

Alzheimer’s Disease Neuroimaging Initiative 4 (ADNI4): Together Exploring Aging Minds (TEAM) – An ADNI Study

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TABLE OF CONTENTS

TABLE OF CONTENTS	2
STATEMENT OF COMPLIANCE	5
1 PROTOCOL SUMMARY	6
1.1 SYNOPSIS	6
1.2 SCHEMAS	7
1.3 SCHEDULE OF EVENTS (SOE)	8
2 INTRODUCTION	12
2.1 STUDY RATIONALE	12
2.1.1 RATIONALE FOR EXPANDED URP OUTREACH FOR TEAM-ADNI	12
2.2 BACKGROUND	13
2.3 RISK/BENEFIT ASSESSMENT	13
2.3.1 KNOWN POTENTIAL RISKS	13
3 OBJECTIVES AND ENDPOINTS	15
4 STUDY DESIGN	16
4.1 OVERALL DESIGN	16
4.1.1 SAMPLE SIZE.....	16
4.2 END OF STUDY DEFINITION	17
5 STUDY POPULATION	17
5.1 INCLUSION/EXCLUSION CRITERIA	17
5.1.1 INCLUSION CRITERIA FOR THE TEAM-ADNI COHORT	17
5.1.2 EXCLUSION CRITERIA FOR THE TEAM-ADNI COHORT	18
5.2 LIFESTYLE CONSIDERATIONS	18
5.2.1 LIFESTYLE CONSIDERATIONS	18
5.3 SCREEN FAILURES	18
5.4 STRATEGIES FOR RECRUITMENT AND RETENTION	18
5.4.1 IDENTIFYING POTENTIAL PARTICIPANTS AND RECRUITMENT EFFORTS:	18
5.4.2 ENROLLMENT OF ELIGIBLE PARTICIPANTS	19
6 DISCONTINUATIONS AND WITHDRAWALS	19
6.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY	19

6.2	LOST TO FOLLOW-UP	19
7	<u>STUDY ASSESSMENTS AND PROCEDURES</u>	<u>20</u>
7.1	VISITS.....	20
7.1.1	DESCRIPTION OF STUDY VISITS.....	20
7.1.2	VISIT SCHEDULING	21
7.1.3	SCREENING	21
7.1.4	BASELINE VISIT	22
7.1.5	ONGOING LONGITUDINAL VISITS	22
7.1.6	OTHER TYPES OF STUDY VISITS	23
7.2	ASSESSMENTS.....	23
7.3	IMAGING (OPTIONAL BUT AIMING FOR HALF OF PARTICIPANTS TO COMPLETE).....	26
7.3.1	PET SCANNING: AMYLOID – FLORBETAPIR (FBP); TAU – FLORTAUCIPIR (FTP).....	26
7.3.2	MRI	27
7.4	BIOSPECIMENS.....	28
7.4.1	BLOOD DRAW & URINE COLLECTION	28
7.5	ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS	29
7.5.1	ADVERSE EVENT (AE) DEFINITION.....	29
7.5.2	SERIOUS ADVERSE EVENT (SAE) DEFINITION	29
7.5.3	EVENT ASSESSMENT, REPORTING, AND FOLLOW-UP.....	29
7.5.4	SERIOUS ADVERSE EVENT REPORTING AND FOLLOW-UP	30
7.5.5	EVENT CLASSIFICATION	30
7.5.6	REPORTING EVENTS TO PARTICIPANTS	31
8	<u>STATISTICAL CONSIDERATIONS.....</u>	<u>31</u>
8.1	POPULATIONS FOR ANALYSES	31
9	<u>REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS</u>	<u>31</u>
9.1	KEY ROLES AND STUDY GOVERNANCE.....	31
9.1.1	ADNI CORES.....	32
9.1.2	DATA AND COORDINATING CENTER.....	34
9.2	REGULATORY CONSIDERATIONS	34
9.3	INFORMED CONSENT.....	34
9.3.1	OVERVIEW OF INFORMED CONSENT.....	35
9.4	INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE	35
9.5	SAFETY OVERSIGHT.....	35
9.6	CLINICAL MONITORING.....	36
9.7	QA/QC.....	36
9.8	PROTOCOL DEVIATIONS	37
9.9	DATA HANDLING AND RECORD KEEPING	37
9.9.1	DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES – Ebisu (ADMIN CORE).....	37
9.9.2	DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES – IN-CLINIC AND REMOTELY DERIVED DATA.....	38
9.9.3	STUDY RECORDS RETENTION.....	40
9.10	CONFIDENTIALITY AND PRIVACY	40
9.10.1	HIPAA.....	41

