Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3) Protocol

Protocol Short Title: ADNI3

Protocol Number: ATRI-001

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LIST OF ABBREVIATIONS

AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive
ADC	Alzheimer's Disease Center
ADEAR	Alzheimer's Disease Education & Referral Center, under the NIA
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADNI1	Alzheimer's Disease Neuroimaging Initiative - 1
ADNI2	Alzheimer's Disease Neuroimaging Initiative - 2
ADNI-GO	Alzheimer's Disease Neuroimaging Initiative – Grand Opportunity
PCORNet	Patient Centered Outcomes Research Network
AE	Adverse Event
AMNART	American National Adult Reading Test
APOE/APOE4	Apolipoprotein E (APOE) epsilon 4 (APOE4)
ATRI	Alzheimer's Therapeutic Research Institute
Aβ	Beta Amyloid
ASL	Arterial Spin Labeling
CBB	Cogstate Brief Battery
CCI	Cognitive Change Index
CDR	Clinical Dementia Rating
CSF	Cerebrospinal Fluid
CT	Computerized Tomography
dbGaP	Database of Genotypes and Phenotypes
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DTI	Diffusion Tensor Imaging
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture (System)
EMCI	Early Amnestic Mild Cognitive Impairment
ECog	Everyday Cognition
FCI-SF	Financial Capacity Instrument – Short Form
FAQ	Functional Activities Questionnaire (Activities of Daily Living)
FDG	Fluorodeoxyglucose
FLAIR	Fluid Attenuation Inversion Recovery
fMRI	Functional Magnetic Resonance Imaging
GCP	Good Clinical Practice

GDS	Geriatric Depression Scale
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IRB	Institutional Review Board
LMCI	Late Mild Cognitive Impairment
LAR	Legally Authorized Representative
LONI	Laboratory of Neuroimaging at USC
LP	Lumbar Puncture
MCI	Mild Cognitive Impairment
MINT	Multi-lingual Naming Test
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 AD
NIA	National Institute on Aging, under the NIH
NIH	National Institutes of Health
NPI	Neuropsychiatric Inventory
PET	Positron-Emission Tomography
PI	Principal Investigator
PT/PTT	Prothrombin Time (PT)/Partial Thromboplastin Time (PTT)
QA / QC	Quality Assurance / Quality Control
REB	Research Ethics Board
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
T	Tesla
TFTs	Thyroid Function Tests
TSH	Thyroid Stimulating Hormone
vMRI	Volumetric Magnetic Resonance Imaging

SIGNATURE PAGE

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PROTOCOL SYNOPSIS

PROTOCOL TITLE	Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3)
PROJECT DIRECTOR	Michael W. Weiner, M.D.
STUDY SPONSOR	National Institute on Aging, National Institute of Health
COORDINATING CENTER	Alzheimer's Therapeutic Research Institute (ATRI)
STUDY DESIGN	Non-randomized natural history non-treatment study
DURATION OF STUDY PARTICIPATION	Screening period will be open for approximately two years followed by a 2-5 year longitudinal follow-up period based on cohort.
SAMPLE SIZE	1,070-2000 total participants will be enrolled across 3 cohorts: cognitively normal (CN), mild cognitive impairment (MCI), and mild AD dementia. Approximately, 700-800 will be rollover participants from ADNI2, and 370-1200 will be newly enrolled
SUMMARY OF KEY ELIGIBILITY CRITERIA	Newly enrolled participants will be 55-90 (inclusive) years of age, willing and able to undergo test procedures that include neuroimaging and lumbar punctures to be carried out longitudinally. Rollover participants must have been enrolled in ADNI previously and willing to continue participation. MMSE, CDR, and Logical Memory meeting cut-off scores for each diagnostic category.
PRIMARY OBJECTIVE	Discover, optimize, standardize, and validate clinical trial measures and biomarkers used in ongoing AD research.
OUTCOME MEASURES / STUDY PROCEDURES	Rates of decline on cognitive, global, and functional tests; rate of conversion to MCI or dementia due to AD; volumetric and structural MRI measures; rates of change on each specified biochemical biomarker; correlations and change among biomarkers; longitudinal extent and rate of amyloid deposition; longitudinal changes in tau; subgroup analyses among all the biochemical and imaging biomarkers.

1.0 INTRODUCTION

Since its launch in 2004, the overarching aim of the Alzheimer's Disease Neuroimaging Initiative (ADNI) has been realized in informing the design of therapeutic trials in AD. ADNI3 continues the previously funded ADNI1, ADNI-GO, and ADNI2 studies that have been combined public/private collaborations between academia and industry to determine the relationships between the clinical, cognitive, imaging, genetic and biochemical biomarker characteristics of the entire spectrum of Alzheimer's disease (AD).

1.1 Primary Aims

ADNI3 will continue to discover, optimize, standardize, and validate clinical trial measures and biomarkers used in AD research.

Aim 1. Longitudinal changes in cognition and associated biomarkers

Determine and define those measures of cognition and function, including composite measures, and those biomarker measures, which capture longitudinal change with the highest statistical power to detect treatment effects in clinical trials. Longitudinal change of cerebral tau measured with ^{18}F-AV-1451 PET (flortaucipir) will be correlated/compared with other measures.

Aim 2. Prediction of cognitive decline

Determine which clinical, cognitive, and biomarker measures that best predict decline of cognition in CN, MCI, and AD participants. In addition, determine which biomarker changes correlate with cognitive decline, with focus on flortaucipir PET.

Aim 3. Validation

Validate biomarker measures obtained at Baseline and longitudinally by correlating results with "gold standard" clinical measurements and pathology.

Aim 4. Clinical trial design

Determine the optimum outcome measures with attention to cognitive decline and flortaucipir PET, predictors of cognitive decline, and inclusion/exclusion criteria for clinical trials of cognitively normal participants (for secondary preclinical AD trials), MCI patients (for prodromal AD trials) and participants with early dementia due to AD.

Aim 5. Discovery

To determine the effects of other known disease proteins found in AD brains and genes, as well as newly discovered genes, proteins, and analytes that provide useful information concerning the pathogenesis/diagnosis of AD.

2.0 BACKGROUND AND SIGNIFICANCE

2.1 Rationale for Study

ADNI plays a central role in improving treatment trials. Since the study's launch, ADNI Investigators with regulators in both the US and abroad have facilitated the design of major completed and ongoing drug trials[1-18].

2.1.1 Rationale for Outcome Measures and Biomarkers

Our strategy is based on the concept that the AD process is characterized by the accumulation of Aβ and phosphorylated tau, synaptic loss and neurodegeneration, leading to cognitive decline. Clinical/cognitive measures lack both sensitivity and specificity to detect AD pathology. Instead, biomarkers are more reliably used to identify participants at risk for cognitive decline and to measure disease progression. This project will collect MRI (structural, diffusion weighted imaging, perfusion, and resting state sequences); amyloid PET using florbetapir F18 (florbetapir) or florbetaben F18 (florbetaben); ^{18}F-FDG-PET (FDG-PET); CSF for Aβ, tau, phosphorylated tau, and other proteins; flortaucipir PET; and genetic and autopsy data to determine the relationship of these biomarkers to baseline clinical status and cognitive decline.

Predictors – We hypothesize that the imaging/biomarker measurements most likely to predict decline from normal or from initial significant memory concern will be measures of Aβ (CSF and PET) and measures of flortaucipir PET scan in combination with measures of CSF tau, FDG-PET, and MRI.

Outcomes – We hypothesize that the biomarkers most likely to correlate with and to augment the utility of cognitive and clinical measures as outcomes in clinical trials are flortaucipir PET and MRI measures of volume (especially of hippocampus and temporal cortex) at early stages. Atrophy throughout the brain may be the most significant correlate with clinical and cognitive measures at later stages of AD.

3.0 STUDY DESIGN & SAMPLE SIZE

This is a non-randomized, natural history, non-treatment study. Approximately 1070 - 2000 participants will be enrolled at approximately 59 sites in the United States and Canada. Approximately, 700 - 800 will be rollover participants from ADNI2, and 370 - 1200 will be newly enrolled. Clinical/cognitive, imaging, biomarker, and genetic characteristics will be assessed across the three cohorts: CN, MCI, and mild AD dementia.

Sample size by cohort

- Cognitively normal (CN) cohort:
  - 295-330 rollover participants
  - 135-500 new participants
- Mild Cognitive Impairment (MCI) cohort:
  - 275-320 rollover
  - 150-515 new
- Mild Alzheimer's Disease dementia (AD) cohort:
  - 130-150 rollover
  - 85-185 new

Clinical/cognitive assessments, 3T MRI and collection of plasma and serum for biomarkers will be conducted annually for MCI and AD, and biennially for CN. Blood

samples will be collected for peripheral blood mononuclear cell (PBMC) banking for genetic analysis at the Baseline Visit for new participants, and at the Initial Visit for rollover participants (if not previously obtained). In addition, blood will be collected for longitudinal DNA and RNA genetic analyses at follow-up visits. Amyloid PET imaging and CSF collection for biomarkers will occur biennially.

All participants will undergo two flortaucipir PET scans, with some receiving additional flortaucipir PET scans dependent on cohort and amyloid status.

MCI and AD participants will undergo one FDG-PET scan at Initial/Baseline Visit only; CN group is not required to conduct FDG-PET.

CN and MCI participants will be asked to perform computerized cognitive testing (Cogstate Brief Battery) at each annual or biennial in-clinic visit, and up to quarterly intervals remotely at a home computer or by other means (e.g., neighbor or community center).

Neuropathological examination of brains obtained by autopsy will be performed.

Visit frequency and assessments are outlined in more detail in section 6.0 (Description of Study Visits) and Appendix 1(Schedule of Events).

4.0 STUDY POPULATION

The study will enroll men and women aged 55-90 years across CN, MCI, and mild AD dementia participant groups, as specified in the entry criteria below. Exceptions to these guidelines may be considered on a case-by-case basis at the discretion of the project director and ADNI-CC.

