visits. The study coordinator may perform several ratings, including the CDR. The ADAS-Cog rater must be a different person from the CDR rater. The Site Study Coordinator will act as the liaison with the SFVAMC Study Coordinator.

**Project interviewer/Psychometrician:** Each site will have at least one clinician to administer the clinic procedures. All Psychometricians will have experience and be fully trained in their assigned duties.

**SFVAMC Study Personnel:**

Michael W. Weiner M.D. is the Principal Investigator for this protocol. He will oversee all study activities and procedures at SFVAMC. He is the Director of the Magnetic Resonance Unit at the VA Medical Center in San Francisco, and Professor of Radiology, Medicine, Psychiatry and Neurology at UC San Francisco. He has published over 310 peer reviewed journal publications, of which 250 have been clinical MRI/MRS studies.

Dr. Thomas Neylan M.D. is the Director of the Posttraumatic Stress Disorders (PTSD) Program at the San Francisco Veterans Affairs Medical Center. He has been an active researcher in the study of sleep, neuroendocrinology, neuroimaging, electrophysiology, gene expression, and treatment of Posttraumatic Stress Disorder for the past 14 years. He has been the Principal Investigator on multiple funded projects sponsored by the National Institutes of Health, the National Institute of Justice, the Department of Defense, and the Department of Veterans Affairs. He will oversee the Clinical Telephone Interviews.

There is already an identified Study Coordinator at the SFVAMC with 20 years experience managing various multi-site research projects. Each ADNI site will also have experienced study coordinators overseeing the above study activities at the sites.

There will be a minimum of two recruiters/screeners and at least one mental health clinician at SFVAMC who will administer the clinical interviews. This person will have at least a bachelor's degree in health care psychology, social work or a related field, and/or well-documented experience in administering interviews and neuropsychological tests.

## 9. Study Sample

From the VA and military records, a sample of Veterans 50-90 years old who served in the Vietnam War and meet the criteria of each of the study groups, PTSD, TBI, and comparable controls will be obtained. Those subjects between 60-80 years of age will be selected first. Those between 50-59 years of age, as well as those over 80 years may be recruited later in the project should recruitment numbers be too low in the 60-80 year age range. Recruitment letters, brochures, and response post cards (with stamped and addressed envelopes in which to return the response postcard) will be mailed to thousands of men and women who meet the study criteria. After mailing the study materials, staff at the SFVAMC will call sample of subjects, explain the study, obtain verbal consent, screen, and then enroll eligible subjects.

Between 195 and 300 Veterans are expected to complete the full battery of assessments at the ADNI Sites.

- 65 - 100 TBI without PTSD or MCI/dementia
- 65 - 100 PTSD without TBI or MCI/dementia
- 65 - 100 Controls without TBI or PTSD or MCI/dementia, comparable in age, gender, and education to the TBI and PTSD groups.

Subjects with mild cognitive impairment (MCI)/dementia will be excluded. Rationale for this approach is that it's already established that 50-60 % of subjects w/MCI have AD pathology in their brain, and it may be difficult to detect added effects of a history of TBI or ongoing PTSD in MCI/demented subjects.

The Sample size of 65-100 Vietnam Veterans in each of the study cohorts is the estimate for how many subjects will successfully enroll and complete all study procedures. Our goal is to enroll and complete one year (as close to one year as possible) follow-up visits on a total of 210 subjects.

Given expected dropouts, we plan to enroll and complete all baseline measurements on 230 subjects. Based on our experience we believe that we will need to refer approximately 300 subjects to the ADNI sites (that is about 100/group).

To achieve this number of subjects who pass the screening examination and the SCID we plan to send out several thousand brochures and will be making many hundreds, perhaps thousands of telephone contacts. At the current time it is not possible to precisely identify the exact number of brochure mailings which will result in satisfactory responses leading to telephone contacts. Therefore our approach will be to begin with sending 1000 brochure mailings to veterans in the zip codes of the ADNI sites and then observe the response rate. If the response rate is high, then fewer additional mailings will be needed. If the response rate is low, we will increase the number of mailings until we achieve a satisfactory number of responses, so that during our follow-up phone calls we obtain a reasonable number of subjects who pass the screening telephone interview.

We also do not know the fraction of subjects who will fail to pass the SCID CAPS telephone interview. However since we are examining the VA and military records of the subjects prior to mailings, we are hopeful that we are targeting subjects who have histories of TBI or PTSD, or neither, and that we are able to exclude subjects with exclusionary criteria by examination of their records. In summary we approximate that 300 persons will come in for the in person visit, that 500 will undergo the clinical telephone interview, that 1000 subjects will undergo the screening interview, and that it will be required to mail 5000 brochures to obtain this number of interested veteran subjects.

## 10. Recruitment and Retention Overview

The Principal Investigator and the Study Coordinator at the SFVAMC have had communication with the office of the Under Secretary of Health to obtain authorization to obtain /view VA and DOD Compensation and Pension records. The information that will be collected from these records will not be re-disclosed except back to the VA, and will not identify any individual patient in any report or otherwise disclose any patient identities. Only the Study Coordinator and study recruitment staff at the San Francisco VA Medical Center will view these records for the sole purpose of identifying potential subjects. The Study Coordinator will be requesting a Waiver of Consent for Authorization for Recruitment.

Study subjects to be selected for the TBI and PTSD cohorts will have a diagnostic code which indicates that TBI or PTSD are probable, or will have received a combat action badge (ribbon for Marines), Purple Heart, Bronze Star or other decoration related to combat, and currently receive disability payments for these conditions. Control subjects will also be selected from VA and DOD records, but will have no history or current diagnosis of TBI or PTSD.

All subjects will be initially contacted by mail with telephone follow-up. After initial mailing, subjects will be contacted by telephone and the study explained and questions answered. After explanation, verbal consent will be obtained, and subject will be screened for eligibility and interest. Eligible subjects will be sent a written consent form. Upon receipt of documented consent, subject will be referred to the PTSD core at SFVAMC for a full clinical diagnostic interview and PTSD evaluation by phone. Subjects who meet criteria will be referred to an ADNI site near them (within a maximum of 150 miles, (though this could be increased if recruitment numbers are too low) for all other procedures.

SFVAMC regulations require all research records to be maintained indefinitely. The VA provides long-term secure storage of research records. All records will be kept, including those subjects who are found to be ineligible and/or refuse to take part in the study, all forms and data will be kept in secure locked file cabinets in a locked storage facility provided by the Veterans Affairs.

Several steps will be taken to assure the high follow up rate that is essential to the validity of the study results. All staff members will be carefully instructed regarding the need for an expectation of full follow up participation and the process of removing barriers to participation. At entry, each participant, and a study partner, if available, will be queried regarding plans to change residence or leave the area. Each participant will receive a thank you note following the clinical evaluation and a personalized greeting card on his or her birthday or on a major holiday, as well as a six month (approximate) follow-up phone call. Progress of the study will be placed in newsletters and distributed to the sites for distribution to subject participants.

Additionally, there is a planned outreach to help inform potential eligible subjects of the existence and importance of the project and to raise the overall awareness of Alzheimer's disease. There will be targeted messages in flyers, and in specific media that cater to Veterans, especially veterans of the Vietnam War. Along with the study brochures and press releases, there will presentations at various Veteran Service Organizations. There will also be an informational DVD explaining the project and the procedures involved.

All of our recruitment materials will have a telephone number and study website address so that respondents can either call or visit the website for more information about the study.

### **Summary of Recruitment and Eligibility Determination:**

- Recruitment letters will only be sent to participants who meet basic eligibility criteria of being a Vietnam veteran with or without PTSD or TBI from the VA Compensation and Pension records and DOD service records.
- Interest and eligibility will be further determined by the trained research associates at SFVAMC who conduct the Initial Screening by Telephone.
- Eligibility will be further determined by the trained clinical assessors who conduct the Clinical Psychological Interview by Telephone at SFVAMC.
- Eligibility will be further determined by the clinic staff at the participating ADNI sites who will further assess that participating in the clinic procedures will be safe for the subject.

### **Summary of Where and How Subjects are approached:**

- Vietnam veterans who meet the basic TBI, PTSD or Control criteria according to government records will be mailed a letter describing the study and asking them to call our screening center.
- Veterans who do not respond to the letter may be contacted directly by phone by our screening center staff.
- We may also place advertisements to which veterans can respond by calling our screening center. Ads will be placed on Craigslist, in newspapers, or in veterans' newspapers, magazines or websites. Flyers may also be posted at study sites.
- Study staff may conduct outreach at veterans' events, or within veterans' organizations.

### **Compensation for Subjects:**

Subjects MAY be reimbursed for time spent completing the various study procedures in both the initial and the follow-up study years depending on a subject's eligibility, as well as the successful enrollment and completion of study procedures. Some travel costs may also be included. Because each clinic site will have its own human subjects' review board, each site may compensate the subject for successfully enrolling and completing in-person clinic procedures depending on each site's regulatory protocols regarding subject compensation.

