**Alzheimer's Disease Neuroimaging Initiative – The ADNI Depression Project (ADNI-D)**

*"Characterizing Cognitive Decline in Late Life Depression"*

**Study Protocol**

| ADNI Depression Project: Schedule of Events | Month 1 | | Month 12 | Month 24 | Month 30 | |
|---|---|---|---|---|---|---|
| Visit Type | Psych | ADNI | Psych | Psych | Psych | ADNI |
| Explain Study | X | X | | | | |
| Obtain Consent | X | | | | | |
| Study Partner Consent | | X | | | | |
| Demographics | X | X | | | | |
| Inclusion and Exclusion Criteria | X | | | | | |
| Family History | | X | | | | |
| Depression History | X | | | | X | |
| Structured Clinical Interview DSM-IV (SCID) | X | | | | X | |
| Hamilton Depression Rating Scale (HDRS) | X | | X | X | X | |
| Generalized Anxiety Disorder -7 (GAD-7) | X | | | | X | |
| Patient Health Questionnaire-9 (PHQ-9) | X | | | | X | |
| Duke Social Support Index (DSSI) | X | | | | X | |
| Stroop Color-Word | X | | | | X | |
| Motor-Free Visual Perception Test-3 (MVPT-3) | X | | | | X | |
| Brief Visuospatial Memory Test (BVMT) | X | | | | X | |
| Benton Judgment of Line Orientation (JLO) | X | | | | X | |
| WAIS Digit Symbol | X | | | | X | |
| WAIS Digit Span | X | | | | X | |
| Stress and Anxiety Measures | X | | | | X | |
| Follow Up Treatment Form | | | X | X | X | |
| Cognitive Change Index -20 Participant | | X | | | | X |
| Cognitive Change Index-20 Informant | | X | | | | X |
| Medical History, Hachinski | | X | | | | |
| Physical Exam, Neurological Exam | | X | | | | X |
| Vital Signs | | X | | | | X |
| Height | | X | | | | |
| DNA Sample Collection for APOE Genotyping, GWAS, Hematology, and Differential | | X | | | | |
| Cell Immortalization and PBMC Sample Collection | | X | | | | |
| American National Adult Reading Test | | 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 (w/ Delayed Recall and Number Cancellation) | | X | | | | X |
| Clinical Dementia Rating Scale | | X | | | | X |
| Activities of Daily Living (FAQ) | | X | | | | X |
| Plasma and Serum Biomarker Collection | | X | | | | X |
| RNA Sample Collection | | X | | | | X |
| Telomere and "TBD" Assay Sample Collection | | X | | | | X |
| Concomitant Medications | | X | X | X | | X |
| Serious Adverse Events | | X | X | X | | X |
| Diagnostic Summary | | X | | | | X |
| Telephone Check –Participant Status | | | X | X | | |
| 3T MRI Imaging | | X | | | | |
| Florbetapir Amyloid Imaging | | X | | | | |

## **Table of Contents**

## 1. Introduction

The overall goal of this project is to characterize the mechanisms contributing to cognitive impairment and accelerated cognitive decline in Late Life Depression (LLD). Cognitive Impairment (CI) occurs in up to 60% of individuals with LLD and is most often characterized by deficits of executive functioning, memory, and expressive language.  CI represents one of the most debilitating and costly aspects of LLD and determining the etiology of CI in LLD represents a significant avenue to improve health and disability outcomes for older adults through interventions and treatments.  Existing data suggests that remission of depression is associated with focal improvements in executive function, whereas, deficits of memory and expressive language typically persist, and that LLD is associated with more rapid rates of cognitive decline across cognitive domains.  Compelling evidence suggests that cerebral hypoperfusion represents a significant aspect of LLD that contributes to remediable deficits of executive function and that cortical atrophy is associated with memory and language deficits in LLD.  Further, while understudied, accelerated cognitive decline in LLD is likely the result of multiple factors including hypoperfusion, amyloid deposition, cortical atrophy, white matter signal hyperintensities, and genetic susceptibility.  In the past, determining the specific mechanisms contributing to CI in LLD has been challenging due to the co-occurrence of neurodegenerative disease and methodological limitations related to small sample sizes.  With the advent of new imaging techniques, including measures of cerebral blood flow, radioligands to evaluate amyloid deposition in vivo, and the establishment of national research consortiums developed to identify neural substrates of CI in older adults, there is now a tremendous opportunity to leverage these resources to clarify the neurobiological substrates of CI in LLD.

Through dynamic partnerships with the Alzheimer's Disease Neuroimaging Initiative (ADNI-II) and industry sponsorship, the ADNI-D study is well positioned to successfully address the impact of reduced cerebral blood flow (hypoperfusion), cortical atrophy, and amyloid deposition on cognitive impairment and accelerated cognitive decline in LLD in the context of previously documented relationships between cognitive impairment and subcortical white matter abnormalities and genetic risk factors.  ADNI-D is focused on establishing improved diagnostic approaches and targeted treatment trials aimed at LLD and CI associated with LLD, ultimately leading to improved health outcomes and reduced healthcare costs.

## 2. Study Aims

The study aims are focused on prediction of clinical outcomes, and fulfillment of these aims will add considerably to what is known about the basic neuroscience of Late Life Depression and disability in the geriatric community.

- **Aim 1:** To clarify neurobiological substrates of cognitive dysfunction in LLD.
- **Aim 2:** To clarify the impact of LLD on rate of cognitive decline over 2.5 years.

- **Aim 3:** Use biomarkers data employed in ADNI-2 and the NIA AD Genetics Consortium to determine the genotypes needed for the genome wide association study (GWAS) for pathways and candidate gene studies that investigators may wish to pursue in future studies. Data from participants will be entered into the NIH Genome-Wide database and made available to the scientific community.

## 3. Study Design

This is a non-randomized non-treatment study. One hundred and twenty (120) subjects who meet criteria for Major Depression or LLD will be enrolled for a period of 30 months. Data from an additional 300 non-depressed subjects will be used from the previous ADNI studies for comparison. Depression history, symptom severity and health information will be collected at the initial psychiatric visit to determine eligibility. A 3T MRI and $^{18}$F-AV-45 amyloid imaging will be conducted at the ADNI site for the initial clinical visit. Collection of plasma and serum for biomarkers, clinical assessments and cognitive assessments will be conducted at both time points. Blood samples will also be collected for genetic analysis.

### 3.1. Site Personnel Requirements

Three staff functions (Site Principal Investigator, psychometrist, and study coordinator) will be required to conduct the protocol at each **psychiatry site**. Depending on the site, two or three persons may suffice.

- **Site Principal Investigator:** This person is responsible for ensuring that the local IRB approves the protocol, ensuring enrollment and protocol adherence and overseeing all site activity for both the psychiatry site and ADNI clinical site. The site principal investigator will supervise project personnel to ensure that raters maintain a high level of skill and accuracy in conducting assessments and will determine eligibility fulfillment of potential participants based on the results of the Structured Clinical Interview of the DSM-IV.
- **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. This person may also serve as the project interviewer/psychometrician.
- **Project interviewer/Psychometrician:** This person will have at least a bachelor's degree in psychology, social work or a related field, and/or well-documented experience in administering interviews and neuropsychological tests.

Along with the site principal investigator, three staff functions (clinician, psychometrist, study coordinator) will be required to conduct the protocol at the **ADNI sites**. Depending on the site, either two or three persons may suffice.

- **Site Principal Investigator:** The site principal investigator will supervise project personnel and ensure that raters maintain a high level of skill and accuracy in conducting

assessments.

- **Study Physician:** This person is responsible for conducting or supervising the clinical evaluation of all participants, including physical and neurological examinations, and reviewing serious adverse events.
- **Study Coordinator:** This person will be responsible for managing the day-to-day conduct of the trial, 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.
- **Project interviewer/Psychometrician:** This person will have at least a bachelor's degree in psychology, social work or a related field, and/or well-documented experience in administering interviews and neuropsychological tests.

### *3.2. Recruitment and Retention*

Recruitment of participants at each of the sites will primarily occur in the context of established geriatric research programs.  At each psychiatry site, psychiatry PIs will identify eligible participants, screen for initial eligibility, and enroll participants into the study.  Specific eligibility criteria will be discussed with the participant at the Baseline Clinic visit as well to screen for physical, MRI, and/or PET specific exclusions.  If at this point the participant is deemed ineligible, the ADNI site may drop them from the study.  ADCS will provide study recruitment materials, including targeted flyers, brochures, press releases, and presentations and will provide additional consultations with recruitment strategies.  Paid newspaper and radio advertisements, direct mail and Internet advertising will be used as needed to supplement recruitment.