9.10.2 CERTIFICATE OF CONFIDENTIALITY..... 41

9.11 FUTURE USE OF STORED SPECIMENS AND DATA42

9.12 PUBLICATION AND DATA SHARING POLICY.....42

9.12.1 PUBLICATION OF RESULTS..... 42

9.12.2 SHARING OF STUDY DATA, BIOSPECIMENS, AND GENETIC MATERIAL..... 42

9.13 CONFLICT OF INTEREST POLICY43

9.14 STUDY DISCONTINUATION AND CLOSURE43

10 ABBREVIATIONS.....43

11 PROTOCOL AMENDMENT HISTORY45

12 REFERENCES.....46

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and applicable United States (US) Code of Federal Regulations (CFR). The investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor, and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the study participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP Training.

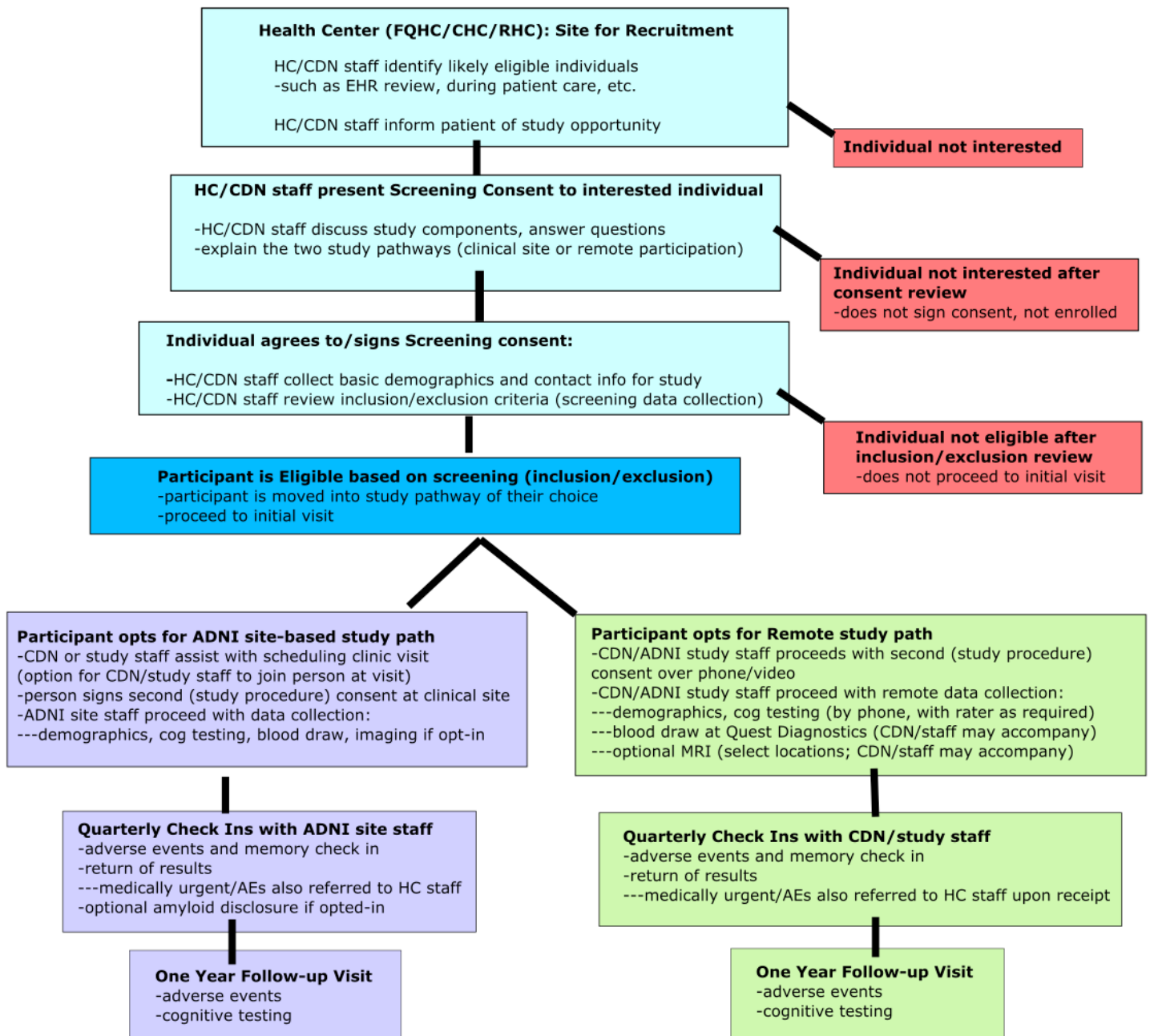
The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