SFVAMC will reimburse subjects at a rate of \$30 per hour for the time spent completing the telephone screener, the telephone clinical interview, and the self-report questionnaires in both the initial and the follow-up study years. Depending on a subject's eligibility, and the successful completion of these SFVAMC tasks, subjects may earn between \$15 and \$135 for time spent (30 minutes - up to 4 hours of time, or so) for both year one and year two.

Time **estimate** for the screening interview is 30-60 minutes, or so, the telephone clinical interviews are approximately 1-3 hours, and the self report questionnaires is 15-30 minutes, or so. Therefore the maximum amount a subject may earn for completing tasks for SFVAMC is \$15-\$135 for year one and \$15-135 for year two - for a total of \$30-\$270 total.

A check will be mailed about 6 weeks after subject completes the SFVAMC interviews for which he/she was eligible. In order to receive payment for the SFVAMC tasks, the subject must provide a social security number.

**Inclusion and Exclusion Criteria:**

These Items are fully discussed on pages 12-16.

**11. Study Procedures at SFVAMC:**

This is a non-randomized natural history non-treatment study.

**Records Search**

Using military and Veterans Affairs (VA) Compensation and Pension records, SFVAMC will identify Vietnam War Veterans with well documented history of moderate/severe Traumatic Brain Injury (TBI) or evidence of ongoing Post Traumatic Stress Disorder (PTSD), and comparable Veteran controls. Subjects meeting criteria for mild cognitive impairment or dementia will be excluded.

**Mail Effort**

Once subjects are identified, SFVAMC will mail out invitation letter, brochure, and response postcard (a stamped addressed return envelope will be included for the subject to use to return the postcard) to large numbers of Veterans who meet above broad criteria (based on diagnostic codes in military and VA Compensation and Pension records), and who live within 150 miles of closest ADNI clinic in subject's area. Selected sites will have the General Electric Diffusion Tensor Imaging / Magnetic Resonance Imaging [GE/DTI MRI] scanner). The mileage distance from the clinics may be extended if the recruitment numbers are low. The timing of the mail out effort to the geographic location of a selected ADNI site will only occur once the specific site has obtained full human subjects approval from both their agency review boards as well as the Department of Defense (DOD).

**Initial Telephone Contact & Verbal Consent for Screening**

SFVAMC will contact subjects by telephone – contact those that have returned the response post card, as well as those who have not. Interviewers will explain the study and answer any questions the subject may have. All interviewers/recruiters are trained in structured interviewing of sensitive questions, and in following research protocols.

- a. Obtain verbal consent to administer screening and TBI questionnaire over the telephone.
- b. Administer screening and TBI questionnaires to determine eligibility criteria to be enrolled in the Psychiatric Assessment (Clinical Interview) part of the study, using the Structured Clinical Interview 1 of the Diagnostic and Statistical Manual of Mental Disorders, Version IV, (Axis 1) - Text Revision (SCID 1 of the DSMIV-TR) and the Clinician Administered PTSD Scale (CAPS) which will be audio recorded for quality control purposes. Audio recording is optional. Subjects who choose not to be audio recorded can still be in the study.
- c. Determine if subject has a study partner. If subject has a reliable study partner, and is found to be eligible after completing the screening and clinical interviews, the partner will be asked to accompany the subject to the clinic visits. Study partners are helpful in confirming memory problems if they exist. However, because many subjects may not have a regular person in their life who can act as a study partner, a study partner is not required for this study.
- d. The screening questions will be an adapted version of the AD8 assessment (70, 71) and will also include some of the questions of the Clinical Dementia Rating (CDR). For this study, subjects with mild cognitive impairment (MCI)/dementia may be screened depending on the answers to the screening questions. The Study Coordinator will discuss subject responses to

- the Subject Matter Experts to assess whether or not the memory issues are exclusionary. Questionable items will be discussed among the clinical core investigators to assess who will be screened out.
- e. At completion of the telephone screener, subjects will be told whether or not they are eligible to be referred to the clinical telephone interview, or if some of their responses need to be discussed with the study doctors. (Some answers to the screening questions will be discussed with the clinical leaders of the study to assess whether there are any exclusionary criteria present, such as MCI/dementia psychological disorders, alcohol or substance abuse, etc.). After the discussion with study doctors, subject will be called back and invited to continue, or will be thanked and compensated for the time spent in study thus far.

## **Documented Consent for Clinical Interview, Audio-Recording & Self Report Questionnaires**

- a. If after the screening interview, subject is eligible for the SCID/CAPS, SFVAMC staff will mail a written consent form w/ stamped addressed return envelope to the home of the subjects along with two self-report questionnaires on MRI safety and medical history, as well as a consent form for audio-recording.
- b. In a few days, Study staff will call the subject to make sure that subject received the consent forms, will go over the consent forms with the subject, answer any questions the subject may have, and assist with the self report questionnaires if needed. Subject will be asked to sign the consent forms and mail them back to SFVAMC in the stamped addressed envelope along with the completed self-report questionnaires.
  - The SCID/CAPS cannot be administered without first receiving the signed consent form for the clinical interview.
- f. The SCID/CAPS cannot be audio-recorded without also receiving the signed consent form giving permission to audio record. Audio recording is optional. Subjects who choose not to be audio recorded can still be in the study.
  - If the consent to audio -record the SCID/CAPS is received, SCID/CAPS will be recorded and the tape will be stored and filed by study code number only, in a locked and secure file in a locked and secure room.

## **Clinical Interview**

- a. As soon as the signed consent form(s) are received back at SFVAMC, by mail or fax, the questionnaires will be reviewed and if eligible, subject will be referred to the PTSD core at SFVAMC for the Clinical Interview which will be administered by a trained and experienced clinician.
- b. Because the project is only enrolling subjects without MCI/dementia, a study partner if available will never act as a surrogate for the subject. All subjects will consent for themselves. A study partner is NOT a requirement for this study.
- c. PTSD core (at the SFVAMC) will call the subject and perform the Structured Diagnostic Interview I for DSM-IV-TR & Clinician Administered PTSD Scale (CAPS) by telephone. If a signed consent for audio recording has been received along with the signed consent for the clinical interview, this interview will be audio recorded for quality control purposes, to ensure that the interview is administered in a consistent manner. The tape will be filed and stored by study code only in a secure locked file system in a locked file room. Audio-recording is optional. Subjects who choose not to be audio recorded can still be in the study.

- d. If after clinical telephone interview, the subject is still eligible, SFVAMC staff will refer subject to local clinic in network of Alzheimer's Disease Neuroimaging Initiative sites (ADNI).

### **Additional Self Report Questionnaires to be Mailed**

- a. SFVAMC staff will mail a packet of self-report questionnaires to subject, with instructions for subject to complete and bring completed packet to his or her first in-person clinic visit.
- b. For this study, SFVAMC will handle the recruitment and telephone screening and telephone clinical interviews. If after the telephone interviews, subjects are still eligible for an in-person clinic visit, then subjects will be referred to the nearest ADNI clinic.

## **12. Study Procedures at the ADNI clinic sites:**

Trained and experienced clinicians will call the subject, answer any questions the subject may have, and then set up an appointment to come to the clinic. On the first appointment day the clinician will go over the consent form with the subject and obtain documented consent for the project as a whole, and also specifically for the collection and storage of DNA, RNA, and cell immortalization.

### **Initial Evaluation /Medical Exam/Cognitive Tests:**

- A trained and qualified clinician will:
- Explain study, answer questions, obtain consent of subject and (if available) a study partner.
- Review the self administered questionnaires for any exclusionary items
- Obtain medical history and record any and all medications subject is taking
- Take blood pressure, pulse, temperature, and record height and weight.
- Collect a urine sample
- Administer cognitive tests which will include tests of daily functioning, behavioral tests, as well as questions about whether or not subject has any current or past depression.

Both the medical exam and the cognitive/functioning tests will help to ensure that there are no medical conditions that might interfere with subject's participation in the study, or that could be responsible for any changes in subject's condition throughout the study period. If any of these test results show that subject is not eligible to continue, subject will not be able to complete the study.

### **Autopsy Discussion**

ADNI staff will also discuss autopsy with subject. An ADNI clinician will lead a discussion about autopsy with all subjects at their initial assessment (study partners and families are welcomed in the discussion). There are 3 objectives of the discussion:

- To convey information about the value of brain autopsy in confirming the clinical diagnosis and advancing knowledge regarding mild cognitive impairment and Alzheimer's disease;
- To initiate consideration of the individual's wishes concerning an autopsy; and
- To answer questions, misconceptions, or concerns about autopsy. The involvement of the physician in these discussions emphasizes the importance of autopsy.
- There is no pressure on an individual to decide; they are encouraged to involve family members, clergy, physicians, or other appropriate persons in their decision-making.

- Participants are assured that a decision not to have an autopsy in no way jeopardizes their research participation or any other patient rights.
- It is important to note that autopsy will not interfere with funerary arrangements nor will it be a financial burden to the participant's family.
- Subjects will be asked to sign whether or not they are interested in considering autopsy at the time of death, and will be told that study personnel will ask permission from the next of kin. Therefore, subjects are encouraged to let their next of kin know their wishes.