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 will be queried regarding plans to change residence or leave the area. Frequent contact by telephone will be maintained with participants at twelve-month intervals. Each participant will receive a thank you note following the clinical evaluation and a personalized reminder notice will be sent on 6 month intervals to participants thanking them for their participation and reminding them of their next scheduled visit or telephone contact.

*3.3. Data Collection and Monitoring*

The Clinical Core will continue to be responsible for providing the operational infrastructure for this project. This infrastructure will be provided by the ADCS Administrative, Clinical Operations, Medical and Data Cores at UCSD. The ADCS Cores occupy approximately 25,000 square feet of space across the street from the UCSD Medical School Campus.

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.

*3.4. Data Sharing*

In order to provide the clinical data from this project to Initiative 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 ADNI-CC will be provided in real-time.

## **4. Subject Selection**

*4.1. Inclusion Criteria:*
1. Current DSM–IV diagnosis of Major Depressive Disorder, unipolar type, without psychotic features and six week minimum duration of current depressive episode.
2. English Speaking
3. 65+ years of age
4. Hamilton Depression Rating Scale score $\geq$ 15
5. Able to give informed consent
6. Willing to undergo one MRI (3 Tesla) and one PET scan (Amyloid imaging)
7. Able to fit in an MRI machine comfortably (BMI $\leq$ 38)
8. Agrees to collection of blood for GWAS, APOE testing and DNA and RNA testing
9. Agrees to collection of blood for biomarker testing
10. Agrees to collection of additional blood sample for "TBD" assays and telomere length measurement
11. Visual and auditory acuity adequate for neuropsychological testing
12. Completed six grades of education or has established work history (sufficient to exclude mental retardation)

13. Study partner is available who has frequent contact with the subject (e.g. an average of 10 hours per week or more), and can accompany the subject to clinical visits for the duration of the protocol.

### 4.2. Exclusion Criteria:

The following additional exclusion criteria apply to all participants:

1.  Current diagnosis of other axis 1 psychiatric disorders (with the exception of Simple Phobias and Generalized Anxiety Disorder)
2.  Evidence of Dementia (MMSE <25)
3.  Any electroconvulsive therapy within the past 6 months
4.  Undergoing anti-depressant or psychotherapy treatment (exceptions listed 4.3. Treatment Exclusion Exceptions)
5.  Any significant neurological diseases (i.e. Parkinson's disease, epilepsy, cortical stroke, traumatic brain injury)
6.  History of alcohol or substance abuse or dependence within the past 2 years (DSM-IV criteria)
7.  Any active and serious suicidal ideation, including ideation, plan and intent to carry out that plan, as assessed by the HDRS
8.  Any significant systemic illness or unstable medical condition which could lead to difficulty complying with the protocol
9.  History of surgical procedures effecting study outcomes
10. Residence in skilled nursing facility
11. Participation in clinical studies involving the same neuropsychological measures used in ADNI-D that may impact study outcomes
12. Investigational agents are prohibited one month prior to entry and for the duration of the trial
13. Exclusion for amyloid imaging with $^{18}$F –AV-45: 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
14. Known history of MRI scans with evidence of infection, infarction, or other focal lesions. Subjects with multiple lacunes or lacunes in a critical memory structure are excluded
15. Presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments or foreign objects in the eyes, skin or body, claustrophobia
16. Pregnant, lactating, or of childbearing potential (i.e. women must be two years post-menopausal or surgically sterile)

### 4.3. Treatment Exclusion Exceptions:
1.  Anti-depressant medication treatment is allowed only if the medication dose is stable for 4 weeks prior to the MRI scan

2. Psychotherapy interventions is allowed only if they have completed at least 4 weeks of individual or group psychotherapy intervention prior to the MRI scan

3. Participants taking cognitive enhancing medications will be able to enter the study

## 5. Study Procedures

New subjects who are enrolling in this study will go through a pre-screening and a Depression Assessment as described below. Assessments completed at each visit are listed below. Visits must be conducted within 2 weeks before or after the target date. All imaging procedures, biofluid collection and cognitive and clinical assessments must take place within this 4-week timeframe.

### 5.1. Procedures for Newly Enrolled Participants

### 5.1.1. Pre-screening

Psychiatry sites will identify potential subjects through a variety of mechanisms: by reviewing subjects enrolled in previously established Late Life Depression registries, recruitment endeavors, and referrals. Pre-screening will involve a phone interview briefly explaining the nature of the study, as well as acquire pre-screening consent, demographic information, and an initial mood assessment. Depression severity will be assessed using the standard 17-item Hamilton Depression Rating Scale. Demographic information gathered during this visit will be used to help determine initial eligibility but will not be entered into the EDC portal until the participant is brought in for their Depression Assessment.

- Phone Interview Consent
- Demographic Information
- Publicity Tracking
- Eligibility Screening
- Hamilton Depression Rating Scale (HDRS)

### 5.1.2. Depression Assessment: Psychiatry Site

The purpose of the Depression Assessment visit is to determine eligibility for the proposed study and to collect measures that will be used as a reference to assess change. A standardized evaluation will be performed at each site with a time interval no later than 6 weeks between pre-screening and Depression Assessment. If the participant is not brought in for assessment by the 6 week cut off a second pre-screening phone interview is required to re-assess depression severity and eligibility criteria. Consent will be obtained before any portion of the Depression Assessment visit is initiated. Eligibility will be determined according to the Inclusion/Exclusion criteria outlined above and confirmed by the psychiatry site PI before the subject can be brought back for Baseline clinical assessment.

- Explain study
- Obtain consent
- Inclusion/Exclusion Criteria

- Publicity Tracking
- Hamilton Depression Rating Scale (HDRS)
- Structured Clinical Interview of the DSM-IV (SCID-IV)
- Depression History
- Mini Mental State Examination

*If by this point in the screening the participant does not meet criteria for Major Depressive Disorder and is deemed ineligible, the Depression Assessment visit will be stopped.*

- Brief Visuospatial Memory Test (BVMT)
- Generalized Anxiety Disorder-7 (GAD-7)
- Patient Health Questionnaire-9 (PHQ-9)
- Duke Social Support Index (DSSI)
- Penn State Worry Questionnaire
- Perceived Stress Scale
- Stroop Color Word
- Benton Judgment of Line Orientation
- WAIS Digit Symbol
- WAIS Digit Span
- Motor-Free Visual Perception Test- 3(MVPT-3)

*5.1.3. Baseline Visit: ADNI site*

If the psychiatry site PI deems the participant eligible for the study, they will be referred to the ADNI clinical site for the MRI and Baseline Assessment. The Baseline visit for the enrolled subjects must be initiated within 14 days of the Depression Assessment. Specific eligibility criteria will be discussed with the participant during this visit to screen for physical, MRI, and/or PET specific exclusions.  If at this point the participant is deemed ineligible, the ADNI site may drop them from the study. A local clinical read of the MRI will be reviewed for clinically significant abnormalities and scans must pass MRI QC evaluation. Demographics information will initially be gathered at the pre-screening interview to assist in determining initial eligibility. The demographics form along with a PDF copy of the signed informed consent will be sent to the ADNI clinical site for review with the participant.  Consent for study partner participation will be signed at this visit.  Any discrepancies found with demographic information will be discussed with the participant and, if necessary, with the psychiatry site.  The ADNI clinical site is responsible for entering confirmed demographic information into the EDC if they find discrepancies.

- Explain study/Review consent
- Study Partner consent
- Demographics
- Family History
- Physical, MRI or PET Exclusionary Criteria
- Medical History
- Physical Exam

- Neurological Exam
- Hachinski
- Height
- Logical Memory I and II
- Geriatric Depression Scale
- Clinical Dementia Rating Scale
- Vital Signs
- DNA Sample Collection for APOE Genotyping and GWAS
- Cell Immortalization and PBMC Sample Collection
- American National Adult Reading Test
- Everyday Cognition (ECog)
- Montreal Cognitive Assessment (MoCA)
- Category Fluency (Animals)
- Trails A & B
- Boston Naming Test (30-item)
- Auditory Verbal Learning Test
- Clock drawing
- Neuropsychiatric Inventory
- Cognitive Change Index 20 Participant version
- Cognitive Change Index 20 Informant version
- ADAS-Cog 13 (with Delayed Word Recall and Number Cancellation)
- Activities of Daily Living (FAQ)
- Collection of Plasma and Serum Biomarkers
- RNA Sample Collection
- Telomere and "TBD" Assay Banking Sample Collection
- DNA Sample Collection (Buffy Coat)
- Concomitant Medications
- MRI (3T) – Baseline MRI only to be conducted after confirmation that the subject has met all other inclusion/exclusion criteria.
- Serious Adverse Events
- Diagnostic Summary
- $^{18}$F-AV-45 Amyloid Imaging

## 5.2. Procedures for Follow up Visits

Every attempt should be made to retain participants for longitudinal follow-up as long as possible. If subjects are not willing or able to complete the full schedule of assessments at the last visit, those assessments or procedures they are willing to complete should be conducted. If subjects are no longer willing or able to travel to the clinic for the follow-up visit, as much information should be collected via telephone as possible.