4.1 Inclusion Criteria

All newly enrolled participants must meet the following criteria:

	CN	MCI	AD
1.	Participant with or without **subjective memory complaints**, verified by a study partner, beyond what one would expect for age	Participant **must express a subjective memory concern** as reported by participant, or recalled by study partner or clinician.	Participant **must express a subjective memory concern** as reported by participant, or recalled by study partner or clinician.
2.	Normal memory function documented by scoring above education adjusted cutoffs on the Logical Memory II subscale (Delayed Paragraph Recall, Paragraph A only) from the Wechsler Memory Scale –Revised (the maximum score is 25): **a. ≥9 for 16 or more years of education** **b. ≥5 for 8-15 years of education** **c. ≥3 for 0-7 years of education**	Abnormal memory function documented by scoring below education adjusted cutoffs on the Logical Memory II subscale (Delayed Paragraph Recall, Paragraph A only) from the Wechsler Memory Scale –Revised (the maximum score is 25): **a. < 11 for 16 or more years of education** **b. ≤ 9 for 8-15 years of education** **c. ≤ 6 for 0-7 years of education**	Abnormal memory function documented by scoring below education adjusted cutoffs on the Logical Memory II subscale (Delayed Paragraph Recall, Paragraph A only) from the Wechsler Memory Scale – Revised (the maximum score is 25): **a. ≤ 8 for 16 or more years of education** **b. ≤ 4 for 8-15 years of education** **c. ≤ 2 for 0-7 years of education**
3.	Mini-Mental State Exam score between **24 and 30** inclusive (Exceptions may be made for participants with less than 8 years of education at the discretion of the Project Director)	Same as CN	Mini-Mental State Exam score between **20 and 26** inclusive (Exceptions may be made for participants with less than 8 years of education at the discretion of the Project Director)
4.	Clinical Dementia Rating = **0**. Memory Box score must be **0**	Clinical Dementia Rating = **0.5**. Memory Box score must be at least **0.5**	Clinical Dementia Rating = **0.5 or 1.0**

5.	**Cognitively normal**, based on an absence of significant impairment in cognitive functions or activities of daily living	**General cognition and functional performance sufficiently preserved such that a diagnosis of Alzheimer's disease cannot be made** by the site physician at the time of the Screening Visit	NINCDS/ADRDA criteria for **probable AD**
6.	Stability of Permitted Medications for at least 4 weeks: a. Stable doses of antidepressants lacking significant anticholinergic side effects (if they are currently adequately treated for depressive symptoms and do not have a history of major depression within the past 1 years) b. Estrogen replacement therapy is permissible c. Gingko biloba is permissible, but discouraged d. Washout from psychoactive medication (e.g., excluded antidepressants, neuroleptics, chronic anxiolytics or sedative hypnotics, etc.) for at least 4 weeks prior to screening	Same as CN plus: **Cholinesterase inhibitors and memantine are allowable if stable for 12 weeks prior to Screening Visit**	Same as MCI

Additional inclusion criteria that applies to all diagnostic categories for newly enrolled participants:

1. Geriatric Depression Scale score less than 6.
2. Age between 55-90 years (inclusive).
3. Study partner who has frequent contact with the participant (i.e., minimum average of 10 hours per week) and is available to accompany the participant to all clinic visits for the duration of the protocol.
4. Visual and auditory acuity adequate for neuropsychological testing.
5. Good general health with no diseases expected to interfere with the study.

6. Participant is not pregnant, lactating, or of childbearing potential (i.e., women must be two years post-menopausal or surgically sterile).
7. Willing and able to participate in a longitudinal imaging study.
8. Modified Hachinski Ischemic Score less than or equal to 4.
9. Completed six grades of education or has a good work history (sufficient to exclude mental retardation).
10. Must speak English or Spanish fluently.
11. Willing to undergo repeated MRIs (3Tesla) and at least two PET scans
12. Agrees to collection of blood for genomic analysis (including GWAS sequencing and other analysis), APOE testing and biospecimen banking.
13. Agrees to collection of blood for biomarker testing.
14. Agrees to at least one lumbar puncture for the collection of CSF (non-minority participants only).
15. Agrees to share genomic data and biomarker samples.

4.1.1 Inclusion Criteria Specific to Rollover Participants

The following additional inclusion criteria apply to all diagnostic categories for rollover participants only:

1. Must have been enrolled and followed in ADNI1, ADNIGO, or ADNI2 for at least one year.
2. Willing and able to continue to participate in an ongoing longitudinal study. A reduced battery of tests is allowable if the participant is not able/willing to complete the full battery.

4.2 Exclusion Criteria

All newly enrolled participants must not meet the following criteria:

	CN	MCI	AD
1.	**Any significant neurologic disease**, such as Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic deficits or known structural brain abnormalities	**Any significant neurologic disease other than suspected incipient Alzheimer's disease**, such as Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic deficits or known structural brain abnormalities.	**Any significant neurologic disease other than Alzheimer's disease**, such as Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic deficits or known structural brain abnormalities.

Additional exclusion criteria apply to all diagnostic categories for newly enrolled participants:

1. Screening/Baseline MRI brain scan with evidence of infection, infarction, or other focal lesions or multiple lacunes or lacunes in a critical memory structure
2. Subjects that have any contraindications for MRI studies, including the presence of cardiac pacemakers, or metal fragments or foreign objects in the eyes, skin or body.
3. Major depression, bipolar disorder as described in DSM-IV within the past 1 year. Psychotic features, agitation or behavioral problems within the last 3 months that could lead to difficulty complying with the protocol.
4. Currently treated with medication for obsessive-compulsive disorder or attention deficit disorder.
5. History of schizophrenia (DSM IV criteria).
6. History of alcohol or substance abuse or dependence within the past 2 years (DSM IV criteria).
7. Any significant systemic illness or unstable medical condition, which could lead to difficulty complying with the protocol.
8. Clinically significant abnormalities in B12 or TFTs that might interfere with the study. A low B12 is exclusionary, unless follow-up labs (homocysteine (HC) and methylmalonic acid (MMA)) indicate that it is not physiologically significant.
9. Residence in a skilled nursing facility.
10. Current use of specific psychoactive medications (e.g., certain antidepressants, neuroleptics, chronic anxiolytics or sedative hypnotics). Current use of warfarin or other anticoagulants such as dabigatran, rivaroxaban and apixaban (exclusionary for lumbar puncture).
11. Current use of any other exclusionary medications.
12. Investigational agents are prohibited one month prior to entry and for the duration of the trial.
13. Participation in clinical studies involving neuropsychological measures being collected more than one time per year.

4.3 Recruitment and Retention Strategies

Serving as the third series of ADNI studies our goal is to retain as many ADNI2 participants as possible. A multi-faceted recruitment and retention plan is being developed for ADNI3. The overall goal is to raise awareness of the ADNI trial among targeted populations.

We will leverage existing resources, infrastructure and registries as recruitment tools to enroll new participants into ADNI3.

Registries such as Brain Health Registry (BHR) will provide potential participants to ADNI3. BHR is a research study that is overseen by University of California, San

Francisco (UCSF). This means that everything that the Brain Health Registry does is reviewed and approved by the UCSF Institutional Review Board (IRB).

Other retention and recruitment efforts may include engaging public relations/communications firm(s) and or partnering with organizations which already serve to honor clinical trial volunteers. ADNI3 will determine the special requirements of each site and pattern its individual public relations/communications support around those needs.

In that context ADNI will develop targeted messages in flyers, brochures, press releases, and presentations. Access to recruitment materials for the sites will also be available. Enrollment will be monitored and tracked. Additional site support will be provided where needed based upon the recruitment tactic data tied to enrollment.

4.3.1 Inclusion of Women and Minorities

Women and members of minority groups will be actively recruited during this protocol. Targeted efforts will include BHR a registry that has successfully enrolled large numbers of African Americans and AD-PCORNet, which utilizes African-Americans Against AD and Latinos Against AD to engage and enroll participants from these groups.

Based on the participating sites data regarding enrollment of minorities, we expect 12% of participants enrolled will be minorities. This is close to the aged minority population in the U.S., which is 14%.

4.3.2 Re-entry into ADNI3

In the event where a participant decides to stop ADNI participation to enroll in a treatment trial, they may be allowed the opportunity to return to full or partial participation in the ADNI3 study. Participants who return to ADNI3 after participation in a treatment trial will be asked to provide information about their participation in that trial. Contact the ATRI Coordinating Center for guidance on re-entry.

5.0 STUDY TIMELINE

The site should expect to spend: 1) approximately 3-6 months for startup activities that include site IRB and regulatory approvals, as well as site training; 2) approximately 2-6 years in screening and longitudinal follow-up visits, with follow-up duration dependent on cohort.

CN and MCI cohorts

Exceptions can be made to extend the time allowed for the rollover's Initial Visit. Screening and enrollment for new participants may occur over 2 years. Longitudinal follow-up period for both rollover and new participants is approximately 4-6 years.

Neuropathology telephone checks should be performed every six months between visits to discuss autopsy consent.

AD cohort

New and rollover AD participants will follow the same timeline as described above. However, the *in-clinic* longitudinal follow-up period is shorter, at maximum 2 years. After that, only Neuropathology telephone checks should be performed every six months or, at minimum, annually, which offer opportunities to discuss autopsy.

6.0 DESCRIPTION OF STUDY VISITS

Frequency of visits will be dependent on cohort and flortaucipir PET imaging schedule. Visits have a scheduling window of 2 weeks before and after the target date. Once the visit begins, all imaging, biofluid collection, and clinical/cognitive assessments must take place within the next 2 weeks.

Where there is insufficient time to complete the full visit, the order of priority for clinical assessments is:

1. Clinical Dementia Rating Scale
2. ADAS-Cog
3. Mini Mental State Examination
4. Logical Memory I and II
5. Concomitant Medications
6. Adverse Events
7. Diagnostic Summary
8. Vital Signs

Subjects should be encouraged to undergo all procedures. Where subjects do not wish to undergo all of the procedures, the order of priority for procedures is as follows. The ordered priority is provided as a guide to the clinical staff and the participants, not a rigid priority list:

1. Amyloid PET scan
2. Flortaucipir PET scan
3. MRI
4. Lumbar puncture
5. FDG-PET scan

Participants will be followed as long as they are willing, and every attempt should be made to retain participants for longitudinal follow-up as long as possible. If participants are not willing or able to complete the full schedule of assessments at any visit, those assessments or procedures they are willing to complete should be conducted. A guide to the order of priority for assessments and procedures is listed above, but it should be emphasized that the major priority is to keep subjects in the study, even if data collection is limited. If participants are no longer willing or able to travel to the clinic for annual visits, as much information should be collected via telephone as long as is possible.

Unless a participant has clearly refused brain autopsy, the neuropathology program should be discussed at each visit.

6.1 Visit Scheduling

CN participants will be seen in the clinic every other year through the end of the study. CN participants may be required to come into the clinic more often for flortaucipir PET scans.

MCI participants will be seen in the clinic annually through the end of the study.

AD participants will be seen in the clinic annually for two years (an initial visit followed by two ongoing visits) and will then be followed by telephone through the end of study.

Diagnostic category converters, even if converted back to CN, will be followed in the clinic annually for the remainder of the study.

All participants should be contacted every six months or, at a minimum, annually (see section 9.5) through the end of the study to obtain autopsy consent, establish and confirm logistical support for autopsy, and maintain updated participant contact information.