### **Magnetic resonance Imaging (MRI) Scan:**

Because MRI will be performed at 3 Tesla, all subjects will be assessed at the ADNI sites for the presence of disqualifying metal objects in the body. People with pacemakers, aneurysm clips, cochlear implants, or certain other metal /foreign objects in the body are not permitted to undergo MRI studies. All participants will be assessed using a standardized checklist of body parts including head, neck, chest, abdomen and pelvis, arms and legs. A thorough physical exam will be performed at the ADNI sites, and any scars which might indicate entry wounds (where metal may be located) will be noted. All participants will also be assessed using a portable magnetic screening wand that detects ferromagnetic objects. Examination for tattoos will also be performed.

An MRI is an electronic picture of the brain created using a strong magnet instead of x-ray energy. Subject will lie on his or her back and enter the MRI machine. Subject will hear a series of loud knocking noises. There are no known biological risks from MRI. For this study no contrast agent will be used.

There is a slight risk of anxiety due to claustrophobia and noise. Any subject who experiences anxiety when placed into the MR scanner will be removed from the scanner, offered reassurance by the MR tech doing the scan, and offered the option of continuing or terminating the study. If the subject decides that the anxiety associated with MRI is uncomfortable for them and they wish to terminate the scan, then the examination will be ended at that time. There will be no attempt to coerce subjects to complete exams that they are uncomfortable with.

Sedation during the baseline MRI scan is not offered for this protocol. Subjects that are uncomfortable with MRI scans should not be included in this study. If a subject is uncomfortable with MRI and refuses to complete the scan without sedation, the study coordinator will be contacted at ADCS ADNI who will consult with the MRI Core. Exceptions may be granted on a case-by-case basis to allow the use of sedatives for MR scans at the follow-up visit.

### **Magnetic Resonance Imaging (MRI) Qualification: *Site Qualification***

Each site must be qualified for MRI. If the machine being used has already been certified by the ADNI MRI Core and has not experienced any software upgrades, re-qualification will not be required. The procedures for site qualification will be identical for 1.5T and 3T scanners and consists of two parts – phantom and human scanning.

In terms of human scanning, each site will image a volunteer subject with the protocol and send the images to LONI. Each parameter in each of the pulse sequences in the protocol will be checked at Mayo. In the event that the protocol has not been performed according to protocol, the site will be asked to perform another human volunteer scan. This will be repeated as many times as necessary until the site has demonstrated exact execution of the MR protocol in a volunteer subject, at which point they will have



passed the human scanning portion of MR site qualification. The volunteers do not need to be elderly controls; in fact scanning for site qualification may be more easily performed with normal younger volunteers. In the event that repeat attempts are needed, repeat scans need not be on the same volunteer subject. Once a site has demonstrated perfect execution of the protocol, the protocol will be stored permanently on the scanner at that site that will be used in the study.

### **Positron Emission Tomography (PET) Scan:**

The PET scan will measure  $\beta$ -amyloid in the brain. B-Amyloid is a protein that is found in the brain in patients with Alzheimer's disease. In this study, brain amyloid will be measured using PET with a radioactive substance, called Florbetapir F18. Blood pressure, pulse, respiration rate, and weight will be recorded before the scan. A small amount of the Florbetapir F18 (10mCi) per procedure will be injected in a vein in the arm. After about a 50 minute waiting period, the subject will be positioned in the PET scanner to take pictures for approximately 20 minutes. During this time, subject must hold head as still as possible.

Current ADNI activities involve the acquisition of amyloid PET images using the radiotracer [18F] AV-45, now known generically as Florbetapir F 18 [21-24]. This tracer was selected for ADNI2 for several reasons, including its long half-life relative to the short 20-min half-life of [11C] that permits delivery to all current ADNI sites. Furthermore, Florbetapir F 18 distribution in the living brain has been shown to correlate well with the presence of amyloid plaques, and the pathological criteria for AD after the same brains were studied pathologically [21-24].

Because the drugs in this study can affect a fetus, pregnant women may not participate. Women of childbearing age will receive a urine test for pregnancy on the date of the Florbetapir F18 scan. Given that the selected age of subjects will be 50-90, it is unlikely that many pregnancy tests will be needed.

### **Procedures for assuring scan quality:**

Involve the following and will be performed on all human PET scans.

- Download all PET data sets from Laboratory of Neuroimaging (LONI) website at University of California, Los Angeles. LONI is a leader in the development of advanced computational algorithms and scientific approaches for the comprehensive and quantitative mapping of brain structure and function.
- Convert raw Image data to store on local computer.
- Raw Image Quality Control (QC) Process
  - Visual inspection of all images: including both frames (temporal) and planes (spatial).
  - Extract and inspect all header information, and check versus required scan protocol.
  - Co-register (six degrees of freedom, rigid-body) all frames to first frame of the raw dynamic image set. Assess subject motion by magnitude of translation and rotation parameters.
  - Recombine co-registered frames to create both registered dynamic and registered average (averaged over all frames) image sets in native image geometry and orientation.
  - Determine image quality metrics (global correlation, global mean square error, global absolute error) both between frames on raw dynamic image data sets both pre- and post-

co-registration. This includes comparisons between all frames pairs (e.g. 15 comparisons for a 6-frame study).

- Inspect PET scan information form completed by site for each scan. Note errors and correct.
  - Complete PET Quality Control (QC) form (e.g. pass, fail with reprocessing, fail with rescan, fail without rescan).
- In the event that the scan fails the quality control procedure and cannot be used, we will repeat the Florbetapir scan. In ADNI to date, less than .5% of scans require repeat.

### **Positron Emission Tomography (PET) Scan: *Site Qualification***

Each site must be qualified for PET. If the machine being used has already been certified by the ADNI PET Core and has not experienced any major software upgrades, re-qualification will not be required. Qualification of the PET scanner applies to 18F-AV-45 Amyloid imaging protocols. Qualification will employ the same methods utilized for site qualification in ADNI. Sites will be provided with a Hoffman brain phantom (if one is not available to the site) and a technical manual for the data acquisition using 18F.

The phantom must be scanned using the protocol identical to that required for human imaging. This enables the PET Core to ascertain the characteristics of the scanner (particularly resolution and uniformity) and assure that sites are capable of performing the protocol for acquisition and image reconstruction. All phantom images will be forwarded to PET Core QC group for review and qualification.

IRB approval at the site level is required prior to doing the volunteer scan.

### **Computed Tomography (CT) Scan**

Subject may also have a computerized x-ray (CT scan) or another type of PET scan (transmission scan) to correct PET images for photon attenuation. After the scans are completed subject will be asked to drink fluids and empty the bladder.

Subject should not receive research PET scans if he/she has received radiation therapy, or has been in another research study involving radiation, or if subject is pregnant. Staff will call to check on subject 1 or 2 business days following procedure.

### **Lumbar Puncture (LP):**

A lumbar puncture is a procedure in which a small amount of the spinal fluid that surrounds the brain and spinal cord is removed by inserting a needle in the lower back. All samples will be collected in the morning before breakfast and after an overnight fast or after 8 hours with no food. The ADNI-preferred method for obtaining CSF is lumbar puncture with a small caliber atraumatic needle (22 gauge Sprotte needle) and collection by gravity into a labeled polypropylene container. To clear any blood from minor trauma associated with needle insertion, the first 1-2 mL of CSF are discarded (or more if needed) to eliminate blood, and then 20 mL of CSF are collected from each patient for use and treatment in the following manner:

The first 2 mL will be used for standard tests such as cell counts, glucose, and total protein with determinations done at local laboratories. The remaining CSF will be collected into labeled polypropylene collection tubes and transferred to labeled polypropylene shipping tubes as outlined in the Procedures manual. CSF is frozen upright on dry ice for at least 20 minutes before being packaged along with the frozen plasma and serum. CSF samples are shipped frozen on dry ice, on the day of collection, if possible, via Federal Express overnight delivery to the Penn AD Biomarker Fluid Bank Laboratory. The day after the Lumbar Puncture each study participant or a person designated to speak for them will be contacted by phone 24 hours after the Lumbar Puncture to confirm the participant's well-being and query about any new adverse events.

### **Blood Draw & Genetic Testing: DNA, RNA, Immortalized Cell Lines:**

A small blood sample, approximately 35 milliliters (7 teaspoons) of blood will be drawn from a vein in the arm. Subject will be asked to NOT eat or drink anything (water is OK) for at least 8 hours before the blood draw visit.

Researchers will perform a genome wide association study (GWAS) that surveys markers through the human genome to discover or validate relationships with AD, aging or other health conditions as well as routine tests.

**Deoxyribonucleic acid (DNA)** will be extracted from subject's blood sample for a variety of type's genetic research and to assess Apolipoprotein (ApoE) gene type. There is evidence that ApoE gene type may influence the rate of AD disease progression or a subject's response to treatment.