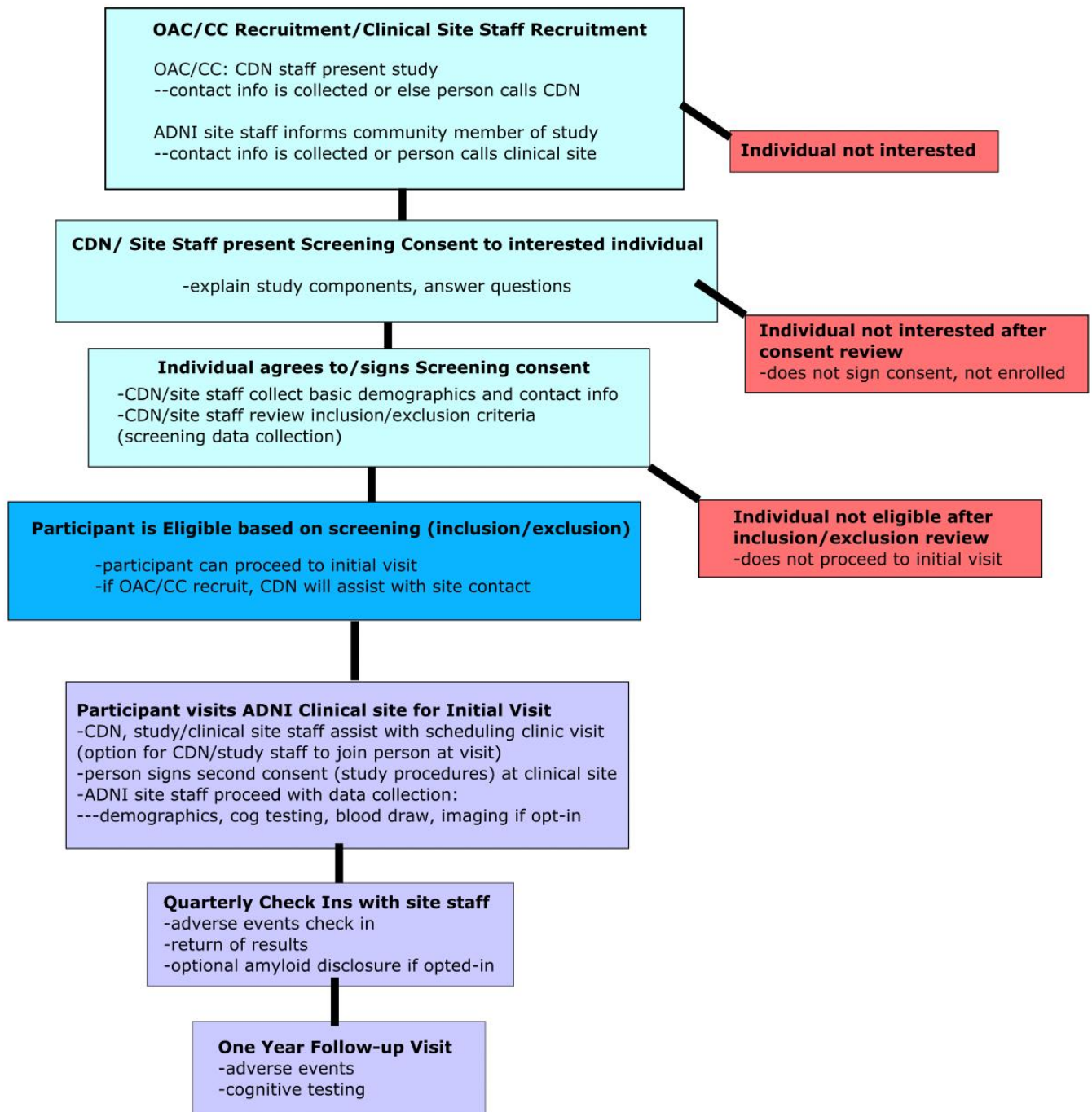
1.1 SYNOPSIS

Title:	Alzheimer’s Disease Neuroimaging Initiative 4 (ADNI4): Together Exploring Aging Minds (TEAM) Cohort
Study Description:	Non-randomized, natural history, non-treatment observational study
Objectives:	<p>Primary Objectives:</p> <ul style="list-style-type: none"> • Enrollment of understudied research populations (URPs), including those with low educational attainment, to improve generalizability of results and advance our understanding of Alzheimer’s Disease (AD) and related Dementias, specifically with individuals recruited from: <ul style="list-style-type: none"> • Health Centers (HCs) including Federally Qualified Health Centers (FQHCs), Rural Health Clinics (RHCs), Community Health Centers (CHCs) • Community Centers (CCs) including Older Adult Centers (OACs) • Community-based events/outreach by ADNI clinical site staff • Assess feasibility of enrollment and data collection using multiple recruitment sources (listed above) and two participant pathways (clinical and remote settings) for these research populations • Validation of biomarker measures in these URPs • Inform clinical trial design
Study Population:	<p>Men and women aged 55-90 years without significant neurological, psychiatric, or other advanced medical conditions that would prevent them from undergoing study procedures.</p> <ul style="list-style-type: none"> • Up to 200 participants will be enrolled into the TEAM-ADNI cohort
Phase:	N/A