6.1.1 Newly Enrolled Participants

New participants will go through Pre-screening and Screening periods as described in section 6.2 below. The Screening and Baseline visits must be completed in-person by both the participant and study partner.

6.1.2 Rollover Participants

Rollover participants who are being followed from ADNI2 should be enrolled into ADNI3 for a complete In-Clinic Visit without any need for screening. This will be the case, even if these participants had a complete (that is with tau PET, amyloid PET, MRI, and/or LP) In-Clinic Visit in the last year of ADNI2.

6.1.3 Retrieved Dropouts

Participants who miss visits will be encouraged to come in for subsequent visits until he/she withdraws consent.

In cases where consent has been withdrawn in previous ADNI studies, participants are invited to consent and participate in ADNI3.

6.2 Procedures for Newly Enrolled Participants

6.2.1 Pre-screening

During the prescreen phase, sites will assess referred potential participants for eligibility criteria, such as age and ability to tolerate procedures.

6.2.2 Screening

The purpose of the Screening Visit is to further determine eligibility and to complete the informed consent process. Only newly enrolled participants will have a Screening Visit. Screening activities are conducted in the following order:

- Consent
- Screening assessments listed in the Schedule of Events (SOE) (see Appendix 1) up to but not including the MRI, which requires both Site PI/Site Clinician and monitor approval
- Proceed to MRI
- Local read of MRI
- Site PI/Site Clinician and monitor verifications of all eligibility requirements

6.2.3 Baseline Visit

The Baseline visit may only be initiated following completion of all Screening assessments and must take place within 28 days of Screening. There is an additional 2 weeks to complete other Baseline procedures. The procedures conducted are based on current diagnosis at the Initial visit.

Baseline procedures include cognitive, functional, and behavioral assessments, review of concurrent medications and adverse events, FDG-PET (MCI and AD groups only), amyloid PET, flortaucipir PET, and biofluid collection (blood and CSF from lumbar punctures). The complete list of all Baseline procedures is provided in the SOE (see Appendix 1).

In no instance should cognitive assessments be performed while the participant is in a fasted state. Procedures that require fasting are the blood draw, lumbar puncture, and FDG-PET. The MRI scan should be conducted prior to the LP to rule out intracranial mass for safety.

6.2.4 Ongoing In-Clinic Visits for New Participants

The ongoing In-Clinic Visits will be timed every 12 months from Baseline Visit day 1. CN participants that are not selected for extra flortaucipir PET scans are seen in-clinic every other year. Ongoing in-clinic visits include cognitive, functional, and behavioral assessments, review of concurrent medications and adverse events, blood collection, and MRI.

Amyloid PET scans and LPs are conducted every two years.

On all participants, flortaucipir PET is conducted at the Initial Visit/Baseline. Additionally:

- AD participants will have a second and third flortaucipir PET scan. Flortaucipir PET scans will be performed at each annual In-Clinic Visit (including the Initial/Baseline, Year 1, and Year 2 visits).
- CN, MCI, and Converter participants will receive a flortaucipir PET scan at the Year 4 visit. Additionally, 20% of amyloid-negative and 80% of amyloid-positive CN and MCI participants will be randomly selected for two additional flortaucipir PET scans (for a total of four flortaucipir PET scans). Randomization

will be done by the ATRI Coordinating Center and the sites will be notified of the flortaucipir PET schedule for CN and MCI participants.
    - CN participants that come into the clinic at Year 1 for a flortaucipir PET scan will also complete an ongoing in-clinic visit as outlined in the SOE.

If a CN participant is not due for an In-Clinic Visit or selected for extra flortaucipir PET scans, then a Phone Check Visit will be conducted on "off years."

6.3 Procedures for Rollover Participants

6.3.1 Initial Visit

Initial Visit procedures include a full battery of assessments for all rollover participants. This includes cognitive, functional, and behavioral assessments, review of concurrent medications and adverse events, FDG-PET (MCI and AD groups only), amyloid, flortaucipir PET, and biofluid collection (blood and CSF). The procedures conducted are based on current diagnosis at the Initial Visit.

6.3.2 Ongoing In-Clinic Visits for Rollovers

Ongoing In-Clinic Visits for MCI and AD participants will be scheduled every 12 months (annually) from the Initial ADNI3 Visit. CN participants that are not selected for extra flortaucipir PET scans will be followed in-clinic every other year.

Assessments collected during ongoing In-Clinic Visits for rollover participants follow the same rules as outlined in the ongoing In-Clinic Visits for newly enrolled participants (section 6.2.4).

6.4 Other Types of Study Visits (Applicable to both Newly Enrolled and Rollover Participants)

6.4.1 Telephone Visits in Replacement of In-Clinic Visits

Participants that are no longer able or willing to be seen in the clinic may opt to have a Telephone Visit instead of an ongoing in-clinic visit. This option is available for ADNI2 rollover participants upon entry into ADNI3, as well as new ADNI3 participants that have completed their Baseline Visit. This requires signature of a new informed consent form acknowledging the replacement procedures and schedules. See SOE for details on assessments collected at a Telephone Visit in replacement of in-clinic visit.

6.4.2 Telephone Checks

- For CN participants, the brief Telephone Check occurs on alternating years for up to 5 years. The brief Telephone Check will be a shorter version of the Telephone visit. Study partner will still join, and similar questions will be asked for the participant and the study partner. See SOE for details.
- For all participants, the purpose of the 6-month Neuropathology Telephone Check is to discuss current wishes with regards to brain donation, update participant contact information to ensure continued contact until time of

death, ensure appropriate autopsy arrangements are in place, and reiterate who should be contacted at the time of death. If a participant decides that he or she is not interested in brain donation program, they will not be called. See SOE for details.

6.4.3 Nursing Home Placement

Transfers to a skilled nursing home will be recorded in the clinical database as part of an AE. All assessments will be completed to the extent possible. If the participant or substitute decision-maker withdraws consent to continue in the study, verbal assent will be obtained to conduct an early termination visit, which will consist of as many evaluations normally performed at the In-Clinic Visit as allowed by the participant or substitute decision-maker. Nursing home placement is associated with increased risk for death. It should be emphasized that long term follow-up of subjects for the purposes of brain collection by autopsy is a very high priority. Therefore, transfer to a skilled nursing home is an appropriate time to again discuss the possibility of long-term follow-up for autopsy with the participant and the family.

6.4.4 Early Termination Visit

If a participant wishes to exit the study, an Early Termination Visit will be scheduled. This should include as many evaluations as possible that are normally performed at the In-Clinic Visit, including clinical evaluation, cognitive tests, MRI, CSF collection, amyloid and flortaucipir PET imaging. The same order of priority as provided in Section 6.

Please contact the ATRI Coordinating Center for guidance on what specific procedures should be conducted at an Early Termination Visit. It should be emphasized that long term follow-up of subjects for the purposes of brain collection by autopsy is a very high priority. Even if a participant requests an early termination, this is an appropriate time to again discuss the possibility of long-term follow-up for autopsy with the participant and the family.

7.0 PERSONNEL REQUIREMENTS

The Site Principal Investigator (PI) is responsible for the overall conduct of the study at the site. The PI is to supervise project personnel and ensure that clinical raters maintain a high level of skill and accuracy in conducting assessments. Additionally, the site PI, to the extent possible, will personally perform or supervise clinical evaluation of all participants and ensure protocol adherence. Additional key personnel may be required as specified in the Procedures Manual.

8.0 INSTRUMENTS

8.1 Cognitive Evaluations

8.1.1 Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog13)

The ADAS-Cog is an in-person examiner-administered, 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[19].

8.1.2 American National Adult Reading Test (AMNART)

The AMNART estimates premorbid verbal intelligence (VIQ) in patients with dementia[20, 21]. The test requires patients to read and correctly pronounce 50 "irregular" words that do not follow common rules of phonography and orthography.

8.1.3 Category Fluency Tests

This is a measure of verbal fluency in which the participant is asked to generate examples from the semantic categories (animals) in successive one-minute trials[22].

8.1.4 Clock Drawing Test

This task tests visuoperceptual constructional function. The Clock Drawing Test is effective for discriminating between participants with AD and normal elderly individuals[23].

8.1.5 Cogstate Brief Battery (CBB)

The CBB is a 10-15 minute computerized cognitive battery developed by Cogstate Ltd. New Haven, CT, USA that measures attention, speed of information processing, working memory and learning. The web-based tests are accessed using a secure website with unique log-in credentials that do not require any protected health information.

8.1.6 Logical Memory Test I and II (immediate and delayed paragraph recall)

We will use a modified episodic memory measure from the Wechsler Memory Scale-Revised (WMS-R) [24]. In this modified version, free recall of one short story will be elicited immediately after it is read aloud to the participant and again after a thirty-minute delay.

8.1.7 Mini-Mental State Examinations (MMSE)

The MMSE is a brief, frequently used screening instrument for Alzheimer's disease drug studies[25]. The MMSE scale evaluates orientation, memory, attention, concentration, naming, repetition, comprehension, and ability to create a sentence and to copy two overlapping pentagons.

8.1.8 Montreal Cognitive Assessment (MoCA)

The Montreal Cognitive Assessment test (MoCA) is, similar to the MMSE, a brief, 30-point cognitive assessment designed to detect participants at the MCI stage of cognitive dysfunction[26]. This instrument has been shown to have adequate

sensitivity and specificity in clinical settings to detect suspected MCI. The performance of the MoCA will be followed to determine its ability to differentiate among the three diagnostic groups in ADNI3.

8.1.9 Multi-Lingual Naming Test (MlNT)

The Multilingual Naming Test (MlNT) is a test of object picture naming designed to include items that are comparable across English, Spanish, Mandarin and Hebrew[27]. It replaces the Boston Naming Test in the Uniform Data Set of the NIA-funded AD centers because the BNT contains items that are not of the same level of difficulty for Spanish and English speakers.

8.1.10 Rey Auditory Verbal Learning Test (AVLT)

The AVLT is a list-learning task, which assesses multiple cognitive parameters associated with learning and memory[28].

8.1.11 Trail Making Test: A and B

These two tests progress from a numerical connect-the-dots puzzle to a more challenging alternation between alpha- and numerical order. 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[29].

8.2 Global, Functional, and Behavioral Evaluations

8.2.1 Modified Hachinski Ischemic Score

The Modified Hachinski Ischemic Score is a brief questionnaire that incorporates questions about medical history, cognitive symptoms and features of stroke, as reported by a study partner and informed by the neurological examination and neuroimaging studies[30].