### 5.2.1. 12 Month Interim Telephone Check

The 12 Month Interim Telephone visits will be timed at the 12-month point between visits.
- Concomitant Medications

- Serious Adverse Events
- Participant Status
- Hamilton Depression Rating Scale (HDRS)
- Follow up Treatment Form

*5.2.2. Month 30 Visit: Psychiatry Site*

The Month 30 visits will be conducted 2.5 years after completion of the ADNI-D Baseline visit. Visits will be scheduled based on the original Baseline date and should be completed within a 1 month window. Every attempt should be made to retain participants for longitudinal follow-up as long as possible.

- Hamilton Depression Rating Scale (HDRS)
- Structured Clinical Interview of the DSM-IV (SCID-IV)
- Mini Mental State Examination
- Brief Visuospatial Memory Test (BVMT)
- Generalized Anxiety Disorder-7 (GAD-7)
- Patient Health Questionnaire-9 (PHQ-9)
- Duke Social Support Index (DSSI)
- Penn State Worry Questionnaire
- Perceived Stress Scale
- Stroop Color Word
- Benton Judgment of Line Orientation
- WAIS Digit Symbol
- WAIS Digit Span
- Depression History (since initial assessment)
- Motor-Free Visual Perception Test- 3(MVPT-3)

*5.2.3. Month 30 Visit: ADNI Site*

The Month 30 Clinic Visit will be conducted 2.5 years after completion of the ADNI-D Baseline visit. Visits will be scheduled based on original Baseline date or must be initiated within 14 days of the follow up psychiatric assessment.
- Vital Signs
- Physical Exam
- Neurological Exam
- Logical Memory I and II
- Everyday Cognition (ECog)
- Montreal Cognitive Assessment (MoCA)
- Category Fluency (Animals)
- Trails A & B
- Boston Naming Test (30-item)
- Auditory Verbal Learning Test
- Geriatric Depression Scale
- Clock drawing

- Cognitive Change Index 20 Participant
- Cognitive Change Index 20 Informant
- Neuropsychiatric Inventory
- ADAS-Cog 13 (with Delayed Word Recall and Number Cancellation)
- Clinical Dementia Rating Scale
- Activities of Daily Living (FAQ)
- Plasma and Serum Biomarker Collection
- RNA Sample Collection
- Telomere and "TBD" Assay Banking Sample Collection
- DNA Sample Collection (Buffy Coat)
- Concomitant Medications
- Serious Adverse Events
- Diagnostic Summary

### 5.3. Early Termination Visit

If a subject wishes to exit the study, a termination visit will be scheduled. This will include all evaluations normally performed at the Month 30 visits.

### 5.4. Retrieved drop-outs

Unless a subject withdraws consent, subjects who miss visits will be encouraged to come in for subsequent visits.

### 5.5. Nursing Home Placement

If a subject is placed in a skilled nursing home, the Participant Demographics eCRF will reflect this. All assessments will be completed, to the extent possible. If the subject withdraws consent to continue in the study, a termination visit will be conducted consisting of all evaluations normally performed at the Month 30 visits.

## 6. Assessments

Participation in other clinical studies with cognitive testing more than one time per year is permitted, but due to the sensitive nature of the cognitive tests being administered multiple trials may affect study outcomes. Studies involving fMRI scans may also increase the participant's amount of radiation exposure to unsafe levels. The participant should be advised to speak with the research coordinator about participating in a new study first, until participation in this study has ended.

### 6.1. Cognitive, Behavioral, Functional, and Global Assessments

The tests and scales chosen for use in this protocol were selected because: (1) they represent the domains of interest in this patient population; (2) they will adequately sample cognitive domains of interest in subjects; (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 proposed study; and (6) they were utilized previously in the ADCS MCI trial and worked well. All of these instruments are widely used in multi-center trials studying CN, MCI, and early AD subjects. Additionally, they are being used by Alzheimer Disease Centers as part of their collection of a Uniform Data Set thereby reducing the amount of testing that subjects will need to undergo who are enrolled in both ADC's and ADNI.

*6.1.1. Cognitive and Mood Assessments: Psychiatry Sites*

*Depression History:* The Depression History form collects information on participants' previous depressive episodes and treatment history, including the total number of episodes, the age of participants at each episode, and length of each individual episode. The form provides a list of DSM symptoms for Major Depressive Disorder, and asks participants to think back onto their previous depressive episodes, assess which symptoms were prominent at each point, and discuss any applicable treatment courses that were taken.

*Structured Clinical Interview for DSM-IV (SCID-IV) (First, et al., 1997)* The SCID is a diagnostic interview used to determine major mental disorders and personality disorders according to the DSM-IV criteria. Participants are asked questions from various modules to help identify mood disorders, psychotic episodes, manic and mixed episodes, substance use disorders, anxiety disorders, and somatoform disorders. The SCID ratings will be followed to ensure that each patient meets eligibility criteria, and identify any exclusionary diagnoses.

*Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960):* The 17-item HDRS assesses severity of depressive symptoms of the past week; high scores indicate greater severity of depression. The HDRS asks the participant questions about mood, work and activities, insomnia, somatic symptoms, sexual interest, appetite and weight loss, feelings of fatigue and loss of energy, feelings of guilt, thoughts of suicide, anxiety, and psychomotor agitation and retardation. Questions are rated on frequency, intensity, and duration of symptoms.

*General Anxiety Disorder-7 (GAD-7) (Spitzer, et al., 2006):* The GAD-7 is a 7-item scale which asks participants questions about anxiety they have experienced within a 2 week period. The scale rates feelings of nervousness, excessive worrying, restlessness, irritability, and fear on frequency, and how much these problems have interfered with daily tasks.

*Patient Health Questionnaire (PHQ-9) (Kroenke, et al., 2001):* The PHQ-9 is a nine symptom checklist which rates issues such as mood, worth, concentration, and suicide ideation based on the frequency of which they occur.

*Duke Social Support Index (DSSI) (Blazer, et al., 1990):* The DSSI asks questions about the support that individuals currently receive from people in their life, based on frequency and severity.

*Stroop Color Word (Golden, et al., 2002):* The oral version of the Stroop Color Word is a motor free measure of executive function, information processing speed, set-shifting/perseveration, and impulsivity. In the first condition, patients are shown a stimulus page with names of colors in black ink and asked to read out loud as quickly but as accurately as they can. During the second condition, patients are presented with a stimulus page with XXXX in different colors of ink and asked to identify the color as fast but as accurately as possible. In the interference stimulus condition, patients are shown a stimulus page with names of colors in different colors of ink, and asked to identify the color of the ink that the words are printed in, ignoring the actual word that is printed. Scaled scores for each condition are calculated based on the total number of words read.

*Motor-Free Visual Perception Test- 3(MVPT-3) (Colarusso, 2005):* This task is designed to assess overall visual perceptual abilities, including spatial relationships, visual discrimination, figure-ground, visual closure, and visual memory. During this assessment, the participant is asked to identify the correct answer from among four alternatives for each item. The total score is calculated by subtracting the number of errors made from the total number of the items administered.

*Brief Visuospatial Memory Test (BVMT) (Benedict, 1997):* The BVMT is an assessment of visuospatial processing and visual memory. During three learning trials, participants are asked to study a sheet that has 6 figures on it for 10 seconds before the sheet is removed, and then asked to draw each figure exactly as it appeared, in its correct location on the page. A delayed recall trial is administered 20-25 minutes after trial 3, in which the participant is asked to draw the figures from memory. Scoring is based on accuracy and location of each figure, and scaled scores are calculated based on total recall and delayed recall.

*Benton Judgment of Line Orientation (JLO) (Benton, 1994):* The JLO is an assessment of visuospatial ability. Participants are presented with a stimulus book of 30 items. Each item shows two lines which correspond to a specific angle and direction, and participants are asked to identify the corresponding angle and direction of each item. Total scores range from 0 to 30, and a scaled score is calculated based off of the total correct score.