Descriptions of Sites/Facilities Enrolling Participants:	Approximately 15 recruitment centers and approximately 15 ADNI clinical sites across the USA, and additional ‘remote/decentralized’ facilities (such as Quest Diagnostics) for participant task completion
Description of Study Intervention:	N/A
Study Duration:	3 years
Participant Duration:	Approximately one year.

1.2 SCHEMAS



Schema 1: Participant flow diagram if individual is recruited from a Health Center (such as a Federally Qualified Health Center (FQHC), Community Health Center (CHC), or Rural Health Clinic (RHC)). CDN = Clinical Directors Network. Where possible, participants will be offered two study pathways to choose from (site-based or remote); some locations may only have one pathway available.



Schema 2: Participant flow diagram if individual is recruited from an Community Center (CC), Older Adult Center (OAC), or individual is recruited by clinical site staff. Note these participants are not offered the remote participant pathway at this time. CDN = Clinical Directors Network.

1.3 SCHEDULE OF EVENTS (SOE)

Individuals who are recruited from health centers (FQHCs, RHCs, CHCs, etc.), older adult centers, community centers, or by ADNI study staff at community events, will undergo a screening visit that includes a screening consent followed by minimal demographic information collection and review of study inclusion and exclusion criteria. Those who are eligible after screening will move forward with an baseline visit.