**Ribonucleic acid (RNA)** will be extracted from the blood sample. RNA helps to study the activity of genes.

**Immortalized Cell Lines** will be developed from blood cells that will allow researchers to continue to study genes for many years.

**Storage of DNA, RNA & Cell Line Samples:** Subjects will be asked to agree to the storage and sharing of their DNA, RNA, and immortalized cell line data or samples, so that important research can be done in the future. This research is expected to include complete analysis (sequencing) of their genetic information and new types of analyses that are just being developed which will utilize the latest molecular and technology resources to identify genes influencing the risk for late onset AD and the age-at-onset of disease.

Data will be stored in a secured database and de-identified data will be sent to the National Cell Repository for Alzheimer's disease. DNA and cell lines will be stored at the National Cell Repository for Alzheimer's disease (NCRAD) at Indiana University School of Medicine in Indianapolis, Indiana. In addition to the blood sample, year of birth, family history of dementia, and diagnosis will be sent to NCRAD. DNA and associated clinical and demographic data will be made available to qualified and approved researchers studying the genetics of AD, aging, and related disorders. If the participant agrees, his/her de-identified samples and data will be made available to investigators studying the genetics of any human disease on a secure password protected National Institutes of Aging (NIA)/National Institutes of Health (NIH) or another NIA approved website. Identity of participants will not be shared with NCRAD or with any investigators. .

NIA may distribute, through National Institute of Aging Genetics of Alzheimer's Disease Data Storage (NIAGADS) at the University of Pennsylvania, any and all Genetic Analysis Data and Associated Phenotypic Data to others and to use it for its own purposes. NIAGADS may also make available upon request from NIA, genetic data to be deposited at an NIH database which will continue to ensure the privacy and confidentiality of the individuals that participated in the original genetic association studies.

The subject will be informed that he/she can withdraw from the study at any time, and that his/her samples will be destroyed if that is the participant's wish; however, subject will also be informed that investigators won't be able to pull back any data that was generated before they withdrew. Additionally, Subject will be told that he/she may request that demographic and clinical data and any unused sample be destroyed. However, data and samples that have already been distributed to approved researchers will not be retrieved.

After a subject's death, if the next of kin agrees to a brain donation/Autopsy, DNA and RNA can be extracted from the autopsy specimen for a variety of genetic and related studies. The specimen must be 3-5 grams of frozen cortex. Fixed tissue will not be accepted. Over the years, AD researchers have been encouraged by National Institute on Aging to utilize the latest molecular and technology resources to identify genes influencing the risk for late onset AD and the age-at-onset of disease. This protocol revision now includes the use of whole genome technologies to accomplish this goal.

### **Plasma / Serum / Buffy Coat for Biomarkers:**

All samples will be collected in the morning before breakfast and after an overnight fast.

Plasma is collected in a uniform fashion using EDTA as anti-coagulant. Blood is collected into two 10 mL EDTA plastic tubes, mixed thoroughly, then centrifuged. Plasma is aliquoted into labeled polypropylene vial, frozen on dry ice and then shipped overnight to Penn AD Biomarker Fluid Bank Laboratory.

Serum is obtained after allowing the samples collected in two 10 mL plain red top plastic tubes to clot at room temperature, then centrifuged. Serum is aliquoted into labeled polypropylene vial, frozen on dry ice and then shipped overnight to Penn AD Biomarker Fluid Bank Laboratory.

Buffy coat is to be extracted from the 2 lavender-top EDTA tubes that are used for the biomarker lab blood draw at baseline and month 12. Using sterile gloves and a sterile pipette, extract the buffy coat from one of the lavender-top EDTA tubes and aliquot it into one of the 2mL cryogenic vials. Repeat this process for the second lavender-top EDTA tube and the remaining, empty 2mL cryogenic vial. Both cryogenic vials are to be shipped to NCRAD.

### **Twelve Month (approximate) Follow-up:**

There will be an approximate 12 month follow-up for this study. In attempt to retain subjects, the SFVAMC staff will mail thank you letters, holiday and/or birthday cards, and make a telephone call around 6 months to remind subjects of the 12 month (approximate) follow-up.

Those subjects who have completed the procedures at the ADNI clinic are eligible for the 12 month (approximate) follow-up screener. At about 6 months, SFVAMC staff will call each subject to remind them of the 12 month (approximate) follow-up screener

The follow-up screener, follow-up clinical telephone interview, and follow-up self administered questionnaires will be identical to the baseline questions, but will only reference the time period since the last baseline clinic visit. The follow-up screener will not be screening anyone out of the study, but will help us determine whether anything has changed since the last clinic visit that may make a particular procedure unsafe, and to determine that the subject is still willing and able to participate. Mild Cognitive Impairment/dementia at the time of the follow-up procedures will NOT be exclusionary, unless it would be unsafe for the subject to participate. With the exception of the lumbar puncture and the PET scan, all procedures at the clinic sites will be repeated at the follow-up visit unless there are specific health reasons that may make it unsafe for the subject to participate (for example, new metal implants).

### 13. Time Commitment

Depending on eligibility and whether or not subjects complete tasks, subject could spend:

#### Baseline Year 1:

- Initial Screening Interview: 30-60 minutes, or so
- Self-Report Questionnaire: 30 minutes, or so
- Clinical Interview: 1-3 hours, or so
- Clinic Visits: about 5-8 hours (over 2-3 days or so, spread over a few weeks), or so

**Total for Year 1: 7-13 hours (approximate)**

#### Follow-Up Year 2:

- Follow-up Screening Interview: 30-45 minutes, or so
- Follow-up Self-Report Questionnaire: 30 minutes, or so
- Follow-up Clinical Interview: 1-3 hours, or so
- Follow-up Clinic Visits: 3-5 hours (over 1-3 days or so)

**Total for Year 2: 5-9 hours (approximate)**

**Total for BOTH Years: 12- to 22 hours (approximate)**

#### **OVERVIEW:**

#### ***Initial Telephone Screening by SFVAMC staff***

Mail out recruitment packet → Contact by phone → Explain Study, Obtain Verbal Consent → Screen for TBI and other exclusionary measures. → If eligible, send written consents and self report questionnaires → When written consent and questionnaires received and reviewed, refer eligibles to PTSD core for SCID/CAPS ↓

***Initial Psychological Assessment (over telephone) by PTSD Core & SFVAMC***

Contact subject for possible phone interview after receiving written consent → Administer SCID/CAPS → If eligible, mail out self – report questionnaires and refer to ADNI site ↓

***Base line ADNI Site Visit (at closest ADNI clinic) - Within 30 days to 4 months of referral, if possible.***

ADNI Site contacts subject within 30 days -4 months of receiving referral, (if possible) → schedule appointment, explains study, obtain written consent → administer clinical/cognitive battery → Blood Draw → Lumbar Puncture → MRI → PET Scan → Discussion of autopsy ↓

***Telephone 6 and 12 Month Follow-up by SFVAMC staff + 12 Month Psychological Assessment (Times are meant to be approximate, not absolute)***

SFVAMC and ADNI sites will follow-up with subjects with Thank you cards, holiday, birthday cards, and an approximate 6 month follow-up call. Around 12 months or so, SFVAMC will contact subject again re-administer screening questions, if still willing and able, refer for follow-up SCID/CAPS ↓

**One Year Follow-up at SFVAMC and ADNI site:**

If after SCID/CAPS subject is still willing and able → refer to in-person clinic visits and administer follow-up clinical/cognitive battery → Blood Draw → MRI. All procedures will be repeated with the exception of the PET and the LP.

**14. List of Assessments that SFVAMC Will Conduct on Telephone**

Measures obtained on all subjects by Evaluators on the Telephone at the San Francisco Veteran's Affairs Medical Center (SFVAMC):

***On telephone at time of screening, by SFVAMC:***

- **Verbal Consent Screener**

Structured interview to document history of traumatic brain injury including military associated injury, as well as all other episodes; Also questions of mental health, substance use, and questions to assess level of cognitive functioning.

*On telephone at time of Clinical Interview, by PTSD core at SFVAMC:*

- **Structured Clinical Interview for SCID-I DSM-IV, Non-Patient edition (SCID-NP), [41]):**

The SCID-I NP is a structured diagnostic interview protocol for the determination of DSM-IV diagnoses.

- **Clinician Administered PTSD Scale (CAPS, [40]):**

The CAPS provides both a dimensional and categorical measure of PTSD. CAPS will determine lifetime and current PTSD. The CAPS measures frequency and magnitude of PTSD-related symptoms.

- **Life Stressor Checklist - Revised (LSC-R):**

Structured clinical interview for lifetime exposure to stressful life events [42]: This structured clinical interview for lifetime exposure to stressful life events will be used to characterize the type of trauma exposure and age of occurrence(s) of different traumas in all subjects.