*WAIS Digit Symbol (Wechsler, 1997):* The Digit Symbol subtest is a measure of attention, working memory, and information processing speed. Participants are presented with a stimulus sheet, and asked to write in the correct symbol that corresponds with a number keyed at the top of the page. A scaled score is calculated based on the number of total correct responses.

*WAIS Digit Span (Wechsler, 1997):* The Digit Span subtest assesses working memory and focused attention. During the first trial, participants are asked to repeat a series of numbers back to the administrator in exactly the order they were said. In the second condition, participants are asked to repeat the numbers to the administrator backwards. A scaled score is calculated based on the total number of correct responses.

*Mini-Mental State Exam (MMSE) (Folstein, Folstein, & McHugh, 1975):* 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. The MMSE is scored as the number of correctly completed items with lower scores indicative of poorer performance and greater cognitive impairment. The total score ranges from 0 to 30 (perfect performance).

*Penn State Worry Questionnaire (Meyer, 1990):* The Penn State Worry Questionnaire is a brief self-reported questionnaire assessing the participant's severity of anxiety. The 16 items included in the questionnaire measure severity of various signs of anxiety/worry on a 5 point scale.

*Perceived Stress Scale (PSS) (Cohen, 1988):* The Perceived Stress Scale is a brief self-reported questionnaire assessing the participant's perception of stress. The PSS is adept at measuring the degree to which situations in one's life are viewed as stressful.

*6.1.2. Cognitive and Mood Assessments: ADNI Sites*

*Montreal Cognitive Assessment (MoCA) (Nasreddine et al, 2005):* The Montreal Cognitive Assessment test (MoCA) is a brief cognitive assessment designed to detect subjects at the MCI stage of cognitive dysfunction. This instrument has been shown to have adequate sensitivity and specificity in clinical settings to detect suspected MCI. The MoCA is believed to be more sensitive than general screening instruments such as the MMSE or the Short Test of Mental Status. The MoCA can be administered in approximately ten minutes.

*Everyday Cognition (ECog) (Farias et al, 2009):* For a functional assessment, we have selected the Measurement of Everyday Cognition (ECog). This instrument has been developed to assess functional impairment of a very mild nature as can be seen in MCI. The ECog is an informant-rated questionnaire comprised of multiple subscales and takes approximately ten minutes to administer. Participants themselves will be asked to complete a self-reported version of the same questionnaire. Previous research on this instrument indicates that ECog correlates well with established measures of functional status and global cognition but only weakly with age and education. ECog was able to differentiate among cognitively normal (CN), MCI and AD subjects. Results of ECog suggest that it is a useful tool for the measurement of general and domain-specific everyday functions in the elderly.

*Alzheimer's Disease Assessment Scale-Cognitive (ADAS-COG) 13 (Rosen, Mohs, & Davis, 1984):* 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. The test is scored in terms of errors, with higher scores reflecting poorer performance. Scores can range from 0 (best) to 70 (worse). Delayed Word Recall and Number Cancellation will be conducted in addition to the eleven standard ADAS-Cog Items.

*Logical Memory Test I and II (Delayed Paragraph Recall) (D Wechsler, 1987):* The Logical Memory test that will be used is a modification of the episodic memory measure from the Wechsler Memory Scale-Revised (WMS-R) (D Wechsler, 1987). 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. The total bits of information from the story that are recalled immediately (maximum score = 25) and after the delay interval (maximum score = 25) are recorded. A retention or "savings" score can be computed by dividing the score achieved during delayed recall by the score achieved during immediate recall.

*Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983):* This measure of visual confrontation naming requires the subject to name objects depicted in outline drawings. In our modification of the full BNT, only 30 items are presented (the odd-numbered items from the full 60-item test). The drawings are graded in difficulty, with the easiest drawings presented first. If a subject encounters difficulty in naming an object, a stimulus cue and/or a phonemic cue is provided. The number of spontaneous correct responses (maximum score = 30) and spontaneous plus semantically-cued correct responses (maximum score = 30) are recorded. The number of perceptual errors, circumlocutions, paraphasic errors, and perseverations can also be used to evaluate the subjects' language performance.

*Category Fluency Test (Butters, Granholm, Salmon, Grant, & Wolfe, 1987):* 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 (Goodglass & Kaplan, 1983):* In the "command" condition of this visuoperceptual constructional task, the subject is given a blank sheet of 8 1/2" 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. A quantitative score (maximum total score = 10) is derived for each drawing by adding the scores of three separate features: a maximum of 2 points is given for the integrity of the clock face; a maximum of 4 points for the presence and sequencing of the numbers; a maximum of 4 points for the presence and placement of the hands. A qualitative analysis can also be performed to note the presence of conceptual, perseverative, stimulus bound, and spatial arrangement errors. The Clock Drawing Test is effective for discriminating between subjects with AD and normal elderly individuals (Cahn et al., 1996).

*American National Adult Reading Test (ANART) (Nelson & O'Connell, 1978):* 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 (Nelson & O'Connell, 1978). The test requires patients to read and correctly pronounce 50 "irregular" words that do not follow common rules of phonography and orthography. The correct pronunciation of such words depends solely on previous familiarity and cannot be accomplished by applying common grammatical rules (e.g., the word 'naive' might be pronounced 'nave' if common English grammatical rules were employed). Thus, the ability to correctly pronounce progressively less common irregular words suggests a large premorbid vocabulary that is correlated with a high premorbid VIQ. The 50 irregular words of the ANART

are printed on a single sheet of paper which is presented to the subject who is instructed to read each word aloud. The number of mispronounced words is recorded by the examiner (maximum errors = 50). Premorbid VIQ can be estimated by applying a formula derived by Grober and Sliwinski: [118.2 - .89 (ANART errors) + .64 (years of education)](Grober & Sliwinski, 1991).

*Rey Auditory Verbal Learning Test (Rey, 1964):* The AVLT is a list learning task which assesses multiple cognitive parameters associated with learning and memory. On each of 5 learning trials, 15 unrelated words (all nouns) are presented orally at the rate of one word per second and immediate free recall of the words is elicited. The number of correctly recalled words on each trial is recorded. Following a 20-minute delay filled with unrelated testing, free recall of the original 15 word list is elicited. Finally, a yes/no recognition test is administered which consists of the original 15 words and 15 randomly interspersed distracter words. The number of target "hits" and false positive responses are recorded.

*Trail Making Test: Parts A and B (Reitan, 1958):* Part A consists of 25 circles numbered 1 through 25 distributed over a white sheet of 8 1/2" X 11" paper. The subject is instructed to connect the circles with a drawn line as quickly as possible in ascending numerical order. Part B also consists of 25 circles, but these circles are either numbered (1 through 13) or contain letters (A through L). Now the subject must connect the circles while alternating between numbers and letters in an ascending order (e.g., A to 1; 1 to B; B to 2; 2 to C). The subject's performance is judged in terms of the time (in seconds) required to complete each trail and by the number of errors of commission and omission. The time to complete Part A (150 second maximum) and B (300 second maximum) will be the primary measures of interest (testing is stopped if the maximum time is reached). Although both Parts A and B depend on visuomotor and perceptual-scanning skills, Part B also requires considerable cognitive flexibility in shifting from number to letter sets under time pressure. Both parts of the Trail-Making Test are available in multiple forms of equal difficulty for purposes of repeated evaluation.

*Clinical Dementia Rating (CDR) (Berg, 1988):* 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. The ratings of degree of impairment obtained on each of the 6 categories of function are synthesized into one global rating of dementia (ranging from 0 to 3), with more refined measure of change available by use of the Sum of Boxes. Reliability and validity has been established, as has high inter-rater reliability. This will be used as a global measure of severity of dementia.

*Activities of Daily Living / Functional Assessment Questionnaire (FAQ) (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982):* Based on an interview with a caregiver or qualified partner, a subject is rated on their ability to carry out ten complex activities of daily living: 1) manage finances, 2) complete forms, 3) shop, 4) perform games of skill or hobbies, 5) prepare hot beverages, 6) prepare a balanced meal, 7) follow current events, 8) attend to television programs, books or magazines, 9) remember appointments, and 10) travel out of the neighborhood. Each activity is rated on a scale from 0 to 3. Scores are summed across items to provide a total disability score (higher scores = greater impairment; maximum score = 30).