Participants recruited from a health center setting (i.e. FQHC, RHC, etc.) may be offered the option to complete study activities remotely. Individuals who elect to do these study activities remotely must identify their medical care team to receive disclosed medically relevant results. As such, remote study activities only exist for individuals recruited from HCs, but not for individuals recruited from OACs or from community events.

For all participants, the baseline visit will begin with consent for study procedures. Participants will answer questionnaires and complete cognitive testing with study staff (by phone or in-person). Participants will provide blood and urine samples for routine laboratory analyses (e.g. basic metabolic panel, lipid panel, etc.), AD biomarkers, and genetics (participants may need separate appointment due to fasting requirements). Participants may complete optional brain imaging (MRI, PET) study components. All participants will have quarterly check-in telephone calls, and then a 12-month visit. At the 12-month visit, participants will only complete questionnaires and cognitive testing (no repeat blood sample collection or brain imaging).

Health Center (HC) recruited participants:

Health center staff or Clinical Director Network (CDN) staff will screen potential participants who they believe can provide consent. Where possible, participants recruited from HCs will be offered two study visit pathways:

- (1) all recruited will complete a screening call/visit including consent # 1 (screening consent) to review study components and inclusion/exclusion criteria
- (2a) participant is eligible and wants to complete TEAM-ADNI study at an existing ADNI clinical site
 - i. consent #2 (study procedures) at clinical site
 - ii. demographics, questionnaires, cognitive testing (*note these could be completed over the phone)
 - iii. provide blood/urine samples (*note this will likely happen on separate day because of fasting requirement)
 - iv. optional brain imaging MRI/PET scans
- (2b) participant is eligible and wants to complete TEAM-ADNI study as a ‘remote’ participant including:
 - i. consent #2 (study procedures) over phone/video call
 - ii. phone/video call to complete demographics, questionnaires, cognitive testing
 - iii. blood/urine samples collected at a Quest Diagnostics or similar facility
 - iv. optional MRI at an imaging facility (select locations only)

OAC/CC/Clinical Site staff recruited participants:

Participants recruited from OAC/CCs or by ADNI clinical site staff will only be offered the option to complete TEAM-ADNI study procedures at an ADNI clinical site:

- (1) all recruited will complete a screening call/visit including consent #1 (screening consent) with CDN team or ADNI study staff if recruited via OAC/CC or with ADNI clinical site staff if site recruited, to review study components and inclusion/exclusion criteria
- (2) participant is eligible and will complete TEAM-ADNI study procedures at an ADNI clinical site
 - i. consent to study procedures at clinical site
 - ii. demographics, questionnaires, cognitive testing (*note these could be completed over the phone)
 - iii. provide blood/urine samples (*note this will likely happen on separate day because of fasting requirement)
 - iv. optional brain imaging MRI/PET scans

Table 1: TEAM-ADNI Schedule of Events (SoE). Remote participants will not complete optional PET (participant must be on in-clinic pathway to complete PET). Remote participants may complete MRI (optional) if a facility is available in their area and they elect to participate.

<u>Visit Activity</u>	<u>Screening</u>	<u>Baseline</u>	<u>Baseline Optional Study Procedures</u>	<u>Telephone Check (months 3, 6, 9)</u>	<u>Month 12</u>
Record contact information for individual in Ebisu ADNI study platform	X				