8.2.2 Cognitive Change Index (CCI)

The Cognitive Change Index is a 20 item self-report and study partner (informant)-report instrument. Items assess primarily memory with some coverage of executive and language changes. The CCI was first implemented in ADNI2[31, 32]. A CCI-Memory Total Score is used to define the SMC group and information the participant and the study partner (informant) can be combined to yield a total score for memory or overall cognition.

8.2.3 Clinical Dementia Rating Scale (CDR)

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[33, 34]. Where a full CDR interview is not possible, the abbreviated CDR can be utilized.

8.2.4 Activities of Daily Living / Functional Assessment Questionnaire (FAQ)

Based on an interview with a caregiver or qualified partner, a participant is rated on his/her ability to carry out ten complex activities of daily living[35].

8.2.5 Financial Capacity Instrument – Short Form (FCI-SF)

The FCI-SF is a brief (15 minutes) performance measure of everyday financial skills that uses both performance and time to completion variables[36]. In prior research the FCI-SF performance and timing variables have discriminated between amyloid-positive and negative CN, as well as CN vs MCI vs mild AD groups.

8.2.6 Measurement of Everyday Cognition (ECog)

This instrument assesses for very mild functional impairment as may occur in MCI. The ECog is an informant-rated questionnaire, but participants will be asked to complete a self-reported version of the same questionnaire[37]. 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.

8.2.7 Neuropsychiatric Inventory (NPI)

The NPI is a well-validated, reliable, multi-item instrument to assess psychopathology in AD based on an interview with a caregiver or qualified study partner (defined in this study as having direct contact 10 hours/week) [38, 39]. It evaluates both the frequency and severity of: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition irritability, lability, apathy, and aberrant motor behavior.

8.2.8 Neuropsychiatric Inventory Q (NPI-Q)

The NPI-Q was designed as a version of the NPI that could be administered more quickly and over the telephone[40].

8.2.9 Brain Health Registry (BHR)

The BHR contains a University of California at San Francisco IRB-approved online battery of tests including self-report questions, neuropsychological tests, and assessments by study partners. BHR may be used for in-clinic assessment and at-home assessment for those subjects and their study partners willing to participate.

8.2.10 Geriatric Depression Scale (GDS) Short Form

The GDS Short Form is a self-report scale designed to screen for symptoms of depression in the elderly[41].

9.0 PROCEDURES

9.1 Assessments

9.1.1 Physical and Neurological Examination

A medically qualified professional will perform a brief physical examination that consists of a review of the major body systems. Vital signs will include height (at screening only), weight, systolic and diastolic blood pressure, pulse, temperature, and respiration. Neurological examination will include an assessment of cranial nerves, strength, coordination, reflexes, sensation, tremor, and gait.

9.1.2 Clinical Laboratory Evaluations

A central laboratory will analyze all routine laboratory samples. Lab reports will be reviewed, signed and dated by the Site PI (or a medically-qualified individual

delegated by the PI). Site clinicians will indicate whether abnormal lab results are clinically significant or not, with additional review by ATRI Medical Monitoring group. Those results that are deemed clinically significant may need to be repeated and follow up with the participant's treating physicians will be recommended by study personnel.

9.2 Biofluids

The Procedures Manual will provide detailed instructions for the collection, processing and shipment of all biofluid samples. Samples will be collected to accommodate the assay of the broadest range of the best antecedent biomarkers/analytes. Fasting overnight (minimum 6 hours) is required for plasma, serum and CSF sample collection. Only water is permitted (no food but water is encouraged) until blood draws and the LP procedure are completed. ADNI3 will continue to measure $A\beta_{1-42}$, total tau, and phosphorylated tau_{181} in CSF samples. Methods used for blood draw will continue as in ADNI2 for longitudinal biomarker and genetic data with the addition of PBMC collection.

9.2.1 Baseline Blood Samples for PBMC and Cell Line Banking

Whole blood samples will be collected at baseline for all participants and used for extraction of peripheral blood mononuclear cells (PBMCs). For newly enrolled participants, an additional blood sample will also be used to derive immortalized cell lines. Whole blood will be collected and shipped overnight under ambient conditions to the National Cell Repository for Alzheimer's Disease (NCRAD). It is important to ship samples drawn for PBMCs the same day they are drawn and that they are received at NCRAD the next day; any delay will affect the viability of the cells. The Genetics Core will request a re-sampling, if the condition of the sample on arrival prevents processing. PBMC collection is being added in ADNI3 as they can be used in a variety of ways.

PBMC has become an important source for the development of induced pluripotent stem cells (iPSCs) and also can support other functional genomic studies. Some cells may be derived into new materials. Processing may be performed at other laboratories in which case aliquots of the derived materials will be returned to NCRAD for distribution to NIA approved investigators.

9.2.2 Longitudinal Blood Samples for Genomic Analysis and Related Bioassays

At baseline and follow-up visits, blood will be collected for extraction of DNA and RNA at NCRAD and to provide plasma and serum for the Biomarker Core (see section 9.2.4 below). Whole blood is processed at each site to separate plasma, serum, buffy coat (white blood cells), and red blood cell (RBC) components. The buffy coat and RBC components are aliquoted at the sites and shipped overnight under ambient conditions to NCRAD where DNA will be extracted, aliquoted and banked. RBCs will be banked for specialized assays requiring RBCs. RNA samples will also be collected at each visit using Paxgene kits supplied by the ATRI Coordinating Center. Paxgene samples will be shipped overnight under ambient conditions to NCRAD and RNA will be extracted, aliquoted and banked. The longitudinal genomic sample collection will be used to analyze changes in gene

transcription (RNA analysis) and epigenetic processes (e.g., DNA methylation, histone modification, and chromatin remodeling) and to enable future genomic analyses.

9.2.3 Genetic and Genomic Analyses

APOE and genome-wide genotyping will be completed for newly enrolled participants. For participants whose samples have not already undergone whole genome sequencing, resources will be sought during ADNI3 to perform these analyses.

9.2.4 Plasma and Serum Collection for Biomarkers

Plasma, serum, and buffy coat will be collected at Baseline from newly enrolled participants, and at the initial ADNI3 visit from rollover participants, and then ongoing during follow-up at In-Clinic Visits for all participants. All samples will be collected in the morning before breakfast and after an overnight fast (minimum 6 hour fast). Plasma and serum must be prepared at the site, frozen and then sent to the Biomarker Core at the University of Pennsylvania (UPENN). As above, buffy coat and red blood cells will be extracted from blood at the site and shipped overnight under ambient conditions to NCRAD.

9.2.5 CSF Collection for Biomarkers

Both newly enrolled and rollover participants, will have CSF samples collected at Baseline and again every two years through the course of the ADNI3 study. All samples will be collected in the morning before breakfast and after an overnight fast (minimum 6 hour fast).

Approximately, 2 ml of CSF should be sent to the clinical laboratory of the Site PI for routine cell count, protein and glucose analyses. The majority of the CSF, at least 20 ml should be immediately frozen and sent frozen on dry ice directly to the UPENN ADNI Biomarker Fluid Bank.

Each study participant or a person designated to speak on their behalf will be contacted by phone 24 hours after the lumbar puncture to confirm the participant's well being and to query about any new adverse events.

At the discretion of the Site PI (or Site Clinician), a coagulation panel (PT/PTT) may be obtained to rule out a clotting disorder. Also, per PI (or Site Clinician) discretion, anti-platelet agents (e.g., aspirin) may be discontinued for a period of time before and after the LP.

9.3 Magnetic Resonance Imaging (MRI)

Participants will have a brain MRI scan as part of the screening evaluation, as well as at each ongoing in-clinic visit.

9.3.1 Site Qualification

Each site must be qualified for MRI. The ADNI3 MRI protocol differs from that used in ADNI2 in that several of the sequences will be modernized. Therefore, all scanners will have to be qualified with the ADNI3 protocol MRI protocol.

The procedure for MRI site qualification will consist of a test imaging session on a human volunteer and/or phantom. In terms of human scanning, each site will image a volunteer participant with the protocol and send the images to LONI. The MRI Core will check each parameter in each of the pulse sequences in the protocol. In the event that the scan 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 participant, 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 participant. 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.

9.3.2 Data Acquisition

All participants will be scanned on a 3T MRI System with a protocol consisting of several sequences that conform to FDA safety standards. The MRI protocol includes: a scout, structural T1-weighted MRI, FLAIR, T2 GRE, diffusion tensor imaging, ASL perfusion MRI, and task free resting state functional MRI. The total scan time will be approximately one hour but may be longer depending on technical factors. The total scan time will not exceed 2 hours. If the subject becomes uncomfortable, they can ask to be removed from the scanner at any time.

Each MRI scan of brain will be performed at Screening (for new participants), or Initial Visit (for rollover participants) and then again annually (or at every In-Clinic Visit).

9.3.3 Clinical Read of MRIs

The research site is responsible to obtain a read from a local radiologist for each MRI completed in the ADNI Protocol.

9.3.4 Data Management and Quality Control

Images are uploaded by site users to the Laboratory of Neuroimaging (LONI) at the University of Southern California (USC). The MRI Core will perform a quality control review on each MRI scan. Quality control for MRI will result in failure of some scans, which may need to be repeated. Repeat scans must be scheduled as soon as possible and no later than four weeks of the visit date.

9.4 PET scanning: FDG, Amyloid (Florbetapir or Florbetaben), and Flortaucipir PET Imaging

Each scan must be done on a separate day at least 12 hours after a prior scan.

9.4.1 Site Qualification

Each site must be qualified for PET. If the PET scanner being used has already been certified by the ADNI PET Core and has not experienced any major software or hardware upgrades, re-qualification will not be required. Qualification of the PET

scanner applies to FDG, florbetapir, florbetaben, and flortaucipir PET scan imaging protocols; a scanner requires qualification only once for all tracer studies. Qualification will employ the same methods utilized for site qualification in ADNI2.

Sites will use a Hoffman brain phantom and a technical manual for the data acquisition using all PET tracers in the ADNI3 protocol. 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.

For all PET scans, either a PET transmission (PET-only scanners) or x-ray CT (PET/CT scanners) will be obtained for attenuation correction.

9.4.2 Data Acquisition for FDG-PET

MCI and AD participants will undergo a single FDG scan at Initial/Baseline visit; CN participants do not have an FDG-PET scan. Participants must be fasting for 4 hours or overnight; prior to the scan a blood glucose measurement will be made by fingerstick and scans will be postponed or rescheduled if the reading is > 180 mg/dL. The procedure may take as long as 2 hours, from participant check-in at the scanning facility to injection of approximately 5 mCi of FDG through an intravenous catheter, followed by 30-minute uptake period until 30-minute image acquisition.