*Neuropsychiatric Inventory (NPI) (Kaufer et al., 2000):* The Neuropsychiatric Inventory (NPI) is a well-validated, reliable, multi-item instrument to assess psychopathology in AD based on an interview with a caregiver or qualified partner. The interview is also relatively brief (15 minutes). These properties make it well suited for a multicenter trial.

*Cognitive Change Index 20:* This self-rating scale asks about abilities, problem areas, daily functioning and activities. Items are rated on severity of changes in one's current level of ability compared to 5 years ago, and the severity of any current problems. Includes both participant and informant rating forms.

*Geriatric Depression Scale (Sheikh & Yesavage, 1986):* 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. The more benign items asked first. Answers to 5 of the items are negatively oriented for depression (e.g., Do you feel full of energy?) and 10 positively oriented (e.g., Do you often feel helpless). One point is given for each appropriate positive or negative answer indicative of a symptom of depression, for a possible total of 15 points. Total scores of 0-5 are considered normal and scores of 6-15 are considered depressed.

### 6.2. Biofluid Collection

The study procedure manual will provide more detailed instructions for collection, processing and shipment of all biofluid samples for ADNI-D. Blood (separated into plasma and serum) will be collected so as to accommodate the assay of the broadest range of the best antecedent biomarkers/analytes. Polypropylene tubes will be utilized for the collection and storage of plasma and serum since some key analytes such as Aβ are known to stick to polystyrene and glass. Fasting overnight is required for plasma and serum collection. Only water is permitted until blood draws are completed. The methods used to assay tau, p-tau and Aβ are identical to those used in ADNI2.

### 6.2.1. Cell Immortalization Samples and PBMC Collection

Blood samples will be collected for Cell Immortalization and Peripheral Blood Mononuclear Cells (PBMC) at Baseline for all newly enrolled subjects. Whole blood will be collected in one ACD-A 8.5 mL tube and one 10 mL Sodium Heparin tube.  Samples will be shipped ambient, day of collection, by overnight delivery to the National Cell Repository for Alzheimer's Disease (NCRAD).

Upon arrival at NCRAD the blood sample in the ACD-A tube is placed in a centrifuge and spun to separate the sample into three main layers: the red blood-cell layer, the plasma layer, and the buffy coat, which contains the white-blood cells. The white-blood cells are needed to establish cell lines and obtain DNA. To establish cell lines, the white-blood cells are placed in a flask along with a solution that allows permanent cell growth. The cells are incubated at 37°C (body temperature) ranging from four weeks to three months. The cell -containing solution is then divided and transferred into two larger flasks for further cell growth. It takes approximately one week for the cells to divide to the desired number. The cells are then placed in a vial along with a

preservative. Each vial holds approximately 1 milliliter of solution containing $1\times10^7$ (10,000,000) cells. The cells are gradually cooled to freezing temperatures. The slow freeze prevents damage to the cell line. The frozen cells are bar code labeled and stored in a tank filled with liquid nitrogen at -316°F. Cells can be preserved this way indefinitely and thawed at any time for additional propagation.

Upon arrival at NCRAD the blood sample in the Sodium Heparin tube is diluted with DPBS to a 1:1 ratio. The diluted blood is then layered onto 10mL of Ficoll-Paque$^{TM}$. The tube is placed in a centrifuge and spun to separate the sample into four main layers: the red blood-cell layer, the Ficoll-Paque$^{TM}$ layer, the peripheral blood mononuclear cell (PBMC) layer and the plasma and DPBS layer. The plasma and DPBS layer is removed and discarded. The PBMC layer is collected and transferred to a clean tube. The PBMCs are washed using DPBS and centrifuged again. The PBMCs are then counted using a V-Cell counter system. The PBMCs are washed using DPBS and centrifuged again. The PBMCs are then placed in a vial along with a preservative. Each vial holds approximately 1 milliliter of solution containing $2\text{-}3\times10^7$ (10,000,000) cells. The PBMCs are gradually cooled to freezing temperatures. The slow freeze prevents damage to the PBMCs. The frozen PBMCs are bar code labeled and stored in a tank filled with liquid nitrogen at -316°F. The PBMCs can be preserved this way indefinitely and thawed at any time for additional propagation.

If a sample does not successfully establish, subjects will be asked to agree to re-sampling.

*6.2.2. DNA Sample collection for GWAS, APOE Genotyping, Hematology, and Differential*

Whole blood is collected for GWAS at Baseline for newly enrolled subjects. APOE genotyping will be done using this sample. Differential analysis and blood slides for Hematology analysis will also be created with this sample. A single 10 mL EDTA tube of whole blood will be sent ambient, overnight, and on the day of collection to the National Cell Repository for AD (NCRAD) for genotyping.

The genetics core will request a re-sampling if the sample condition is compromised or if there is poor sample yield.

*6.2.3. RNA Sample Collection*

In order to measure gene expression across time, a RNA sample will be collected at Baseline and at Month 30. Three (3) 2.5 mL tubes will be collected at each visit using kits supplied by the ADNI-CC and following these steps:

1. If the PAXgene Blood RNA Tube is the only tube to be drawn, a small amount of blood should be drawn into a "Discard Tube" (A) prior to drawing blood into the PAXgene Blood RNA Tube. Otherwise, the PAXgene Blood RNA Tube should be the last tube drawn in the phlebotomy procedure.
2. Using a BD (Becton, Dickinson and Company) Vacutainer® Safety-Lok™ Blood Collection Set, collect blood into the PAXgene Blood RNA Tube using your institution's recommended standard procedure for venipuncture.

3. Hold the PAXgene Blood RNA Tube vertically, below the blood donor's arm, during blood collection.
4. Allow at least 10 seconds for a complete blood draw to take place. Ensure that the blood has stopped flowing into the tube before removing the tube from the holder.
5. Gently invert the PAXgene Blood RNA Tube 8 to 10 times.

After freezing on dry ice, RNA samples are packaged and shipped day of collection via Federal Express overnight delivery on dry ice to the National Cell Repository for AD (NCRAD). **Please note:** PAX tubes need to sit at room temperature for 2 hours before freezing.

*6.2.4. Plasma and Serum 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. Once blood is collected into two 10 mL EDTA plastic tubes, as described in the procedures manual, it is mixed thoroughly, then centrifuged for 15 min. at ~3000 rpm. The plasma sample is transferred to approximately 18-20 labeled polypropylene vials containing about 0.5ml volume each and frozen on dry ice for 20 minutes.

Serum is obtained after allowing the samples collected in two 10 mL plain red top plastic tubes to clot at room temperature, and it is spun as above for plasma preparation, aliquoted into approximately 8-10 polypropylene vials used as shipping containers and containing about 0.5ml volume each and frozen on dry ice for 20 minutes.

This change from 1 polypropylene vial to 18-20 will reduce the freeze thaw cycles that sample goes through allowing more samples to be distributes to qualified researchers.

After freezing on dry ice, plasma and serum are packaged and shipped day of collection via Federal Express overnight delivery on dry ice to the National Cell Repository for AD (NCRAD).

*6.2.6 Telomere Collection*

Whole blood samples will be collected for telomere length measurement (TL) analysis to be frozen and stored for future research.  One (1) 4 mL EDTA tube of whole blood will be drawn. Invert the tube 30-40 times immediately after the blood draw.   Pipette whole blood into five (5) 2 ml aliquot screw cap tubes containing approximately 700 ul each within four hours of blood draw and allow freezing on dry ice for 20 minutes.

After freezing on dry ice, the telomere samples are packaged and shipped day of collection via Federal Express overnight delivery on dry ice to the National Cell Repository for AD (NCRAD).

*6.2.8 Banking for Future "TBD" Assay Plasma and Serum Collection*

Both plasma and serum samples will be collected and stored for to be determined future analysis at NCRAD.  Plasma is collected in a uniform fashion using EDTA as anti-coagulant. Once blood is collected into three 10 mL EDTA plastic tubes, as described in the procedures manual, it is

mixed thoroughly, then centrifuged for 15 min. at ~3000 rpm. The plasma sample is transferred to approximately 30 labeled polypropylene vials containing about 0.5 ml volume each and frozen on dry ice for 20 minutes.

Serum is obtained after allowing the samples collected in three 10 mL plain red top plastic tubes to clot at room temperature, and it is spun as above for plasma preparation, aliquoted into approximately 30 polypropylene vials used as shipping containers and containing about 0.5ml volume each and frozen on dry ice for 20 minutes.

This change to 30 polypropylene vial will reduce the freeze thaw cycles that sample goes through allowing more samples to be distributes to qualified researchers.