Screening consent (HC/CDN/ADNI staff)	X				
Participant assigned Ebisu ADNI Online ID	X				
Basic demographics questionnaire	X				
Inclusion/exclusion criteria questionnaire ¹	X				
Collect Study Partner information	X				
Area Deprivation Index Score (ADI) ²	X	X (if moved)			X (if moved)
Study procedures consent (may include additional consent for EHR data sharing)		X			
EDC PTID assigned		X			
GUID creation		X			
Detailed demographics (includes Hollingshead)		X			
Brief Medical History		X			
Height, weight, blood pressure (for remote participants self-report, if available)		X			
Adverse Events		X		X	X
Subjective cognitive decline questionnaire		X		X	X
Current Medications (self-report; possibly also shared from EHR)		X			X
Clinical Dementia Rating (CDR)*		X*			X*
Montreal Cognitive Assessment (MoCA) (all will receive telephone (blind) version)		X			X
Rey Auditory Verbal Learning Test (RAVLT)		X			X
Category Fluency Test (CFT): Animals		X			X
Geriatric Depression Scale (GDS)		X			X
Rural-Urban Commuting Area (RUCA) and Rural-Urban Continuum Codes (RUCC) ³		X			X (if moved)
Participant feedback questionnaire		X			X
American National Adult Reading Test (AMNART) ⁴ or The Word Accentuation Test – Chicago (WAT-C; Spanish-language) ⁴			X		
Abbreviated Multidimensional Acculturation Scale (AMAS) ⁵			X		
Perceived Stress Scale 10-item (PSS-10)			X		X (optional)
Brief Perceived Ethnic Discrimination Questionnaire-Community Version (Brief PEDQ-CV)			X		X (optional)
Quick Dementia Rating Scale (QDRS; participant report version)*			X*		X*
Brain donation motivators/barriers questionnaire					X (optional)
-----	-----	-----	-----	-----	-----
Blood & Urine Labs (Hematology, Chemistry panel, Urinalysis, B12, TSH, HbA1c, high sensitivity CRP, BUN, Creatinine, Cystatin C, Lipoprotein A) ⁶		X			
Blood/Urine labs – return of results if participant requested (by phone with staff)			X		
Plasma and Serum AD Biomarker Sample Collection ⁶		X			
PBMC Sample Collection ⁶		X			
Lipid Panel ⁶		X			

DNA Sample Collection ⁶		X			
RNA and Buffy Coat Sample Collection ⁶		X			
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3T MRI Imaging			X**		
Amyloid PET Imaging			X***		
Tau PET Imaging			X***		
Ryff Psychological Well-Being Purpose of Life subscale ⁷			X#		X# (if completed at baseline)
Pre-Amyloid Scan assessments ⁸			X#		
Disclosure Visit ⁹			X#		
Disclosure Visit_optional STAI-AD ⁹ and Suicide Ideation Questionnaire			X#		
Post-Disclosure Visit ¹⁰			X#		
Impact of Events Scale (IES) ¹¹			X#		X# (if completed at baseline)
Ongoing Disclosure Assessments¹²					X#

only applicable if participant completes amyloid PET scan and opts to receive their result

*At study onset, participants will be asked to complete the CDR. However, it is possible that during the course of the study, ADNI leadership will determine that the CDR is not feasible in this population. A decision may be made to stop using the CDR and instead the QDRS would be used on all participants going forward. Therefore all participants will have either a CDR or a QDRS, no participant will have both.

** MRI is optional. Remote pathway participants can only opt-in for MRI if a facility is in their area. If no MRI facility is available and they want to opt-in for MRI, the participant will have to be on the in-clinic pathway.

***PET is optional. Remote pathway cannot complete PET and participant must be on the in-clinic pathway if they want to opt-in to PET imaging.

¹**Inclusion/exclusion criteria** are reviewed to ensure participant eligibility for full study enrollment.

²**ADI** only needs to be collected once unless the participant has moved.

³**RUCC & RUCA** only need to be collected once unless the participant has moved.

⁴**The AMNART** is conducted on English-speaking participants (optional). **The WAT-C** is conducted to replace the AMNART for Spanish-speaking participants (optional).

⁵**AMAS** will only be given to participants who self-identify as Latino/a (optional).

⁶**Fasting requirement** for biospecimens including plasma/serum, Buffy Coat, and some clinical labs is a minimum of 6 hours.

⁷**Ryff Psychological Well-Being Purpose of Life subscale** collected on all eligible participants who have consented to receive their amyloid PET results prior to their amyloid PET scan and at every in-clinic visit.