9.4.3 Data Acquisition for Amyloid PET Scans with Florbetapir or Florbetaben

All ADNI rollover participants will continue to complete amyloid PET scans every two years with florbetapir. A proportion of newly enrolled participants will have longitudinal florbetaben PET imaging instead of florbetapir. Any subject who has their first scan in ADNI with florbetapir or florbetaben will have longitudinal scans done with the same ligand. Scans must be completed within 2 weeks before or 2 weeks after the in-clinic assessments at Initial/Baseline visit and at two-year intervals.

This procedure may take as long as 2 hours. Florbetapir scanning entails 10mCi injection of tracer through an intravenous line and a 50-minute uptake until 20-minute image acquisition begins. Florbetaben imaging has a longer uptake period between injection and image acquisition, starting 90 minutes after 8mCi injection. Image acquisition occurs over a 20-minute period.

9.4.4 Amyloid PET Early Frames Data Acquisition (optional)

Participants at select sites will have the option to participate in obtaining early amyloid PET sequences. Participants that choose to participate and consent to the additional imaging, will be positioned in the scanner identically as they are positioned for the regular amyloid PET scan and data will be collected for 20 minutes beginning immediately with the injection of the amyloid tracer. Participants

will continue with the same amyloid tracer based on participant classification; new or rollover, which is defined in above Section 9.4.3. Refer to the ADNI PET technical manual for procedural details.

Data will be collected on approximately 100 participants distributed across the diagnoses of CN/MCI/AD once at their next annually scheduled amyloid PET scan. The identical procedure will be repeated again in two years following initial early frames PET scan.

Sites are selected based on PET scanner and imaging center capabilities. Eligible sites must be collecting florbetapir and/or florbetaben images on a scanner capable of rapid dynamic images (peak 4 per min or list mode) for a total of 16 frames. Also, the site must have the capacity for injection with simultaneous scan start (typically requires two technologists).

9.4.5 Data Acquisition for Flortaucipir PET

AD participants will receive flortaucipir PET scans at each in-clinic visit for a total of three flortaucipir PET scans; AD participants are evaluated at Initial/Baseline, Year 1 and Year 2. CN, MCI and Converter participants will receive flortaucipir PET scans at the Initial/Baseline and Year 4 visit. Based on the likelihood that amyloid-negative participants will show slower rates of tau deposition, 80% of amyloid positive and 20% of amyloid negative CN and MCI participants will be randomly selected to receive two additional annual flortaucipir PET scans, for a total of four flortaucipir PET scans. Randomization will be done by the Clinical Core and the site will be notified of the flortaucipir PET schedule as soon as possible. The site will then notify the participant of the proposed schedule. Per schedule, normal controls (CN) are seen in-clinic every other year, therefore, if they are selected to complete four flortaucipir PET scans, it will require them to come into the clinic on Year 1 for flortaucipir PET imaging.

Flortaucipir PET Standard Protocol

ADNI3 will utilize flortaucipir PET for quantification of phosphorylated tau burden. The IND for this radioligand will be held by the USC ATRI.

The data acquisition protocol for tau PET with flortaucipir will entail injection through an intravenous line of approximately 10 mCi of the tracer. Participants will be scanned beginning at 75 minutes post tracer injection, for 30 minutes.

9.4.6 Data Management and Quality Control

Images are uploaded by site users to the Laboratory of Neuroimaging (LONI) at the University of Southern California. Data are de-identified as part of the upload and placed into quarantine until they pass quality assurance evaluation conducted by the PET Core. 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 also 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.

Quality control of scans could necessitate salvage with reprocessing of the raw imaging data. All sites are required to save original PET data for the duration of the study.

9.5 Neuropathology

9.5.1 Discussing Autopsy and Obtaining Provisional Consent

Participants should be contacted every six months to discuss autopsy with the goal of brain donation. At minimum, site clinicians will discuss brain donation at every visit (including In-Clinic Visits, Telephone Visits that have replaced in-clinic visits, and Phone Checks) unless the participant indicates refusal. There are 3 objectives of the discussion: 1) to convey information about the value of brain autopsy in confirming the clinical diagnosis and advancing knowledge regarding MCI and AD; 2) to initiate consideration of the individual's wishes concerning an autopsy; and 3) to answer questions, misconceptions, or concerns about autopsy. This repeated dialogue will not be offered where the participant has refused autopsy.

It should be emphasized that an excellent time to revisit this issue is if and when a participant no longer wishes to participate in ADNI or experiences cognitive or physical decline to the extent that they are no longer able to participate. A participant may be retained in the ADNI study for "brain donation only." Every effort should be made to reenroll ADNI2 participants who had consented to brain donation or were undecided about brain donation into the ADNI3 study with "brain donation only" status. "Brain donation only" participants may also be reenrolled into subsequent ADNI studies upon the completion of ADNI3.

The decision to participate in brain autopsy is entirely voluntary and designed not to involve pressure; participants are encouraged to involve family members, clergy, physicians, or any other appropriate persons in their decision-making. Participants are assured that refusing autopsy in no way jeopardizes their research participation or any other patient rights. It is important to note that the autopsy will not interfere with funerary arrangements (e.g., an open-casket funeral is acceptable as there will be no visual disfigurement) nor will it be a financial burden to the participant's family. As a supplement to this discussion, the ADNI Neuropathology Core makes available an Autopsy Brochure, which dispels some of the common myths and concerns regarding the autopsy. We encourage clinicians to use this tool when discussing autopsy with participants. Once the neuropathologic assessment is complete, a report describing the findings will be available to consenting members of the participant's family.

Although ADNI does not directly support the performance of complete autopsies, a complete autopsy may still be arranged locally at the discretion of the participant/family, if that service is available and can accommodate the ADNI NPC

protocol for brain donation. Complete autopsy and even organ and/or body donation to a separate organization need not be contraindications for brain donation to ADNI.

Regular contact (e.g., at each In-Clinic Visit, Neuropathology phone checks every 6 months) with individuals who have provided provisional consent will help ensure that autopsy arrangements are made in advance, which aids successful brain donation. This includes In-Clinic Visits and, to the extent possible, phone checks every 6 months after completion of the ADNI study and until the death of the participant. Periodically reviewing the procedures that should be followed at the time of death and reiterating the participant's wish for donation to family members will increase the likelihood of a completed brain donation at time of death.

9.5.2 After Obtaining Provisional Consent

When voluntary autopsy consent is granted, more detailed information should be provided to the participant about procedures to follow at time of death, including telephone numbers to call and other guidelines. The ADNI Neuropathology Core has developed autopsy notification materials such as wallet cards and letters to primary care physicians and nursing homes to communicate the participant's wishes regarding autopsy. Participants are strongly encouraged to share this information with the next-of-kin, legally authorized representatives (e.g., Durable Power of Attorney (DPOA)), and private physicians. In many states, final legal authorization by the DPOA or next-of-kin must be obtained at the time of death. As ADNI is a multi-center study involving many sites across the US and Canada, sites must follow their own state and local laws regarding autopsy consent procedures.

Sites will emphasize to ADNI participants and caregivers the procedure for notifying the ADNI site at the time of death so that the autopsy protocol may be initiated. Wallet cards should be given to all participants and their family members that list contact information for the person they should notify at the time of death.

9.5.3 At the Time of Expiration

Sites will follow standard autopsy procedures as outlined in the ADNI Neuropathology Manual upon notification of the death of an ADNI participant. Sites with co-enrolled participants and established neuropathology programs may conduct their own neuropathologic examination, as long as the ADNI Neuropathology protocol can also be accommodated. Brain tissue should be provided to the ADNI Neuropathology Core within 3-6 months of autopsy. After completion of the ADNI neuropathologic examination, a copy of the resulting report will be provided to the site PI so that the participant's family members will have the option to learn what brain illnesses (if any) were identified.

9.5.4 Infectious Disease Policy for Brain Donation

If a participant expires with a potentially transmissible illness of high concern (including but not limited to COVID-19, Creutzfeldt-Jakob Disease [CJD], HIV, Hepatitis C, tuberculosis, MRSA or VRE sepsis/bacteremia) the ADNI site is advised to consult the ADNI Neuropathology Manual and contact the ADNI Neuropathology

Core for guidance regarding brain donation. Local restrictions on brain autopsy may differ from provider to provider. Further, policies governing the appropriate handling, treatment, shipment, and acceptance of potentially infectious brain specimens into the ADNI NPC laboratory are subject to change over time.

9.6 Global Unique Identifiers (GUIDs)

ADNI3 will be incorporating Global Unique Identifiers (GUIDs) for all ADNI participants. Each GUID unambiguously identifies a research study participant across different research studies without exposing protected health information (PHI). When investigators pool data together from multiple studies, GUIDs provide the means to detect participants who participate in more than one study.

ADNI sites will download a GUID generator to convert participant PHI (e.g., birth name, birth date, place of birth) into irreversible hash codes. These hash codes will be sent to the GUID authority operated by LONI, which will assign GUIDs and store them along with ADNI participant information in the clinical database.

10.0 FITBIR

For some ADNI3 participants, the tau PET scans (flortaucipir) will be funded by the Department of Defense. Therefore, for those participants having flortaucipir scans and have consented, will have all their study data uploaded to the Federal Interagency Traumatic Brain Injury Research (FITBIR) Informatics System. FITBIR Informatics System is a collaborative effort involving the NIH Institutes and Centers (ICs) and the US Army Medical Research and Materiel Command (USAMRMC) to develop a biomedical informatics system and data repository for Traumatic Brain Injury (TBI) research. The purpose is to promote collaboration, accelerate research, and advance knowledge on the characterization, prevention, diagnosis and treatment of traumatic brain injury (TBI). Data submitted to the FITBIR will be de-identified such that the identities of participants cannot be readily ascertained or otherwise associated with the data through the generation of Global Unique Identifiers (GUIDs).

While this is not a Department of Defense (DOD) funded study, the DOD has funded a portion of the flortaucipir PET scans in ADNI3 participants, and in part explains the collaboration with FITBR. The DOD funds will cover 150 initial flortaucipir scans and up to 150 longitudinal flortaucipir scans.

11.0 POTENTIAL RISKS

11.1 FDG-PET, Florbetapir, Florbetaben, and Flortaucipir PET

The primary risk related to PET is that of radiation exposure associated with the injected radiotracers and accompanying CT. There is also minor risk associated with the venipuncture, placement of an intravenous catheter, and radioisotope injection, (pain and bruising or painful infiltration of a failed injection).