After freezing on dry ice, plasma and serum are packaged and shipped day of collection via Federal Express overnight delivery on dry ice to the National Cell Repository for AD (NCRAD).

*6.2.9. Buffy Coat Collection*

Buffy coat will be collected and stored for future analysis at both Baseline and Month 30. The buffy coat is the thin layer in between the red blood cells and plasma after centrifugation of the lavender-top tubes used for plasma sample collection during the biomarker and "TBD" assay lab procedures. A pipette tip will be placed into the buffy coat layer after plasma sample collection. Move the pipette tip in a circular fashion collecting the buffy coat layer. The residual plasma and some RBCs will be collected during this process. Buffy coat will be aliquoted into 5 2mL cryogenic vials and frozen on dry ice.

After freezing on dry ice, buffy coat samples will be packaged and shipped day of collection via Federal Express overnight delivery on dry ice to the National Cell Repository for AD (NCRAD).

*6.2.10. Laboratory Procedures at University of Pennsylvania.*

Plasma and serum samples will be shipped for analysis from NCRAD to the Penn AD Biomarker Fluid Bank Laboratory at the 2 year mark. There they will be bar code labeled, and placed in designated locations in the -80°C freezers. All samples will be inventoried and tracked using commercially available software. A database will be created and used for the inventory of stored samples, in conjunction with a bar code reading system. Bar code labels affixed to each sample vial will contain the following information: sample ID# (to preserve confidentiality), date of collection and processing, total initial volume collected, sample type (plasma or serum), volume, aliquot number, freezer, shelf, rack, box, location in the box. A bar code label will be used on the sample tracking form that is used by the technologist when processing and storing samples. This will be done to avoid manual entry errors of sample numbers. When the data are entered into the database the bar code label is scanned in and the sample aliquots entered. Removals of samples will also be tracked on the database, including the date removed and the recipient center.

*6.2.11. Sharing of Banked DNA, RNA, Plasma, and Serum*

Specific procedures for requesting and accessing DNA, RNA, cell lines or plasma or serum 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.

*6.3. Magnetic Resonance Imaging (MRI)*

*6.3.1. Site Qualification*

Each site must be qualified for the MRI portion of the study using the specific ADNI-Depression MRI protocol. The procedure for site qualification will consist of one of two parts – either phantom or human volunteer scanning.

Phantom scanning for MRI certification.  If pulse sequences and scanner types are familiar to the MRI Imaging Core, typically a dry run on a phantom is all that is needed for MRI site qualification.  However, if either of these cases is not true, then a human scan may be necessary. *(It should be noted that currently for ADNI-Depression all sites would qualify for a phantom only scanning session)*

Human scanning for MRI certification.  If deemed necessary by the ADNI-D MRI Core, in terms of human scanning, a site will image a volunteer subject with the ADNI-D MRI protocol. 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.

Image Transfer.  Once images on either a phantom or volunteer have been acquired.  The images will be sent electronically to LONI.

Quality Control.  Each parameter in each of the pulse sequences in the protocol will be checked by the Mayo ADIR QC team. In the event that the protocol has not been performed according to protocol, the site will be asked to perform an additional scan. This will be repeated as many times as necessary until the site has demonstrated exact execution of the MR protocol, at which point they will have passed MR site qualification portion of the study.

*6.3.2. Data Acquisition*

All subjects will be scanned using the ADNI-Depression 3T scanning protocol.

The MRI protocol consists of 9 sequences that are acquired in every subject and on every MRI vendor system these are:

    (1) Localizer,
    (2) Accelerated 3D T1 Sequence (MPRAGE or IR-FSPGR
    (3) Axial fMRI (Functional)

        (4) Axial ASL (Arterial Spin Labeling)
        (5) Axial FLAIR
        (6) Axial T2 Star
        (7) Axial DTI (Diffusion Tensor Imaging)
        (8) Axial T2 FSE with Fat Sat
        (9) Field Mapping

MRI measurements of brain structure have been shown to demonstrate brain atrophy (which correlates with neuron loss) in MCI and AD and increasing rates of brain atrophy as subjects become more impaired. Therefore, structural MRI is used as a measure of the rate of disease progression. Cerebrovascular disease (especially white matter lesions (WMLs)) will be assessed with FLAIR. Iron imaging especially micro bleeds (T2* GRE); has been used to detect microbleeds; this will be measured with T2* GRE.

The data may be used to test our hypotheses as well as to examine relationships between: 1) baseline and rates of change of structural MRI to clinical, PET, and plasma biomarker measures 2) baseline MRI WMLs and microbleeds and cognitive measures. 3) MRI assessments of microbleeds/ WMLs and PET measures of brain amyloidosis. 4) baseline/rate of change of ASL and MRI.

### 6.3.3. Clinical Read of MRIs

The research site is responsible to obtain a read from a local radiologist for each MRI completed for the ADNI-Depression Protocol. This read must be retained in source documents and a de-identified report included in the forms scanned and submitted to the ADNI-CC.

### 6.3.4. Data Management and Quality Control

Study Images are uploaded by site users to the Laboratory of Neuroimaging (LONI) at the University of Southern California (USC).

Each MRI will be assessed in terms of quality control by the MRI Core. Quality control for MRI will result in failure of some scans which may need to be repeated. Repeat scans must be scheduled within four (4) weeks of the visit date.

### 6.4. Florbetapir Amyloid PET Imaging

### 6.4.1. 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 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 [18]F. The phantom must be scanned on two sequential days 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.

### 6.4.2. Data Acquisition

All subjects that will be studied in this protocol will receive a florbetapir imaging scan. Scans must be completed within 2 week before or 2 week after the in-clinic Baseline Assessment.

The florbetapir protocol will entail the injection of 10 mCi of [18F]AV-45 administered by intravenous bolus injection (over 5 to 10 seconds) followed by an uptake phase of 50 minutes during which time the subject may wait in a quiet room. Depending on the type of scanner, the subject should be placed on scanning table at 40 minutes post-injection to allow time for an attenuation scan. The PET scan must begin at approximately 50 minutes post AV-45 injection. Brain images will be acquired continuously for a period of 20 minutes as four 5-minute frames. The images will be immediately assessed for technical validity. If considered inadequate, the subject will have an additional 20 minutes of continuous imaging, collected as four 5-minute frames. Transmission scans should be done prior to the scans to allow for reconstruction of the images after the scan. If there is a repeat scan, transmission can be done after the scan. PET/CT scans will precede this acquisition with a CT scan for attenuation correction; PET-only scanners will perform a transmission scan following the emission scan. As we have done to date in ADNI, sites will be required to use a single iterative reconstruction for all scans that is optimized for the instrument and which cannot change during the protocol. The vast majority of sites are experienced with this; new sites will be instructed as part of the qualification procedure. This information is detailed in the PET technical manual. Vital signs will be taken in a supine position immediately prior to administration of florbetapir F 18 (within 5 minutes prior to injection) and again at the end of the study visit, prior to discharge (approximately 70 minutes after florbetapir F 18 administration). Each study participant or a person designated to speak for them will be contacted by phone 24 hours after the imaging session to confirm their well-being and query them about any new serious adverse events.

### 6.4.3. Data Management and Quality Control

Images are uploaded by site users to the Laboratory of Neuroimaging (LONI) at the University of Southern California (USC). Data are de-identified as part of the upload and placed into quarantine until they pass quality assurance evaluation conducted by the PET Core. There will be several steps in the quality assurance and pre-processing of the $^{18}$F-AV-45 images that are obtained from the scanning sites. The aim of this work is not only to make sure that all PET scans are acquired and reconstructed using the appropriate protocols and that image quality is good, but to standardize the images from the different sites, and hence the different PET scanner vendors and models, as much as possible in order to reduce inter-site differences.

The following are specific steps will be taken:
1. Visual inspection of all images: both frames (temporal) and slices (spatial);
2. Extract and inspect header information;

3. Co-register all frames of the multi-frame studies to the first frame of the image set;
4. Assess motion by magnitude of translate/rotate parameters;
5. Recombine co-registered frames to create registered dynamic and registered average (averaged over all frames) image sets;
6. Reorient /resample images into a standard image matrix and image orientation (160x160x96 voxels 1.5 mm in all dimensions);
7. Perform normalization on all image sets, based on cerebellar gray matter for amyloid imaging;
8. Smooth images from all scanner models by amounts determined from Hoffman phantom scans to achieve uniform 8mm effective resolution;
9. Complete PET QA forms;
10. Upload post-processed PET images sets to LONI (image repository).