## 15. List of Assessments SFVAMC Will Mail to Subjects

- **MRI Safety Checklist (mail before SCID/CAPS)**
- **Medical History Questionnaire (mail before SCID/CAPS)**
- **Symptom Check-List-90-Revised (SCL-90-R, [43]) mail after SCID /CAPS):**

The SCL-90-R is a standard self-report measure of general psychopathology.

- **Pittsburgh Sleep Quality Index [44] (mail after SCID/CAPS):**

This self-report measure provides a subjective assessment of sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances (including nightmares), use of sedative-hypnotics, and daytime energy. This widely-used index will be used in exploratory analyses to examine the effect of sleep quality on specific brain regions (e.g. CA3/dentate [45] and cognitive performance).

- **Smoking/Lifetime smoking (mail after SCID/CAPS):**

Will be assessed using two measures: 1) Smoking status [46] is a two-question categorical measure employed by the Centers for Disease Control and Prevention National Health Interview Survey, and categorizes individuals into one of three groups: (a) “Never smokers”, adults 18 or over who have smoked fewer than 100 cigarettes in their lifetime; (b) “Former smokers”, adults who have smoked at least 100 cigarettes in their lifetime but are not smoking at time of interview; and (c) “Current smokers”, adults who have smoked at least 100 cigarettes over their lifetime and who are still smoking at time of interview; 2) Number of pack years [199] is a two-question continuous measure of smoking that utilizes the number of cigarettes per day multiplied by the number of years of smoking to calculate pack years of smoking.

- **Addiction Severity Index Lite (ASI-Lite) (mail after SCID/CAPS):**  
Alcohol use and non-alcohol substance use; Alcohol and non-alcohol substance use will be assessed using portions of the Addiction Severity Index Lite (ASI-Lite) [48, 49]. The ASI-Lite Composite Score for Alcohol Use will provide past month alcohol use severity and the ASI-Lite number of years of alcohol use will provide a marker of lifetime alcohol use. The ASI-Lite Composite Score for Drug Use will provide past month non-alcohol substance use severity, and the ASI-Lite number of years of drug use will provide a marker of lifetime non-alcohol substance use. The ASI-Lite is a valid and reliable standardized research interview to assess the occurrence and severity of alcohol and non-alcohol substance abuse. The ASI-Lite includes questions about the frequency, duration, and severity of problems over the subject's lifetime and in the past 30 days.
- **SF-12 Health Survey (SF-12) [50] (mail after SCID/CAPS):**  
This is a brief inventory measuring functional status in 6 domains and measuring global daily functioning. Published normative age-adjusted means for each domain and a global functioning score were derived from US residents.
- **Combat Exposure Scale (CES) [51] (mail after SCID/CAPS):**  
This is a brief but reliable and valid 7-item Combat Exposure Scale to quantify the subjective report of wartime traumatic stressors experienced by combatants in the Vietnam War.

## 16. List of Assessments Conducted by Local ADNI Site:

Upon arrival at the ADNI sites, all subjects will complete the standardized ADNI assessments. The subjects will be screened and tested for conditions which might affect cognition including B12 and TSH. The subjects will be asked about the presence of all medical conditions and use of medications. Subjects with medical conditions or taking medications which are judged to affect cognition will be excluded.

### **Cognitive, Behavioral, Functional, and Global Assessments:**

The tests and scales chosen for use in this protocol represent the ADNI battery to take fullest advantage of the APOE genotype, amyloid and AD trajectories of decline as a reference for interpretation of the data from this study. ADNI measures were themselves selected because: (1) they represent the domains of interest in the aging population at risk for AD; (2) they will adequately sample cognitive domains of interest in subjects who are cognitively normal (CN), have MCI or AD; (3) they can measure change over two to three years in these patient populations; (4) subjects enrolled will not demonstrate floor or ceiling effects; (5) they are reasonably efficient and can meet the practical demands of the ADNI as well as this proposed study. The measures are briefly described below.



- **Montreal Cognitive Assessment (MoCA) [52]:** The Montreal Cognitive Assessment test (MoCA) is a brief cognitive assessment designed to detect subjects at the MCI stage of cognitive dysfunction.
- **Everyday Cognition (ECog).** This instrument is an informant-rated questionnaire developed to assess functional impairment of a very mild nature as can be seen in MCI. Results of ECog suggest that it is a useful tool for the measurement of general and domain-specific everyday functions in the elderly. The performance of the ECog will be followed to determine its ability to differentiate among the three cognitive groups.
- **Mini-Mental State Exam (MMSE) [53]:** The MMSE is a fully structured screening instrument frequently used for Alzheimer’s disease drug studies. The scale evaluates orientation, memory, attention, concentration, naming, repetition, comprehension, and ability to create a sentence and to copy two overlapping pentagons.
- **Alzheimer’s Disease Assessment Scale-Cognitive (ADAS-COG 13 [54]:** The ADAS-COG is a structured scale that evaluates memory (word recall, word recognition), reasoning (following commands), language (naming, comprehension), orientation, ideational praxis (placing letter in envelope) and constructional praxis (copying geometric designs). Ratings of spoken language, language comprehension, word finding difficulty, and ability to remember test instructions are also obtained. .
- **Logical Memory Test I and II (Delayed Paragraph Recall) [55]:** The Logical Memory test that will be used is a modification of the episodic memory measure from the Wechsler Memory Scale-Revised (WMS-R) [55]. In this modified version, free recall of one short story (Story A) that consists of 25 bits of information will be elicited immediately after it is read aloud to the subject and again after a thirty-minute delay.
- **Boston Naming Test [56]:** This measure of visual confrontation naming requires the subject to name objects depicted in outline drawings.
- **Category Fluency Test [57]:** This is a measure of verbal fluency in which the subject is asked to generate examples from the semantic categories (animals) in successive one-minute trials. The primary performance measure is the number of correct, unique examples generated. Perseveration (repetitions of a correct item) and intrusion (non-category items) errors are also noted.
- **Clock Drawing Test [58]:** In this visuoperceptual constructional task, the subject is given a blank sheet of 8 ½” x 11” paper and instructed to “Draw a clock, put in all of the numbers, and set the hands for 10 after 11.” After that task is completed, the “copy” condition ensues in which the subject attempts to copy a drawing of a clock with the hands set at ten past eleven.

- **American National Adult Reading Test (ANART): [59]** The ANART is a method for estimating premorbid verbal intelligence (VIQ) in demented patients based upon their ability to read words aloud, a skill that is thought to remain relatively preserved until the later stages of Alzheimer's disease [60].
- **The Auditory Verbal Learning Test:** will be used to assess memory function in normal subjects and has been used extensively in all ADNI protocols [60]. This test has an extensive normative database and has been used in many Alzheimer's Clinics and population-based studies of aging [61]. Since it is a more difficult memory test than others, it is useful in identifying individuals at risk for AD.
- **Trail making A and B:** are measures of attention, cognitive flexibility and executive function [62]. It has been used for decades and is included in ADNI. It was originally developed for military purposes and has an excellent track record while being efficient to administer.
- **Clinical Dementia Rating (CDR) [63]:** The CDR describes five degrees of impairment in performance on each of 6 categories of cognitive functioning including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care.
- **Activities of Daily Living | Functional Assessment Questionnaire (FAQ) [64]:** Based on an interview with a study companion or qualified partner, a subject is rated on their ability to carry out ten complex activities of daily living.
- **Neuropsychiatric Inventory (NPI) [65]:** The Neuropsychiatric Inventory (NPI) is a well-validated, reliable, multi-item instrument to assess psychopathology in AD based on an interview with a study companion or qualified partner.
- **Geriatric Depression Scale [66]:** The Geriatric Depression Scale (Short Form) is a self-report scale designed to identify symptoms of depression in the elderly. The scale consists of 15 questions that the subject is asked to answer yes or no on the basis of how they felt over the past week.
- **Armed Forces Qualification Test (AFQT)/Army Classification (ACT):** Preinjury intelligence is a strong predictor of long term decline in many cohorts including those with Traumatic Brain Injury among these variables [25]. Preinjury intelligence [67, 68] can be estimated by the Armed Forces Qualification Test/Army Classification Test which was administered prior to the completion of basic training. As part of the ADNI cognitive battery these exact same tests will be re-administered to the subject and the difference in score of these tests will be used as a major dependent variable in data analysis. The AFQT and ACT will be used as 1) measures of cognitive reserve; 2) the change in the score from its original use in Basic Training to the time of the study will be used as an important outcome measure to test hypotheses.

## 17. Risks

All of the study procedures are well-established test methods, involving minimal discomfort, though there could be some risks or discomforts from being in the study. Possible risks for each procedure are discussed

**Initial Screening and Clinical Interview:** The screening and interview questions may be distressing to some participants. It is possible that being asked questions about mental health or traumatic military experiences may distress subject.

- Subject is free to decline to answer any question or to complete any portion of the interview or, to stop the interview at any time.
- The interview will be conducted by an experienced mental health professional trained to ask sensitive questions, so it is very likely that these feelings will be temporary.

**Self-Report Questionnaires:** There are no physical risks from answering questionnaires. Some of the questions may be upsetting.