The early frames study does not entail additional radiation exposure from the injected radiopharmaceuticals, but it does require an additional CT scan with an effective dose of 0.4 mSv. Assuming that a participant has all of the PET scans described in this protocol, and undergoes the early frames protocol:

- An individual undergoing FDG, florbetapir, and flortaucipir would have an annual effective dose exposure of 20.83 mSv over a single year of the study.
- An individual undergoing FDG, florbetaben, and flortaucipir would have an annual effective dose of 19.42 mSv over a single year of the study.

The table below shows effective doses for participants who do not enroll in the early frames study with a consequential 0.4 mSv lower dose. All of these doses are roughly equivalent to 7 years of background radiation. The organ that receives the maximum exposure is the gallbladder, which receives an annual dose of 6.949 rem for the combination including a florbetapir study, slightly less for florbetaben.

The radiation doses for each PET scan are not themselves expected to produce any harmful effects, although there is no known minimum level of radiation exposure considered to be totally free of the risk of causing genetic defects or cancer. The risk associated with the amount of radiation exposure participants receive in this study is considered low and comparable to everyday risks. No PET studies will be performed on pregnant or potentially pregnant women, as the protocol requires that female participants are postmenopausal.

Details on the clinical information to date regarding flortaucipir exposure and risks will be provided in the informed consent form (ICF). More information about the known and expected benefits, risks, and reasonably anticipated AEs of flortaucipir may be found in the Investigator's Brochure (IB).

	microSv/ MBq	mSv/ study	mSv/ Scan with CT	mrem/ Scan with CT
FDG	19	3.5	3.9	390
Florbetapir	19	7.03	7.43	743
Florbetaben	19	5.62	6.02	602
Flortaucipir	24	8.70	9.10	910

Organ dosimetry for each of these scenarios is provided below.

Organ dosimetry for a participant receiving 5 mCi FDG, 10 mCi florbetapir and 10 mCi flortaucipir

Organ	mrad/ 5 mCi FDG	mrad/ 10 mCi florbetapir	mrad/ 10 mCi flortaucipir	Total dose
Adrenals	240	519	526	1284
Brain	350	370	311	1031
Breasts	170	222	264	656
Gallbladder wall	245	5296	1407	6949
Lower Large Intestine Wall	255	1037	1289	2581
Small Intestine	235	2444	3130	5809
Stomach	205	444	467	1116
Upper Large Intestine wall	230	2741	3537	6508
Heart wall	1100	481	1100	2681
Kidneys	370	519	1478	2366
Liver	290	2370	2119	4779
Lungs	320	333	1256	1909
Muscle	195	333	333	861
Ovaries	265	667	767	1698
Pancreas	480	519	533	1532
Red marrow	235	519	374	1128
Osteogenic Cells	205	1037	426	1668
Skin	150	222	221	593
Spleen	700	333	378	1411
Testes	205	259	257	721
Thymus	220	259	318	797
Thyroid	195	259	249	703
Urinary bladder wall	1600	1000	1393	3993
Uterus	310	593	674	1577
Total Body	215	444	441	1100

Organ dosimetry for a participant receiving 5 mCi FDG, 8 mCi florbetaben and 10 mCi flortaucipir

Organ	mrad/ 5 mCi FDG	mrad/ 8 mCi florbetaben	mrad/ 10 mCi flortaucipir	Total dose
Adrenals	240	385	526	1151
Brain	350	385	311	1046
Breasts	170	207	264	641

Gallbladder wall	245	4059	1407	5712
Lower Large Intestine Wall	255	1037	1289	2581
Small Intestine	235	919	3130	4283
Stomach	205	356	467	1027
Upper Large Intestine wall	230	1126	3537	4893
Heart wall	1100	415	1100	2615
Kidneys	370	711	1478	2559
Liver	290	1156	2119	3564
Lungs	320	444	1256	2020
Muscle	195	296	333	824
Ovaries	265	474	767	1506
Pancreas	480	415	533	1428
Red marrow	235	356	374	965
Osteogenic Cells	205	444	426	1075
Skin	150	207	221	579
Spleen	700	296	378	1374
Testes	205	267	257	729
Thymus	220	267	318	804
Thyroid	195	237	249	681
Urinary bladder wall	1600	2074	1393	5067
Uterus	310	474	674	1458
Total Body	215	326	441	982

11.2 MRI

There are no proven biologic risks associated with MRI scanning. All participants 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 pacemakers. 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 participant. There is a slight risk of anxiety due to claustrophobia and noise. Any participant 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. There will be no attempt to coerce participants to complete exams that they are uncomfortable with. Use of anxiolytic agents for completion of MRI scans is at the discretion of site clinicians, in consultation with the Project Director.

11.3 Lumbar Puncture

Lumbar puncture may be associated with pain during the performance of the procedure. This is usually temporary and confined to the lower back. Headache may

occur in about 5% of elderly people who undergo lumbar puncture. Less commonly, in about 1-4% of participants, a persistent low-pressure headache may develop, probably due to leakage of CSF. Lower rates of post-LP headache have been noted in elderly patients, and when atraumatic (Sprotte) needles are used. If a post-LP headache persists it may need additional treatment, e.g. additional fluids and analgesics. Uncommonly a blood patch (injection of some of the participant's blood to patch the CSF leak) may be needed. Potential but rare risks of lumbar puncture include infection, damage to nerves in the back, and bleeding into the CSF space. The risk of these is much less than 1%. In an effort to mitigate these risks, an experienced clinician must perform the LP.

11.4 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.

11.5 Genetic Risks

NIH policy requires that de-identified genomic data is uploaded to a secure government sponsored health research database for broad sharing with approved investigators (see section 12.5.3 below). This information will be de-identified and will not contain any traditional identifiers. There is a slight risk that there could be a breach in the security of this database system resulting in the unauthorized access to de-identified information. Safeguards at the government health database are in place to minimize this risk.

Another possible risk from participation in this study involves a loss of privacy as a result of providing genetic material (nucleic acids) for research. Although genetic information is unique to each individual it is also shared with their children, parents, brothers, sisters, other blood relatives and other members of their ethnic group. Although prohibited by NIH and ADNI policy, it may be possible that genetic information could be used to identify study participants or relatives. Methods to allow someone to link the genetic or medical information back to the study participant could be developed in the future but authorized users agree to not attempt to identify any study participants.

11.6 Loss of Privacy

This project collects a great deal of information about participant health status. Individuals at the clinic sites will be collecting personal protected health information such as name, date of birth, social security number, address, phone number, and emails. All participants will be given a participant code number and all data will be associated with the code number. The clinic site will maintain the personal protected health information (such as name, date of birth, social security number, address, phone number, and emails) in a secure and locked location. The data, associated with the code number will be distributed widely, but it will not be possible to identify an individual subject from the data. However, there is a very unlikely possibility that there will be a security failure, and that somehow the protected health information will be no longer protected. This is an extremely

unlikely, but possible occurrence, and is a risk of this study (and almost all other medical research studies).

There is also a risk that MRI scans could be re-identified using facial recognition technology. Prior to receiving shared data, all investigators must agree that they will not attempt to identify any study participant.

12.0 ADVERSE EVENTS

All participants will be evaluated for adverse events at each clinical visit.

12.1 Definition of an Adverse Event (AE)

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

12.2 Following up and reporting on Adverse Events

The investigator is obliged to follow participants with AE's until the events have subsided, the conditions are considered medically stable, or the participants are no longer available for follow up. Participants 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.

12.3 Definition of a Serious Adverse Event (SAE)

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. Medical and scientific judgment should be exercised in deciding whether reporting a serious adverse event is appropriate. All Serious Adverse Events (SAEs) will be reported to the independent Data Safety Monitoring Board (DSMB).

12.4 Reporting Serious Adverse Events (SAEs)

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 ATRI Coordinating Center within 24 hours after learning of the event. This in turn will trigger an alert to the appropriate ATRI Coordinating Center personnel, which will lead to the initiation of the creation of a report. A notification will be distributed to all participating sites, the study's DSMB and the NIA. Sites will report SAEs based on local IRB requirements.

A serious adverse event (SAE) reported to have occurred within 24 hours of amyloid or tau PET tracer administration (florbetapir, florbetaben, or flortaucipir) will be reported, regardless of the investigator's opinion of causation. Thereafter, sites must

continue to report any serious or life-threatening adverse event whether or not it is related to study procedures. A subset of those SAEs may then be reported to Avid and Life Molecular Imaging (LMI), formerly Piramal, for events related to florbetapir, flortaucipir and florbetaben, respectively.

12.5 Data and Safety Monitoring Board

The ATRI Coordinating Center currently has an active DSMB that reviews the safety of all participants enrolled in trials on an ongoing basis. The DSMB will review Serious Adverse Event reports on a quarterly basis.

12.6 Research Monitor

The Research Monitor will provide an independent evaluation of serious adverse events and unanticipated problems involving risk to subjects or others, to the principal investigator. The Research Monitor has the authority to recommend stopping research study in progress, and take whatever steps are necessary to protect the safety and well-being of research volunteers. In coordination with the ATRI Clinical Core, 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), 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.

13.0 ETHICS AND REGULATORY CONSIDERATIONS

13.1 Good Clinical Practice

This study will be conducted in compliance with the protocol, in accordance with GCP guidelines, and in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46 – Protection of Human Subjects, 21 CFR Part 50 – Protection of Human Subjects, 21 CFR Part 56 - IRBs, and/or the ICH E6, HIPAA, State and Federal regulations and all other applicable local regulatory requirements and laws.

Study personnel involved in conducting this study will be qualified by education, training and experience to perform their respective task(s) in accordance with GCP.

No study document shall be destroyed without prior written agreement between the ATRI Coordinating Center and the investigator. Should the investigator wish to assign study records to another party or move them to another location, he/she may do so only with the prior written consent of the Coordinating Center.

13.2 Institutional Review Boards (IRB) / Research Ethics Boards (REB)

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. Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate IRB registered with the Office for Human Research Protections (OHRP). Any amendments to the protocol or consent materials must also be approved before they are placed into use. In the United States, only institutions holding a current US Federal-wide Assurance (FWA) issued by OHRP may participate. Refer to: http://www.hhs.gov/ohrp/assurances/.

The Site PI must obtain approval from the IRB for all subsequent protocol amendments and, when warranted, changes to the informed consent document. Protocol and informed consent form amendments can be made only with the prior approval of the Coordinating Center. The Site PI may not implement any protocol deviation without prior notification to the ATRI Coordinating Center and prior review and documented approval of the IRB, except where necessary to eliminate an immediate hazard to study participants, or when change(s) involve only logistical or administrative aspects of the trial (ICH 4.5.4). The investigator shall notify the IRB of deviations from the protocol or serious adverse events occurring at the site, in accordance with local procedures.

13.3 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 and ICH Good Clinical Practice. Applicable HIPAA privacy notifications will be implemented and HIPAA authorizations signed before protocol procedures are carried out. Information should be given in both oral and written form as deemed appropriate by the site's IRB.