Quality control for the $^{18}$F-AV-45 will result in failure of some scans. Many of these scans are expected to be useful if the data are reprocessed. Sites must retain all raw, unprocessed images at least until image quality control has been performed and the determination has been made as to whether the image requires reprocessing. Based on our experience in ADNI, approximately 1-2% of scans will need to be repeated. For this reason, our dosimetry projections include the radiation exposure that a subject would encounter if the $^{18}$F-AV-45 scans were repeated. Repeat scans must be conducted within 2 weeks of the visit date.

## 7. Serious Adverse Events Reporting

All subjects will be evaluated for serious adverse events at each clinical visit and telephone check.

### 7.1. Definition of an Serious Adverse Event

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.

### 7.2. Following up on Serious Adverse Events

The investigator is obliged to follow subjects with SAE'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 serious adverse events will be treated and followed according to established medical practice. All pertinent information will be entered into the eCRF.

### 7.3. 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 is in turn will trigger a report to be distributed to all participating sites and the NIA. Each site is responsible for submitting SAE's to their IRBs as required.

## 8. Statistical Considerations

All hypothesis testing will employ 2-sided testing with a significance level of $\alpha=0.05$ used for all primary hypotheses.

### 8.1. Assessing normal/binomial assumptions

Some statistical procedures we will use assume that responses follow a normal distribution and we will use standard diagnostic methods such as quantile-quantile plots and direct tests of normality to examine the appropriateness of this assumption. Other models for binary outcomes assume that the outcomes follow a binomial distribution and we will additionally fit models that allow for over-dispersion departures from the binomial to test whether the assumption is reasonable. If we detect severe departures from our distributional assumptions, we will perform data transformations, use over-dispersed models, or apply non-linear/non-parametric modeling approaches.

### 8.2. Outliers

We will examine plots of data and residuals from fitted models to detect potential outlying and influential points. If we detect such points we will flag and check them with the sites for accuracy. If any outliers are not in error, then we will assess the effect of these points on the analysis by re-running the analysis without the points. If the two sets of analyses differ substantially, we will report the results separately.

### 8.3. Missing Data

Every attempt will be made to determine the reason for any missing data, in particular for missing observations caused by loss to follow-up. If a subject's observation is deemed missing at random (i.e. missing follow-up for reasons unrelated to the outcome) then we can continue to apply models "as is" with the missing observation simply left out of the analysis. When missing outcome data is deemed informative (i.e. not missing at random), we will perform sensitivity analysis. The sensitivity analysis will examine multiple approaches to imputing the missing data (e.g. simple carry last one forward, or advanced methods such as Expectation Maximization), as well as outcomes corresponding to different extreme case scenarios for the missing data mechanism. When just covariates are missing, we will compare results with the subject dropped versus that when imputation methods are applied.

## 9. Ethics

*9.1. Human Subjects, Ethical and Regulatory Considerations*

This study will be conducted according to Good Clinical Practice guidelines, US 21CFR Part 50– Protection of Human Subjects, and Part 56 – Institutional Review Boards (IRBs) / Research Ethics Boards (REBs), and pursuant to state and federal HIPAA regulations. Phone consents will be obtained for all pre-screening procedures and written informed consent for the study must be obtained from all participants and/or authorized representatives and the study partners before in person assessments are carried out.

*9.2. Institutional Review Board / Research Ethics Boards*

Institutional Review Boards and Research Ethics Boards must be constituted and their authority delegated through the institution's normal process of governance according to applicable State and Federal requirements for each participating location. The protocol will be submitted to appropriate Boards and their written unconditional approval obtained and submitted to Regulatory Affairs at the ADNI-CC prior to commencement of the study. The ADNI-CC will supply relevant data for investigators to submit to their IRBs/REBs for protocol review and approval. Verification of IRB/REB unconditional approval of the protocol and the written informed consent statement with written information to be given to the participants and/or their authorized representatives and study partners and will be transmitted and validated by the ADNI-CC in order to obtain approval for shipment of study supplies and worksheets to study sites. Sites' approval must refer to the study by exact protocol title and number, identify documents reviewed, and state the date of review. IRBs/REBs must be informed by investigators of all subsequent protocol amendments and of serious or unexpected adverse experiences occurring during the study that are likely to affect the safety of the participants or the conduct of the study. IRB approval for such changes must be transmitted in writing to the ADNI-CC.

*9.3. Informed Consent and HIPAA Compliance*

Informed consent will be obtained in accordance with US 21 CFR 50.25, the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada, ICH Good Clinical Practice and applicable HIPAA privacy notifications will be implemented before in person assessment procedures are carried out. Information should be given in both oral and written form as deemed appropriate by the Site's IRB.

Participants, their relatives, guardians or authorized representatives and study partners must be given ample opportunity to inquire about details of the study. The consent form generated by the investigator with the assistance of the CC must be approved, along with the protocol, and HIPAA privacy notifications by the IRB/REB and be acceptable to the CC. Consent forms must be in a language fully comprehensible to the prospective participants and/or their authorized representatives and study partners. Informed consent will be documented by the use of a written consent form approved by the IRB/REB and signed by the participant and/or an authorized representative and study partner. Consent must be documented by the dated signature of the participant and/or authorized representative pursuant to local regulations. Each participant's signed informed consent and/or HIPAA research authorization must be kept on file by the investigator for possible review by regulatory authorities and/or ADCS monitors. HIPAA

privacy requirements will be met by either inclusion of required HIPAA text within the IRB-approved consent document or by separate HIPAA research authorization, pursuant to local regulations.

## *9.4. Informed Consent for Biomarkers, Genetic Material, and Imaging Data*

The informed consent will not only cover consent for the trial itself, but for the genetic research, biomarker studies, biological sample storage and imaging scans as well. The consent for storage will include consent to access stored data, biological samples, and imaging data for secondary analyses. Consent forms will specify that DNA and biomarker samples are for research purposes only; the tests on the DNA and biomarker samples are not diagnostic in nature and participants will never receive results. MRI scan findings of clinical significance, determined by the site radiologist, will be shared with participants The informed consent and/or HIPAA notification will specify that the ADCS will receive and store all research data; that Mayo Clinic Rochester will receive MRI images, the University of Michigan will receive and store PET images, the National Cell Repository for AD (NCRAD) located at Indiana University will receive and store blood, DNA, RNA, biomarker samples and develop and store immortalized cell lines and PBMCs, while the University of Southern California Laboratory of Neuroimaging will house a full set of all the data. All data will be made available to: the pharmaceutical industry, academic investigators and other interested parties in the public domain. A policy for distribution of data has been developed.

To ensure the ability to broadly share data, the consent documents should include the following wording:

> "By signing this consent you are authorizing the use of your data and biological materials for large scale, multi-center studies that will combine data from similar populations. These multi-center studies are being conducted by the Alzheimer's Disease Neuroimaging Initiative (ADNI), a neuroscience consortium of universities and research institutes. Your data and biological samples will be stored with a coded research identifier to protect your identity. Only coded data, which does not include anything that might directly identify you, will be shared with the general scientific community for research purposes. This data will be entered into study databases to be used from this date and going forward. Genetic data may be made available on NIH-approved, secure databases."

Please refer here to established NIH guidelines: http://www.ncbi.nlm.nih.gov/gap

## *9.5. Procedures to Maintain Confidentiality*

### *9.5.1. Genetic Research and Storage of Genetic Material*

The ADNI laboratories at The National Cell Repository for AD will follow procedures to ensure that no reasonable chance of the subject's genetic data can be linked to her/his identity. Confidentiality will be sincerely attempted, but cannot be guaranteed.

The de-linking of the sample from the participant occurs at the time the sample is sent to the National Cell Repository for AD at Indiana University. All samples will be inventoried and tracked using commercially available software. A database will be created and used for the inventory of stored samples in conjunction with a bar code reading system. Bar code labels affixed to each sample vial will contain the following information: sample number (to preserve confidentiality) and a bar code.

Immortalized cell lines, PBMCs, hematology slides, differential panel, DNA and RNA will also be prepared at The National Cell Repository for AD. A unique bar-code number is affixed to all tubes as well as affixed to the Sample Form/Draw Sheet. The yellow and green top tubes are spun down immediately. All transfer tubes, vessels and storage vials are pre-labeled prior to sample processing. NCRAD maintains a secure database for tracking all incoming ADNI samples. The only information that will be maintained in this database is an individual number (to preserve confidentiality), kit number (assigned to all tubes that come in a single shipment for an individual), sample number (barcode #), type of sample received, date drawn, date received, initial volume collected for each tube type, time of draw, year of birth and gender.