- Subject can take a break from a questionnaire, or call the study staff to discuss.

**Cognitive Testing:** May be slightly frustrating or produce fatigue and boredom.

- Subject is free to take a break and /or ask study staff for assistance
- Cognitive Testing is administered by trained clinicians who work with patients with dementia. They will stop the testing if the subject appears to be excessively disturbed.

**Magnetic resonance Imaging (MRI) Scan:** There are no known biological risks associated with MR imaging. An MRI may cause possible anxiety for people due to the loud banging noise made by the machine and/or the confined space of the testing area. There is also a risk of injury if metal is brought into the imaging room, which might be pulled into the MRI magnet. People with pacemakers, aneurysm clips, artificial heart valves, ear implants, or other metal/foreign objects in the body are not permitted to have an MRI.

- The subject is screened for medical history issues at the screening interview and at the clinic visit, specifically to exclude a subject with any medical conditions that would make it unsafe for a subject to participate - this includes history such as cardiovascular disease, and immune system disorders, medications that are not allowed, psychiatric disorders and substance abuse that may make it unsafe for a subject to participate. See exclusions.
- Subjects are checked for metal of any kind by use of a magnetic wand, including tattoos.
- There is a communication system set up such that subjects inside the scanner talk to the investigators, and they are removed from the scanner if they become uncomfortable.
- There is a slight risk of anxiety due to claustrophobia and noise. Any subject who experiences anxiety when placed into the MR scanner will be removed from the scanner, offered reassurance by the MR tech doing the scan, and offered the option of continuing or terminating the study. If the subject decides that the anxiety associated with MRI is

uncomfortable for them and they wish to terminate the scan, then the examination will be ended at that time. There will be no attempt to coerce subjects to complete exams that they are uncomfortable with.

- Sedation during the baseline MRI scan is not offered for this protocol. Subjects that are uncomfortable with MRI scans should not be included in this study. If a subject is uncomfortable with MRI and refuses to complete the scan without sedation, the study coordinator will be contacted at ADCS ADNI who will consult with the MRI Core. Exceptions may be granted on a case-by-case basis to allow the use of sedatives for MR scans at the follow-up visit.

**Lumbar Puncture (LP):** To minimize any and all risks of this procedure, the LP will only be performed by a neurologist specifically trained in performing LP's. In total, up to 20 milliliters (about 1 1/2tablespoons) of spinal fluid may be taken during the study. The human body will make up for the loss in about 1-2 hours. During this procedure subject may have temporary pain and discomfort in the back or in some cases a headache. If the headache persists, it may require additional treatment. Although uncommon, a small leak of spinal fluid may occur. If so, injecting some of the blood into the lumbar puncture site will patch the spinal fluid leak. If necessary, this often relieves the headache immediately.

Although very rare it is possible that subject may have an allergic reaction to the local anesthetic (lidocaine 1%) used for the lumbar puncture. This would cause swelling and a rash on the skin where the anesthetic was injected. Subject will be asked if he/she ever had a reaction to local anesthetic before, such as when visiting the dentist.

There is a very small and rare chance of infection, damage to some nerves in your back, or bleeding into the spinal fluid space.

- Again, to minimize any of these rare events, only a neurologist trained in the LP procedure will administer the LP.
- The needle used in the LP has been used in evidence based practice. Findings show that it does help prevent side effects.

### **Research Blood Draws/DNA/RNA/Cell Line:**

There is a small risk of pain with a blood draw when the needle enters the skin. Bruising at the site of the needle stick may occur, but this is temporary. Some people may experience fainting or dizziness, and there is also a slight risk of infection at the site of the needle stick.

- To minimize these risks, experienced medical personnel will handle all the blood drawing procedures and sterile conditions will be maintained

A possible risk from participation in this phase of study involves loss of privacy as a result of providing genetic material (DNA) for research. Although genetic information is unique, we share some genetic information with children, parents, brothers, sisters, other blood relatives and other members of ethnic group. Consequently, it may be possible that genetic information from these others could be used to help identify subject. Similarly, it may be possible that genetic information from subject could be used to help identify others. While information traditionally used to identify subject will not be released (i.e. name,

date of birth, address, and telephone number), people may develop ways in the future that would allow someone to link your genetic or medical information back.

A new Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally prohibits health insurers or health plan administrators from requesting or requiring genetic information of an individual or an individual's family members, or using such information for decisions regarding coverage, rates, or preexisting conditions. GINA also prohibits employers from using genetic information for hiring, firing, or promotion decisions, and for any decisions regarding terms of employment. Furthermore, the researchers have adopted strict privacy and confidentiality procedures for maintaining your genetic information as described in this consent form. You should be aware, though, that if your genetic information were accidentally released to the wrong source, federal law does not protect against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance or by adoption agencies.

**Confidentiality:** Participation in research inherently involves a loss of privacy. Every effort will be made to limit the loss of privacy due to participation in this study, as a loss of privacy might adversely affect the patient's reputation and/or his/her ability to get insurance in the future.

Safeguards are in place to minimize loss of privacy and to maintain confidentiality. All data are de-identified and coded, meaning data will not include anything that might directly identify a subject. There is a slight risk that there could be a breach in the security of the database system resulting in the access of information. However, safeguards are in place to minimize this risk as well. All data from questionnaires, audio-recording, medical exams, imaging, and specimens will be de-identified.

Data are coded. A subject's protected health information (PHI) is not located on any data collection documents or on any audio-recording, nor is it kept with data. Hard copies of data are kept in locked file cabinets, while electronic data are password protected and maintained on a secure network. A data key linking the subject's personal information to their study code number is kept securely with access limited to staff designated by the PI.

### **Positron Emission Tomography (PET) Scan:**

Florbetapir F18 is an imaging agent which includes a small amount of radioactivity necessary to create the PET images. Florbetapir F18 is used in very small doses (10 mCi per procedure) that earlier research studies indicated were well below the levels known to have effects on your body. The total amount of radiation from the Florbetapir F18 PET scan, and associated "low dose" computer tomography (CT) scan performed as part of the PET scan, is approximately 7.0 mSv, equivalent to 2.5 years of background radiation in the U.S. ( 3 mSv/yr). Exposure to large amounts of radiation increases the risk of developing cancer.

To date, Florbetapir F18 has been tested in approximately 2,200 people in completed and ongoing trials. The most common side effects were headache, injection site reactions, musculoskeletal pain, nausea and fatigue in the completed registration trials. Back pain, anxiety/claustrophobia, insomnia, hypertension, and neck pain were also reported. There were other adverse events, but none that occurred

in more than one subject in the registration trials. Although the side effects from Florbetapir F18 noted so far have been relatively limited, subject may experience side effects that are not listed above.

In the event that the scan fails the quality control procedure and cannot be used, we will repeat the Florbetapir scan. In ADNI to date, less than .5% of scans require repeat. Because of this, we include the total dose in the case of the necessity for repeating the scan once. Please see the dosimetry table below:

<b>Dosimetry Table</b>			
<b>Organ</b>	<b><sup>18</sup>F-AV-45 rad/mCi</b>	<b><sup>18</sup>F-AV-45 rad/10 mCi</b>	<b>Total Dose if Both Scans Repeated</b>
Adrenals	0.05	0.5	1
Brain	0.037	0.37	0.74
Breasts	0.023	0.23	0.46
Gallbladder wall	0.529	5.29	10.58
Lower Large Intestine Wall	0.103	1.03	2.06
Small Intestine	0.242	2.42	4.84
Upper Large Intestine wall	0.276	2.76	5.52
Heart wall	0.048	0.48	0.96
Kidneys	0.048	0.48	0.96
Liver	0.238	2.38	4.76
Lungs	0.032	0.32	0.64
Muscle	0.032	0.32	0.64
Ovaries	0.065	0.65	1.3
Pancreas	0.053	0.53	1.06
Red marrow	0.053	0.53	1.06
Skin	0.022	0.22	0.44
Spleen	0.033	0.33	0.66
Testes	0.025	0.25	0.5
Thymus	0.027	0.27	0.54
Thyroid	0.025	0.25	0.5
Urinary bladder wall	0.1	1	2
Uterus	0.058	0.58	1.16
Effective Dose	0.069	0.69	1.38
<b>Total Body</b>	<b>0.043</b>	<b>0.43</b>	<b>0.86</b>

#### **Procedure for administering Florbetapir F18:**

A needle will be used to inject Florbetapir F18 into your vein. Insertion of the needle may cause pain or a stinging sensation at the injection site. On rare occasions the insertion of a needle can cause bleeding, a blood clot, swelling or infection at the site of insertion. There is currently no information on the effects of Florbetapir F18 on unborn children. However it is known that higher levels of radiation can cause damage to unborn children. Subject should not participate in this study if pregnant or breastfeeding. Women of childbearing potential must not be pregnant (negative urine beta-chg. on the day of imaging) or breast feeding at screening. Women must avoid becoming pregnant and must agree to refrain from sexual activity or to use reliable contraceptive methods for 24 hours following administration of Florbetapir F18. Because the age of subjects recruited will be between 50-90 years old, very few subjects with child bearing potential will be enrolled, nonetheless, should a subject be of childbearing age, a pregnancy test will first be administered. Pregnancy or breast feeding are exclusionary criteria.