Prior to the beginning of the trial, the investigator should have the IRB's approval of both, the informed consent form and any other information to be provided to participants. The ATRI Regulatory Affairs department, at the ATRI Coordinating Center, will collect, QC, and maintain the IRB's approval documents. Consent forms must be in a language fully comprehensible to the prospective participants and/or their authorized representatives and study partners. Participants, their relatives, guardians, or authorized representatives and study partners will be given ample opportunity to inquire about the details of the study. Prior to a participation in the trial, the informed consent form should be signed and personally dated by the participant or by the participant's legally acceptable representative, and by site personnel who conducted the informed consent discussion. Participants should be provided a copy of the signed ICF.

The informed consent will not only cover consent for the trial itself, but also for the genetic samples/data/storage, biomarker samples/data/storage, and imaging

scans/data/storage to be shared with study collaborators and co-investigators. Consent forms will specify that genetic and biomarker samples are for research purposes only; the tests on the genetic and biomarker samples are not diagnostic in nature and participants will never receive results.

It is the general policy of this study not to reveal research results to participants. However, if information is obtained that is viewed by the physician caring for the participant to be clinically relevant, such information can be disclosed. The ATRI Coordinating Center must be notified in these instances. Similarly, MRI scan findings of clinical significance, determined by the site radiologist, may be shared with participants.

13.4 Data Collection and Monitoring

The Site PI or designee will record all data collected (either written or electronic record of data). Written or electronic data of record must be entered on the electronic Case Report Form (eCRF) provided for that purpose. In some instances, no prior written or electronic record of data may exist, and data recorded directly on the eCRF is considered source data. The site will be suitably trained on the use of the eCRF and appropriate site personnel will be authorized to provide electronic signatures. The Site PI is responsible for verifying the integrity of the data and acknowledge as such by signature.

All site entries will be made in a secured web site and the Site PI will review the record for completeness. If corrections are necessary to the eCRFs, the Site PI or designee will update the eCRF and provide documentation for the reason for change.

Completed eCRFs will be submitted according to the ATRI Coordinating Center instructions and reviewed by the ATRI Coordinating Center to determine their acceptability. If necessary, data correction requests will be generated for resolution by the study site.

The clinical monitor is responsible for inspecting the electronic case report forms and source documentation at regular intervals throughout the study to verify adherence to the protocol, completeness and accuracy of the data, and adherence to local regulations on the conduct of clinical research. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements and continued adequacy of the investigational site and its facilities. The Site PI will cooperate in the monitoring process by ensuring the availability of the eCRFs, source documents and other necessary documents at the time of the monitoring visits. Site PI will promptly address any matters brought to his/her attention by the monitor. The Site PI may also be asked to meet in-person with the site monitor during certain visits.

13.5 Procedures to Maintain Participant and Data Confidentiality

Patient confidentiality is strictly held in trust by the participating investigators and research staff. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants.

All data will be transmitted securely via the Internet to ATRI at USC. Access is granted to study team members based on role. Each user of the system has an individual account with a password which is required to be reset at set intervals. Users are logged out of the system after a period of inactivity. All communication to and from the data system is encrypted. Data transmission will occur through a secure internet connection-https (hypertext transfer protocol secured) at 128-bit SSL.

The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the sponsoring institution. Authorized representatives of the sponsoring institution may inspect all documents and records required to be maintained by the Site PI including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records. Any data, specimens, forms, reports, and other records that leave the site will be identified only by a participant identification number (Participant ID, PTID) to maintain confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PTIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by IRB, the FDA, the NIA, and the OHRP.

Information about study participants will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed participant HIPAA Authorization informing the participant of the following:

- What protected health information (PHI) will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI.

In the event that a participant revokes authorization to collect or use PHI, the Site PI, by regulation, retains the ability to use all information collected prior to the revocation of participant authorization. Each Site PI, under the guidance of his/her IRB, is responsible for ensuring that all applicable HIPAA regulations and State laws are met.

To further protect the privacy of study participants, a Certificate of Confidentiality will be obtained from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

13.5.1 Clinical data - ATRI / LONI

In order to provide the clinical data from this project to ADNI investigators, Pharmaceutical Industry and the public through LONI in an anonymized manner (free of any identifying information such as name, address, or phone number), this will be linked to the imaging database at LONI. The database will be frequently updated, and all clinical data acquired by the ATRI Coordinating Center will be provided to LONI in real-time. No personal identifying data will be in this database. All the personal identifying data will be kept in a secure location at the clinic where the participant is seen.

All study data is stored and maintained on servers hosted on Amazon Web Services under an Enterprise Agreement with USC. Study data is not stored at USC facilities. All communication with the servers is encrypted. Access is controlled on a per-user basis and access logs are kept and monitored on an ongoing basis to ensure data security and integrity, keeping data protected from improper use and disclosure.

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.

All subjects will be assigned a code, and this will be used for all data storage and communication between sites. PHI will be recorded and kept under the “need to know” principle (i.e., only when necessary). The data key linking the participant personal information and participant study code numbers will only be available to a limited number of authorized study staff at the sites. The ADNI Coordinating Center does not have access to these keys. At the sites, a participant's PHI is not located on any data collection documents or on any audio recording, nor is it stored with data. Hard copies of data are stored in locked file cabinets at the study sites, while electronic data are password protected and maintained on a secure network. PHI that the study team at ATRI has access to in the EDC system is limited to the minimum necessary for authorized oversight of the research study and includes participant’s DOB and hospital admission/discharge dates.

All data will be transmitted securely via the Internet to ATRI at USC. Access to the database is role-based and will be limited to key personnel at sites and USC. Access

is granted to study team members based on role. Each user of the system has an individual account with a password that is required to be reset at set intervals to comply with USC password requirements. Users are logged out of the system after a period of inactivity. All communication to and from the data system is encrypted. Data transmission will occur through a secure internet connection. The ATRI Clinical Operations and Informatics Cores will also provide real-time web-based reporting on data flow; assure optimal data security and redundant data backups.

13.5.2 MRI and PET Imaging and Data Storage - LONI

MRI and PET scans will be labeled according to each site's imaging machine capabilities using ADNI participant identifiers and scanner specific series descriptions. All MRI and PET scans will undergo de-identification, which is embedded within the LONI Image Upload process to ensure that no participant identification information is present in the image files. MRI scan findings of clinical significance, determined by the site radiologist, will be shared with the participant and the participant's local physician.

13.5.3 Genomic Material - NIH/NIA & NCRAD

De-identified samples including immortalized cell lines, PBMCs, DNA, RNA, buffy coats, and their derivatives will be processed and stored indefinitely at NCRAD. All samples are stored in a secure freezer within a secure facility at Indiana University. Since NCRAD is a NIH dedicated specimen repository designed for 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 genetic specimens will be in accordance with the rules and procedures established by the Indiana University IRB.

The de-linking of the sample from the participant identity occurs at the time the biospecimen is sent by each site to NCRAD. The identity of participants will not be shared with NCRAD or with any investigators. A unique bar-code number is affixed to all specimen tubes as well as affixed to the Sample Form/Draw Sheet. 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 genomic individual number (to preserve confidentiality), Kit number (assigned to all tubes that come in a single shipment for an individual), specimen 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.

Genomic and all other data can be linked to other clinical research data for purposes of scientific analyses, but the only linkage of genetic test results to participant identity is at the specific clinical site where they are enrolled.

NIH/NIA Databases

For genetics, genomics, and related data, data will be shared with other researchers pursuant to the NIA Alzheimer's Disease Genetics sharing Policy: http://www.nia.nih.gov/research/dn/alzheimers-disease-genetics-sharing-plan.

NIAGADS, along with other NIA-approved sites, will make these genetic data and associated phenotypic data available to qualified investigators in the scientific community for secondary analysis in accordance with standards established by NIA. These data repositories are under strict security provisions, including multiple firewalls, separate servers, and data encryption protocols. Investigators and their sponsoring institutions seeking access to data from the NIA-approved data repository must submit a data access request that specifies both the data to which access is sought and the planned research use, and agree to the terms of access set forth in the Data Use Certification (DUC). Investigators are approved by a Data Access Committee (DAC) for access to specific datasets for a specific use(s). In addition, the DUCs include a provision that approved users and their institutions agree to store the requested data securely and to not share the requested data with third parties.

13.5.4 Biomarker Data and Storage of Biomarker Material - UPENN

At the University of Pennsylvania (UPENN), the ADNI Biomarker Core has established and maintains a database for the inventory of stored samples in conjunction uses 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, serum, CSF), volume, aliquot number, freezer, shelf, rack, box, location in the box. A bar code label will be used on the sample tracking form. The database system, LDMS, is powered by Oracle database version 11b resides on the University of Pennsylvania Healthcare System (UPHS) network under the high level protection with the UPHS Enterprise class perimeter firewall that includes a default deny policy. Access to LDMS has 4 layers of security: controlled building access, controlled laboratory access, PC password and LDMS password. VPN access is disabled so data is available only locally. The data is backed-up daily with 256-bit encryption and a copy is stored in a secure location.

Samples handled by the ADNI Biomarker Core are banked in a secure facility, in locked and alarmed freezers at 80°C with 24/7 temperature monitoring, dedicated to the ADNI study.

13.6 Requesting Genetic and Biomarker Samples for Research

Specific procedures for requesting and accessing genetic and biomarker specimens have been created by the Resource Allocation Review Committee (RARC) in accordance with recommendations proposed in the NBAC Human Biological Materials Report. These 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.

14.0 NIH DATA SHARING POLICY

All de-identified ADNI data is shared with investigators who request it on the USC/LONI/ADNI website and are approved by the ADNI DPC. Instructions concerning how to access this data are on the public ADNI website.

Data from this research will be shared in compliance with the NIH's Policies on Data Sharing for NIH funded research. The ADNI3 grant contains a data sharing policy consistent with the goals of the NIH, but which also respects the rights of commercial partners. The NIH Data Sharing Polices and Related Guidance for NIH-Funded Research can be found online at: https://grants.nih.gov/policy/sharing.htm.

NIH believes that data sharing is important for further translation of research results into knowledge, products, and procedures to improve human health. The NIH endorses the sharing of final research data to serve these and other important scientific goals. As above, to protect participants' rights and confidentiality, identifiers will be removed from the data before they are shared.

15.0 STATISTICAL CONSIDERATIONS

15.1 Analysis Goals and Strategies

The Biostatistics Core will carry out interim and final analyses of ADNI3 data, separately and in combination with previous phases, for the primary aims and hypotheses. Strategies for the five analysis goals are summarized briefly below.