Neither the ADNI-CC nor NCRAD will have information regarding the participant's name and thus all are unable to link the DNA analysis results to the person. To gain the maximum utility for research on genetic material and biological markers, the ADNI-CC will be able to analyze clinical research data collected on each participant in relation to biological specimens from that participant. However, there will be no link to research done on these specimens with participants' names. It is important to note that the linkage is between DNA research data and study research data, none of which includes identifying information. The data centers (UCSD, USC) do not have any record of the names of the study participants, or of specific medical identifiers such as clinical medical record numbers. Therefore, even though DNA results can be linked to clinical research data for purposes of analyses, the only linkage of DNA test results to names of participants that can happen is at the clinical site.

Since NCRAD is an NIH specimen repository whose focus is on sample sharing, a general protocol has been approved by the IRB at Indiana University that covers all sample receipt, processing and distribution. The protection of patient confidentiality and the use of stored DNA specimens will be in accordance with the rules and procedures established by the Indiana University IRBs. NCRAD stores all samples in a secure freezer within a secure facility at Indiana University. The samples are without a link to identity of the participant from whom the sample came. All samples are bar coded for identification.

Specific procedures for requesting and accessing DNA have been created by the Resource Allocation Review Committee (RARC) of the ADNI in accordance with recommendations proposed in the NBAC Human Biological Materials Report. These DNA guidelines have also been developed in accordance with the American Society for Human Genetics' position paper on the NBAC report and the Ad Hoc Committee on Stored Tissue of the College of American Pathologists.

*9.5.2. Biomarker Samples and Research*

Biomarker fluid samples will be labeled by barcoding samples. Samples will be stored by barcode number and no other identifying information will be provided.

*9.5.3. MRI and PET Imaging and Data Storage*

MRI and PET scans will be labeled according to each site's imaging machine capabilities using ADNI subject identifiers and scanner specific series descriptions as detailed in the MRI procedures manual and the PET procedures manual. All efforts will be made to have scans sent with this information. All scans will undergo a de-identification process, which is embedded within the LONI Imaging process to ensure that no subject identification information is present in the image files. MRI scan findings of clinical significance, determined by the site radiologist, will be shared with the subject and the subject's local physician.

## **10. Potential Risks**

*10.1. Florbetapir($^{18}$F-AV-45)*

Florbetapir F 18 injection is approved by the United States Food and Drug Administration (FDA) to estimate amyloid levels in adult patients with memory problems who are being evaluated for AD and other causes of cognitive decline. Florbetapir (F 18) is an imaging agent that includes a small amount of radioactivity (radiation) necessary to create the PET scan image. The dose used in this study is below the level shown to have an effect on the body.

The total amount of radiation from the florbetapir (F 18) PET scan is slightly more than a patient receives from a routine CT scan and about 3 to 6 times as much as the average person receives per year from natural and man-made radiation. Exposure to large amounts of radiation increases the risk of developing cancer.

The most common side effect in completed studies with florbetapir was headache. Additional uncommon side effects reported were nausea, dysgeusia (bad taste in the mouth), flushing, pruritus (itching), urticarial (hives), and infusion site rash. Musculoskeletal (muscle or bone) pain in the neck, shoulders, and back, fatigue, anxiety, claustrophobia (fear of being in closed or narrow spaces), insomnia (inability to sleep), dizziness, chills/feeling cold, and hypertension (high blood pressure) were also reported. There were other side effects, but none that occurred in more than one subject in the research studies.

There is currently no information on the effects of florbetapir F 18 on unborn children. However, it is known that higher levels of radiation can cause damage to unborn children. This study excludes women who are able to become pregnant.

*10.2. MRI*

There are no proven biologic risks associated with MRI scanning. All subjects will be rigorously screened by MR personnel to be certain that they do not have any medical contraindications for MRI which include metallic foreign bodies in the brain or eye or cardiac pacemaker. This safety screening is part of routine clinical practice at MRI centers and is performed before any subject

is permitted to enter the scanning room. However there is a slight risk that someone will accidently bring metal into the MRI scanner room, which might be pulled into the MRI magnet and injure the subject. 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. Use of anxiolytic agents for completion of MRI scans is at the discretion of site clinicians.

### *10.3. Blood Draw*

The risks of blood draw include pain from the needle, bruising or infection at the site of venipuncture, or fainting as a response to blood draw.

## 11. Study Glossary

| | |
|---|---|
| AD | Alzheimer's Disease |
| ADAS-Cog | Alzheimer's Disease Assessment Scale-Cognitive |
| ADC | Alzheimer's Disease Center |
| ADCS | Alzheimer's Disease Cooperative Study |
| ADEAR | Alzheimer's Disease Education & Referral Center, under the NIA |
| ADNI | Alzheimer's Disease Neuroimaging Initiative |
| ADNI1 | Original NIH grant, funding began October 2004 |
| ADNI2 | Additional NIH funding, October 2010 |
| ADNI-D | Alzheimer's Disease Neuroimaging Initiative-Depression Project |
| ADNI-CC | Alzheimer's Disease Neuroimaging Initiative Coordinating Center |
| ADNI-GO | Alzheimer's Disease Neuroimaging Initiative-Grand Opportunity |
| ADC's | Alzheimer's Disease Centers (under NIA) |
| 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 |
| Aβ | Beta Amyloid |
| ASL | Arterial Spin Labeling |
| BJLO | Benton Judgment of Line Orientation |
| BMI | Body Mass Index |
| BNT | Boston Naming Test |
| BVMT | Brief Visuospatial Memory Test |
| C-11 PIB | [N-methyl-11C]2-(4'-(methylamino)phenyl-6-hydroxy-benzothiazole |
| CCI-20 | Cognitive Change Index-20 |
| CDR | Clinical Dementia Rating |
| CI | Cognitive Impairment |
| CN | Cognitively Normal |
| CSF | Cerebral Spinal Fluid |
| CT | Computerized Tomography |
| DNA | Deoxyribonucleic Acid |

| | |
|---|---|
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition |
| DSSI | Duke Social Support Index |
| DTI | Diffusion Tensor Imaging |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| EMCI | Early Amnestic Mild Cognitive Impairment |
| ECog | Everyday Cognition |
| FAQ | Functional Activities Questionnaire (Activities of Daily Living) |
| $^{18}$F-AV-45 | Florbetapir F 18 |
| FLAIR | Fluid Attenuation Inversion Recovery |
| GAD-7 | Generalized Anxiety Disorder-7 |
| GDS | Geriatric Depression Scale |
| GWAS | Genome Wide Association Studies |
| HIPPA | Health Insurance Portability and Accountability Act |
| HDRS | Hamilton Depression Rating Scale |
| ICH | International Conference on Harmonisation |
| IRB | Institutional Review Board |
| IR SPGR | Inversion Recovery Spoiled Gradient-Recalled |
| LLD | Late Life Depression |
| LMCI | Late Mild Cognitive Impairment |
| LONI | Laboratory of Neuroimaging |
| MCI | Mild Cognitive Impairment |
| MDD | Major Depressive Disorder |
| MMSE | Mini Mental State Examination |
| MoCA | Montreal Cognitive Assessment |
| MPRAGE | Magnetization Prepared Rapid Gradient Echo |
| MR/MRI | Magnetic Resonance / Magnetic Resonance Imaging |
| MVPT-3 | Motor-Free Visual Perception Test-3 |
| NCRAD | National Cell Repository for Alzheimer's Disease |
| NIA | National Institute on Aging, under the NIH |
| NIH | National Institutes of Health |
| NINCDS/ADRDA | National Institute of Neurological and Communicative Diseases and Stroke / Alzheimer's Disease and Related Disorders Association |
| NPI | Neuropsychiatric Inventory Questionnaire |

| | |
|---|---|
| PET | Positron-Emission Tomography |
| PHQ-9 | Patient Health Questionnaire-9 |
| PI | Principal Investigator |
| Pitt | University of Pittsburg Medical Center |
| 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 |
| SCID | Structured Clinical Interview for the DSM-IV |
| SDMT | Symbol Digit Modalities Test |
| T | Tesla |
| TFT's | Thyroid Function Tests |
| T2*GRE | T2 Star-Weighted Gradient-Echo |
| UCSD | University of California, San Diego |
| UCSF | University of California, San Francisco |
| USC | University of Southern California |
| VIQ | Premorbid Verbal Intelligence |
| WMS-R | Wechsler Memory Scale-Revised |
| WML | White Matter Lesions |

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