- Subject is monitored during the scan for blood pressure, pulse, respiration,
- A telephone check will be made one to two business days after the procedure to check on how subject is feeling, and to see if there are any adverse reactions.

**Computed Tomography (CT) Scan.** During the Florbetapir F18 PET scan, it is sometimes necessary to have a CT or another type of scan to help correct the scans for photon attenuation. If so, the CT or transmission scan also uses a very small dose of radiation.

## 18. Adverse Events Reporting

All subjects will be evaluated for adverse events at each clinical visit. Adverse events (AE) will be continuously monitored during the imaging session. Subjects who experience any adverse event will not be discharged until the event has resolved or stabilized. A follow-up phone call to the patient (or the caregiver as applicable) will be conducted approximately 2 (+/- 1) business days after the imaging session to confirm patient well-being and to collect information about any new adverse events. The injection site will be observed for excessive inflammation or damage to the surrounding tissue where the dose was injected, and a physician or physician designee will see the patient prior to dosing and prior to discharge.

The most common adverse events in previous human clinical trials include headache, injection site reactions, musculoskeletal pain, nausea and fatigue. Back pain, anxiety/claustrophobia, insomnia, hypertension, and neck pain were also reported. Because these events could be related in part to the PET scan apparatus and procedures, careful attention will be taken to make the subject aware of the planned procedures and to maximize subject comfort in the scanner. Previous human clinical trials have revealed no clinically meaningful changes in vital signs, ECG or laboratory changes.

### Definition of an Adverse Event

An adverse event is any adverse change from the subject's baseline condition including clinical or laboratory tests, or abnormalities that occur during the course of the study after consent.

### Following up on Adverse Events

The investigator is obliged to follow subjects with AE's until the events have subsided, the conditions are considered medically stable, or the participants are no longer available for follow up. Subjects who discontinue due to adverse events will be treated and followed according to established medical practice.

All pertinent information will be entered into the eCRF. All serious adverse events (SAEs) will be reported to the independent Data Safety Monitoring Board.

Serious adverse events include any event that is fatal, life threatening, significantly or persistently disabling or incapacitating, results in hospitalization, prolongs a hospital stay, or is associated with a congenital abnormality or birth defect. In addition, any experience which the investigator regards as serious, or which would suggest significant hazard, contraindication, side effect, or precaution associated with participation in the study should be reported as a serious adverse event.

### **Reporting Serious Adverse Events**

Any such experience due to any cause, which occurs during the course of the investigation or within 30 days of the last study visit, must be reported to the Project Director within 24 hours after learning of the event. This in turn will trigger a report to be distributed to all participating sites, DSMB and the DOD. Sites will report based on local IRB requirements.

Eli Lilly must be notified immediately (as soon as possible, and in all cases within 24 hours) of a florbetapir F 18 drug experience, condition, development, or event, which is considered serious. Eli Lilly must be notified immediately of any findings with the use of florbetapir F 18 that may suggest significant hazards, contraindications, adverse drug reactions (ADRs) and precautions pertinent to the safety of the drug. The investigator will be requested to complete a separate report form.

A Serious adverse event (SAE) spontaneously reported to have occurred within 24-48 hours of florbetapir F 18 administration will be reported, regardless of the investigator's opinion of causation. Thereafter, SAEs are not required to be reported unless the investigator feels the events were related to either florbetapir F 18 or the drug delivery system, or a protocol procedure.

If an SAE is determined to be unexpected (not previously reported or described by Avid), and study drug-related, Eli Lilly, will notify the investigator in writing. The investigator should forward this notification to the IRB within 24 hours of receipt.

### **Data and Safety Monitoring Board**

The ADNI-CC currently has an active Data and Safety Monitoring Board (DSMB) that reviews the safety of all subjects enrolled in trials on an ongoing basis. The DSMB will review serious adverse event reports on a quarterly basis.

### **Medical Monitor**

The medical monitor may be assigned to assess one or more of the following phases of the research project: volunteer recruitment, volunteer enrollment, data collection, or data storage and analysis. The medical monitor will provide an independent evaluation of serious adverse events and unanticipated problems involving risk to subjects or others to the Institutional Review Board (IRB) /Human Research Protection Office (HRPO). The medical monitor may be assigned to discuss research progress with the



principal investigator, interview volunteers, consult on individual cases, or evaluate adverse event reports. Medical monitor, Adam Fleisher, will promptly report discrepancies or problems to the IRB and the HRPO. He shall have the authority to stop a research study in progress, remove individual volunteers from a study, and take whatever steps are necessary to protect the safety and well-being of research volunteers until the IRB can assess the medical monitor's report.

All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study and subject deaths related to participation in the study should be promptly reported by phone (301-619-2165), by email (hsrrb@det.amedd.army.mil<mailto:hsrrb@det.amedd.army.mil>), or by facsimile (301-619-7803) to the USAMRMC, Office of Research Protections, Human Research Protection Office. A complete written report will follow the initial notification. In addition to the methods above, the complete report will be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-ZB-PH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.

Our Medical Monitor for this study, Adam Fleisher, M.D., M.A.S., is the Associate director of brain imaging at the Banner Alzheimer's Institute and Associate Professor in the Department of Neurosciences at the University of California, San Diego.

## **19. Benefits:**

### **Benefits to Subjects:**

This is not a treatment study. There is no direct benefit to subjects who participate in this study. However, with subject permission, should there be any significant clinical findings from the medical exam, blood test, MRI, PET scan or lumbar puncture, the results will be given to the subjects' physician, or the subject, should no primary care physician be available.

### **Benefits to Society:**

AD is the most common cause of dementia. TBI and PTSD are common problems resulting from military service, and both may be associated with increased risk of cognitive decline and dementia due to AD or other causes. The results will have major implications for identifying subjects at increased risk for AD, as well as possibly establishing a need for early detection of AD in military Veterans with histories of TBI and PTSD, and a possible need to employ prevention and treatment measures to avoid accelerated development of AD in US military Veterans. This study is a first step towards a larger, more comprehensive study of dementia risk factors in Veterans. The result will lead to a design and statistical powering of a prevention trial. Therefore, this project could be first step towards the prevention of AD in Veterans, and in the general population.

While the long-term health risks from participating in this study are small, the benefit to society lies in having better tests for diagnosis of Alzheimer's disease as well as better tests for assessing drug efficacy.

## **20. Neuropathology**

The ADNI Neuropathology Core will continue to be responsible for coordinating brain autopsies at the participating sites, shipment of postmortem brain tissues to the Neuropathology Core, and performing a standardized neuropathological assessment. The Neuropathology Core will maintain a tissue bank to facilitate clinicopathological research

## **21. Data Collection and Monitoring**

The ADNI Clinical Core will be responsible for providing the operational infrastructure for the ADNI sites. This infrastructure will be provided by the ADCS Administrative, Clinical Operations, Medical and Data Cores at UCSD.

Clinical data collection and monitoring are standardized with well-established and successful ADCS operating procedures. Data will be entered directly by sites using web-based data entry screens. Imaging data collection and monitoring are handled by LONI. Imaging data are handled using a combination of data entry via web-based forms and automated file transition modules embedded within the web-based Image Data Archive application. The file translation modules extract metadata directly from the imaging data, ensuring accuracy and reducing the amount of data entry required.

## **22. Inclusion of Women and Minorities**

Both women and members of minority groups will be recruited during this protocol. Based on the participating sites data regarding enrollment of minorities, it is expected that 12% of subjects enrolled will be minorities. This is close to the aged minority population in the U. S. which is 14%. The enrollment of women will be included, though it is expected that the number of women enrolled will be quite small given the relatively small number of women who participated in the Vietnam War.

## **23. Data Sharing Policy**

In order to provide the de-identified clinical data from this project to investigators, the Pharmaceutical Industry, and the public, the entire clinical database (free of any identifying information such as name, address, or phone number) will be placed on a public web site, which will be appropriately linked to the imaging database at LONI. The database will be frequently updated and all cleaned clinical data acquired by the DOD-ADNI study will be provided in real time. Dr Robert Green, from Harvard University, who chairs the ADNI Data and publications committee, will continue to monitor all requests for permissions to access the data and will treat all publications coming forth from this DOD ADNI grant similar to the ADNI publications. All publications must be submitted to the committee for review, prior to submission to journals. The committee tracks these and insures that the DOD ADNI project is properly given acknowledgement in the author line of the paper. There will be no cost to his for this project.

### **Sharing of Banked DNA, RNA, Plasma, Serum and CSF**

Specific procedures for requesting and accessing DNA, RNA, or plasma, serum or CSF have been created by the Resource Allocation Review Committee (RARC) of the ADNI in accordance with

recommendations proposed in the National Bioethics Advisory Commission (NBAC) Human Biological Materials Report.