All analyses will follow best practices for reproducible research. Final validated code for data preparation and analysis will be share on the LONI website and via GitHub.

15.1.1 Specific Analysis Goals

ADNI3 will continue to discover, optimize, standardize, and validate clinical trial measures and biomarkers used in AD research.

Goal 1

Baseline characteristics of biomarkers and distribution of clinical variables will be summarized by standard descriptive statistics and graphics. Performance of baseline biomarkers as predictors of cognitive and functional change, disease progression, and post-mortem findings will be assessed by regression models (linear, logistic, survival, et al.)

Goal 2

We will assess potential of biomarkers for reducing sample size or shortening follow-up by use for inclusion/exclusion, stratification, or covariate analysis.

Goal 3

Will use longitudinal models to characterize change in biomarkers and its association with clinical, functional, and other biomarkers changes and post-mortem findings.

Goal 4

We will assess longitudinal biomarker change for potential use in clinical trials as an outcome measure, considering signal-to-noise ratio for various study designs.

Goal 5

We will formally compare performance across biomarkers for all 4 previous aims. The role of genes and gene expression in these analyses will be examined in collaboration with the Genetics Core.

15.1.2 Sample Size

Sample sizes have been chosen to have both adequate numbers of participants in each diagnostic group and adequate numbers of observations per participant to yield minimum 80% power for aims 1-4 above. Examples: we will have 80% power to detect a difference between high-risk and low-risk groups in ADAS change/ year of 0.43 (0.96, 2.28) for CN (MCI, AD). We will be able detect correlations between imaging biomarker change and cognitive or functional change as small as 0.16 for CN or MCI and 0.21 for AD.

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APPENDIX 1 SCHEDULE OF EVENTS

Rollover Participants: CN, MCI, and AD

Clinic Visit Name	Initial[1]	Year 1[2, 3,4]	Year 2	Year 3	Year 4	Year 5	CN Phone Check[5]	Telephone Visit In replacement of in-clinic
Explain Study and Obtain consent[13]	X							X[13]
Neuropath discussion / Provisional consent[6]	X	X	X	X	X	X	X	X
Demographics	X							
Medical History	X							
Vital Signs	X	X	X	X	X	X		
Mini Mental State Examination (MMSE)	X	X	X	X	X	X		
Cogstate Brief Battery (CBB)[7]	X	X	X	X	X	X		
Logical Memory I and II	X	X	X	X	X	X		
Everyday Cognition (ECog)	X	X	X	X	X	X		X
Montreal Cognitive Assessment (MoCA)	X	X	X	X	X	X		
Category Fluency (Animals)	X	X	X	X	X	X		
Trails A & B	X	X	X	X	X	X		
Multi-Lingual Naming Test (MlNT)	X	X	X	X	X	X		
Auditory Verbal Learning Test	X	X	X	X	X	X		
Geriatric Depression Scale	X	X	X	X	X	X		X
Clock drawing	X	X	X	X	X	X		
Neuropsychiatric Inventory (NPI) / (NPI-Q for Phone Check)	X	X	X	X	X	X	X	X
ADAS-Cog 13 (w/ Delayed Recall and Number Cancellation)	X	X	X	X	X	X		
Clinical Dementia Rating Scale	X	X	X	X	X	X		X
Activities of Daily Living (FAQ)	X	X	X	X	X	X		X
Financial Capacity Instrument – Short Form (FCI-SF)	X	X	X	X	X	X		
Plasma and Serum Biomarker Collection	X	X	X	X	X	X		
DNA Sample Collection	X							
PMBC Sample Collection	X							
RNA and Buffy Coat Sample Collection	X	X	X	X	X	X		
Concomitant Medications	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X
Diagnostic Summary	X	X	X	X	X	X		
3T MRI Imaging[8]	X	X	X	X	X	X		
FDG-PET Imaging[9]	X							
Florbetapir Imaging[10]	X		X		X			
Flortaucipir PET Imaging[11]	X	X[11]	X[11]		X			
CSF Collection by Lumbar Puncture (LP)[10]	X		X		X			
LP Safety lab test: PT/PTT (coagulation profile) [12]			X		X			

[1]**Rollover participants** who are being followed from ADNI2 begin ADNI3 with a complete Initial in-clinic visit or Telephone visit in replacement of in-clinic visit.

[2]**CN** participants are seen in the clinic biennially (every other year) unless they are required to come in on an off year for flortaucipir PET imaging (see footnote 11).

[3]**MCI and Converter** participants are seen in the clinic annually.

[4]**AD** participants are seen in-clinic for 24 months from Baseline (total of 3 in-clinic visits at Initial, Year 1, and Year 2) and then ongoing phone follow-up should continue every 6 months or, at minimum, annually for those that have consented or are undecided about Neuropathology program.

[5]**Applies to CN participants on off years** when an ongoing in-clinic visit is not called for or needed for flortaucipir PET imaging.

[6]**Neuropath discussion** to confirm consent/interest should occur every 6 months or, at minimum, annually (see section 9.5). If a participant has refused to participate, no further inquiry should take place.

[7]**CBB** will be conducted at each In-Clinic Visit and up to quarterly interval remotely for the CN and MCI cohorts only.

[8]**Onoging MRI** conducted at each in-clinic visit.

[9]**FDG-PET** is only assessed at baseline for MCI and AD participants only; CN participants are not required to conduct FDG-PET.

[10]**Florbetapir and LP for CSF** starts at Initial Visit and is then repeated every two years.

[11]**Flortaucipir PET Imaging** is at the Initial/Baseline Visit for all participant groups. AD participants will have a flortaucipir PET scan at each in-clinic visit (for a total of three scans). CN, MCI, and Converter participants will receive a scan at the Y4 visit (for a total of two scans). Additionally, 20% amyloid negative, and 80% amyloid positive CN and MCI participants will have two more scans (for a total of four scans).

[12]**PT/PTT test** is an optional procedure at the discretion of PI or Site Clinician

[13]**Telephone visit in replacement of in-clinic visit:** new consent form is required for those participants opting into a Telephone visit in replacement of in-clinic visit for Initial visit or Ongoing Visits.

Newly Enrolled Participants: CN, MCI, and AD

Clinic Visit Name	Screen	Base-line[1,2,3]	Year 1	Year 2	Year 3	Year 4	Year 5	CN Phone Check[4]	Telephone Visit In replacement of in-clinic
Explain Study and Obtain consent [12]	X								X [12]
Neuropath discussion / Provisional consent[5]	X	X	X	X	X	X	X	X	X
Demographics, Family History, Inclusion and Exclusion Criteria	X								
Medical History, Physical Exam, Neurological Exam, Modified Hachinski Ischemic Score	X								
Vital Signs	X	X	X	X	X	X	X		
Height	X								
Screening Labs (hematology, chemistry panel, urinalysis, B12, TSH)	X								
American National Adult Reading Test		X							
Cognitive Change Index (CCI)	X								
Mini Mental State Examination (MMSE)	X		X	X	X	X	X		
Cogstate Brief Battery (CBB)[6]		X	X	X	X	X	X		
Logical Memory I and II	X		X	X	X	X	X		
Everyday Cognition (ECog)		X	X	X	X	X	X		X
Montreal Cognitive Assessment (MoCA)		X	X	X	X	X	X		
Category Fluency (Animals)		X	X	X	X	X	X		
Trails A & B		X	X	X	X	X	X		
Multi-Lingual Naming Test (MlNT)		X	X	X	X	X	X		
Auditory Verbal Learning Test		X	X	X	X	X	X		
Geriatric Depression Scale	X		X	X	X	X	X		X
Clock drawing		X	X	X	X	X	X		
Neuropsychiatric Inventory (NPI) / (NPI-Q for Phone Check)		X	X	X	X	X	X	X	X
ADAS-Cog 13 (w/ Delayed Recall and Number Cancellation)		X	X	X	X	X	X		
Clinical Dementia Rating Scale	X		X	X	X	X	X		X
Activities of Daily Living (FAQ)		X	X	X	X	X	X		X
Financial Capacity Instrument – Short Form (FCI-SF)		X	X	X	X	X	X		
Plasma and Serum Biomarker Collection		X	X	X	X	X	X		
DNA Sample Collection		X							
Cell Immortalization Sample Collection		X							
RNA and Buffy Coat Sample Collection		X	X	X	X	X	X		
PBMC Sample Collection		X							
Concomitant Medications	X	X				X		X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Diagnostic Summary	X	X	X	X	X	X	X		
3T MRI Imaging[7]	X		X	X	X	X	X		
FDG-PET Imaging[8]		X							
Amyloid Imaging[9]		X		X		X			
Flortaucipir PET Imaging[10]		X	X[10]	X[10]		X			

CSF Collection by Lumbar Puncture (LP)[9]		X		X		X			
LP Safety lab test: PT/PTT (coagulation profile) [11]		X		X		X			

[1]**CN** participants are seen in the clinic biennially (every other year) unless they are required to come in on an off year for flortaucipir PET imaging (see footnote 10).

[2]**MCI and Converter** participants are seen in the clinic annually.

[3]**AD** participants are seen in-clinic for Screening, Baseline, two Ongoing in-clinic visits and then AD phone checks should continue every 6 months or, at minimum, annually for those that have consented or are undecided about Neuropathology program.

[4]**Applies to CN participants** on off years when ongoing in-clinic visit is not called for or needed for flortaucipir PET imaging.

[5]**Neuropath discussion** to confirm consent/interest should occur every 6 months or, at minimum, annually (see section 9.5). If a participant has refused to participate, no further inquiry should take place.

[6]**CBB** will be conducted at each In-Clinic Visit and up to quarterly interval remotely for the CN and MCI cohorts only.

[7]**Onoging MRI** conducted at each in-clinic visit.

[8]**FDG-PET** is only assessed at Baseline for MCI and AD participants only; CN participants are not required to conduct FDG-PET.

[9]**Amyloid Imaging (florbetapir or florbetaben) and LP for CSF** starts at Baseline and is then repeated every two years.

[10]**Flortaucipir-PET Imaging** is at the Initial/Baseline Visit for all participant groups. AD participants will have a flortaucipir PET scan at each in-clinic visit (for a total of three scans). CN, MCI, and Converter participants will receive a scan at the Y4 visit (for a total of two scans). Additionally, 20% amyloid negative, and 80% amyloid positive CN and MCI participants will have two more scans (for a total of four scans).

[11]**PT/PTT test** is an optional procedure at the discretion of PI or Site Clinician

[12] **Telephone visit in replacement of in-clinic visit**: A new consent form is required for those participants opting into a Telephone visit in replacement of in-clinic visit for Ongoing Visits. Not allowed at Baseline.