All analysis data will be uploaded to the clinical database at ADCS and will be available on the UCLA/LONI/ADNI website without embargo

## 24. Data Analysis

**Primary analyses involve comparing groups on baseline** levels of CSF, Neuroimaging (MRI and amyloid PET), and cognitive measures associated with AD pathology and annual change in MRI and cognitive measures to assess whether PTSD or TBI is associated with increased evidence for AD compared to Veteran controls. Further analyses will focus on within-group correlations to assess a dose-response association between outcomes and severity of PTSD or TBI and whether TBI or PTSD reduces cognitive reserve. Additional exploratory analyses will also be conducted. The specific analytic methods for hypothesis testing are listed below followed by an assessment of power.

**The primary hypotheses to be tested** (all data analyses will be covaried for age, gender, and APOe4 genotype) are that Veterans without MCI (or dementia, with a history of moderate to severe TBI during military service, as well as Veterans with ongoing PTSD, have increased evidence for AD, when compared with Veteran controls (without TBI or PTSD) manifested as: 1) greater uptake on Florbetapir amyloid PET scans; 2) lower CSF amyloid beta levels; 3) increased CSF tau/P tau levels; 4) brain atrophy in hippocampus, entorhinal cortex, and parietal/temporal cortices; and 5) greater rates of brain atrophy in hippocampus, entorhinal cortex and parietal/temporal cortices; 6) reduced cognitive function, especially delayed recall.

**The second major hypotheses to be tested** is that TBI and/or PTSD reduce brain reserve causing greater cognitive impairment after accounting for age, brain amyloid load or hippocampal volume. Greater cognitive impairments at a given level of brain A $\beta$  or brain volume in the TBI or PTSD group compared with controls would support the hypothesis of reduced cognitive reserve.

**The third hypothesis will be that TBI**, when compared to controls, is associated with changes detected with DTI in brain regions previously reported to be associated with TBI [37-39].

**Finally, the hypothesis that there will be significant correlations between severity** of TBI (determined from medical records) and severity of PTSD (CAPS score) on the above-listed outcomes in the TBI and PTSD groups respectively will be tested.

**Exploratory analyses** will be performed to examine other questions; although, after correction for multiple comparisons, the statistical significance of these will be low, requiring future replication. Nevertheless, the patterns of amyloid deposition (from Florbetapir uptake) and brain atrophy between TBI, PTSD, and control subjects will be compared, with similar patterns from non-Veteran subjects in ADNI. These results of these studies may provide insight into the question of whether or not TBI and PTSD alter the pattern of amyloid distribution or brain atrophy. Such analyses may also give insight into

the question of whether TBI or PTSD is associated with reduced cognitive reserve. The relationship between cortical areas with amyloid plaque (from amyloid PET) and underlying white matter integrity as assessed with DTI will also be studied to determine if axonal injury resulting from TBI was associated with greater amyloid accumulation, or whether regions of brain with axonal damage have less amyloid accumulation due to disconnection and reduced brain activity.

### **Primary Analyses: Comparing Groups on Baseline Level (Hypothesis sets 1 & 3):**

Primary outcomes for these analyses include uptake on Florbetapir scans, CSF amyloid beta, CSF tau and Ptau, volumes of the hippocampus, entorhinal cortex, and parietal/temporal cortices, DTI summary measures (in the third set of hypotheses) and measures of cognitive function, including delayed episodic memory.

The analyses will begin with: 1) numerical and graphical summaries of the measures within each group to assess the underlying distribution and detect outliers or questionable values which will be flagged and checked with the sites for accuracy. 2) Analysis of variance (ANOVA) for a simple unadjusted comparison between the groups. If the global F-test for group difference is significant, there will be a follow-up with post-hoc pairwise tests, specifically between the TBI or PTSD groups and the Veteran control group, adjusted for multiple comparisons using the Bonferroni or Tukey's Honestly Significant Difference (HSD) approach. 3) linear regression models that include group as an independent variable to adjust for potential confounders including age, gender, APOe4 genotype, and alcohol dependence. Model assumptions will be assessed through graphical and numerical approaches and transformations or non-linear models will be used if suggested by the diagnostics. Hypotheses will be supported if the TBI and PTSD groups show significantly higher levels of uptake on amyloid PET scans and CSF tau or Ptau than the Veteran controls and significantly lower levels of CSF amyloid beta, MRI volumes, and cognitive function than the Veteran controls.

### **Primary Analyses: Comparing Groups on Annual Change (Hypothesis sets 1 & 3):**

Primary outcomes for these analyses include annual change in volumes of the hippocampus, entorhinal cortex, and parietal/temporal cortices and annual change in cognitive function such as delayed recall. There will be two assessments for each person, approximately one year apart. Therefore, for each participant as a measure of annual change, there will be a construction of difference scores between the measures obtained at the follow-up visit and the baseline visit. The scores will be divided by the time between the assessments to account for variability in timing of the follow-up assessments between participants. Analyses will be similar to those described above for comparing groups on the baseline level except that the final linear regression models will also be adjusted for baseline level of the outcome measure. Hypotheses will be supported if the TBI and PTSD groups show significantly faster rates of atrophy and cognitive decline than the Veteran controls.

### **TBI or PTSD associated with reduction in cognitive reserve (Hypothesis set two):**

The main outcomes for these analyses will be level and annual change in cognitive function, particularly memory while the predictors of interest are group, baseline hippocampal volume, and uptake from the amyloid PET scans. Linear regression methods similar to those described above will be used. Of particular interest for these analyses are the interactions between group and the imaging predictors. Power will be limited for these analyses, so results will mainly serve as support for future studies of PTSD, TBI, and cognitive reserve. However, significant interactions suggesting worse cognitive function

in the TBI or PTSD groups relative to Veteran controls at a given level of MRI, or amyloid imaging measures would support the hypotheses.

### **Within-group correlations to assess dose-response:**

Outcomes for these analyses will be the same as those used for hypothesis sets one, two, and three. Interest lies in assessing whether the baseline levels or rates of atrophy or cognitive decline are associated with severity of TBI or PTSD. Analyses will be performed within each of those groups separately. Severity of TBI or PTSD will be the predictor of interest. Simple linear regression models that include severity of TBI or PTSD as the independent variable will be used. Multiple regression models to adjust for potential confounders including age, gender, and APOe4 genotype and alcohol dependence will be used next. As stated above for the primary analyses, model assumptions will be assessed and transformations or non-linear models will be used if suggested by the diagnostics. Secondary hypotheses will be supported if increased severity of TBI or PTSD is significantly associated with lower levels of CSF amyloid beta, MRI volumes, and cognitive function, higher levels of CSF tau or Ptau, and increased rates of brain atrophy and cognitive decline.

### **Exploratory Analyses:**

As described earlier, exploratory analyses will be performed to examine other questions; although, after correction for multiple comparisons, power will be low requiring future replication. Nevertheless, there will be a comparison of the patterns (using voxel based methods) of amyloid deposition (from amyloid PET) and brain atrophy between TBI, PTSD, and control subjects, and with similar patterns from non-Veteran subjects in ADNI. The results of these studies may provide insight into the question of whether or not TBI and PTSD alter the pattern of amyloid distribution or brain atrophy. Furthermore, the relationships between amyloid deposition, atrophy, and cognitive function may provide insight into the question of whether TBI or PTSD is associated with reduced cognitive reserve. Further exploratory analyses will assess the relationship between cortical areas with amyloid plaque (from amyloid PET) and underlying white matter integrity as assessed with DTI to determine if axonal injury resulting from TBI was associated with greater amyloid accumulation, or whether regions of the brain with axonal damage have less amyloid accumulation due to disconnection and reduced brain activity. Linear regression methods, described above, will be used to assess the association between regional measures of amyloid accumulation and axonal damage.

### **Power Analysis:**

Power analyses are presented for each class of primary hypotheses assuming a two-sided test and were calculated using nQuery. For comparison of the TBI or PTSD group to the Veteran controls, assuming  $\alpha = 0.025$  to account for multiple comparisons and 65 individuals per group at baseline and 61 per group for longitudinal measures, there will be an 80% power to detect a difference as small as 0.55 standard deviations in level and as small as 0.56 standard deviations in rate of atrophy or cognitive decline. For example, using means and standard deviations from measures in the normal controls within ADNI-1, this difference would translate to at least a 6.7% lower hippocampal volume, and at least a 14.7% lower CSF amyloid beta. Because there is little change in the ADNI normals, differences in change will be much more difficult to detect. However, these data will provide initial estimates of how much change is experienced in the TBI and PTSD groups which will help in planning larger scale

longitudinal studies of these groups. The power analysis will be able to detect at least a doubling of the rate of hippocampal atrophy and at least a quadrupling of the rate of decline in delayed recall in the TBI or PTSD groups compared to the Veteran controls. For within group correlations, there will be an 80% power to detect a correlation as small as 0.33 with cross-sectional outcomes and 0.34 with outcomes of change.

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