⁸**Pre-Amyloid Scan assessments** collected on all eligible participants who have consented to receive their amyloid PET results prior to their amyloid PET scan.

⁹**The Disclosure Visit** should only occur on eligible participants who have consented to receive their amyloid PET results and who the site PI deems psychologically well to receive their results. Disclosure visits can only be performed by an experienced site clinician or site PI. The disclosure visit is to occur in-person or virtually within 3 months after the site has completed data entry for this visit, but may be delayed. Study partners or someone who is available and has a personal, supportive relationship with the participants are suggested to be in attendance for the disclosure visit. Additional optional assessments of psychological well-being (STAI-AD 6-item and questions regarding suicide ideation) may be completed by the site PI based on site clinician discretion.

¹⁰**The Post-Disclosure Visit** should occur within 1 week of the disclosure visit. At the site PI's discretion, the post-disclosure visit can be performed by study coordinators who have completed amyloid disclosure training. Post-disclosure assessments will be collected at this visit, including Impact of Events.

¹¹**Impact of Events** collected at each 'Post-Disclosure Visit' and at every subsequent in-clinic visit on all eligible participants who have consented to receive their amyloid PET results.

¹²**Ongoing Disclosure Assessments** to assess participant's understanding of their result will be collected at 12month visit on all eligible participants who consented to receive their amyloid PET results.

Table 2: TEAM-ADNI Study Partner Schedule of Events (SoE)

<u>Visit Activity</u>	<u>Screening</u>	<u>Baseline</u>	<u>Baseline Optional</u>	<u>Month 12</u>
Record contact information for potential Study Partners in Ebisu ADNI study platform	X			
Potential Study Partners contacted to establish interest	X			
Study Partner consent ¹		X		
Study Partner information		X		
Clinical Dementia Rating (CDR) Scale (SP interview)*		X*		X*
Functional Activities Questionnaire (FAQ)		X		X
Neuropsychiatric Inventory (NPI) / Neuropsychiatric Inventory-Questionnaire (NPI-Q) for Telephone collection			X	X (if completed at baseline)
Quick Dementia Rating Scale (QDRS)*			X*	X* (if completed at baseline)
Study Partner brain donation motivators/barriers questionnaire				X (optional)
Study Partner feedback questionnaire				X (optional)

¹SP must have minimum number of contact hours with participant to be eligible study partner, and must be able to speak/read/write English or Spanish

* At study onset, study partners will be asked to complete the CDR. However, it is possible that during the course of the study, ADNI leadership will determine that the CDR is not feasible in this population. A decision may be made to stop using the CDR and instead the QDRS would be used on all participants going forward. Therefore all study partners will have either a CDR or a QDRS, no study partner will have both.

2 INTRODUCTION

2.1 STUDY RATIONALE

ADNI plays a central role in improving treatment trials. Since the study’s launch, ADNI Investigators with regulators in both the United States (US) and abroad have facilitated the design of major completed and ongoing drug trials. One of the most pressing challenges in the AD field, with immense scientific and ethical ramifications, is the chronic lack of generalizability in research and trial populations, including in ADNI. ADNI4’s TEAM cohort aims to address this by enhancing recruitment of understudied research populations, specifically individuals with lower education, lower socioeconomic status, and/or under or uninsured persons. ADNI4’s TEAM cohort addresses this by recruiting participants who are: (1) patients at Health Centers (HCs) such as Federally Qualified Health Centers (FQHCs), Rural Health Clinics (RHCs), or Community Health Centers, or (2) who visit Older Adult Centers (OACs) or Community Centers (CCs), or (3) who are lower education individuals recruited by ADNI clinical site study staff (such as at a community outreach event), and enrolling them into the TEAM-ADNI study cohort. This cohort will complete many of the same procedures that ADNI4 In-Clinic participants undergo, and will serve as a feasibility study to recruit and enroll these populations who are largely absent from Alzheimer’s disease research and clinical trials.

2.1.1 RATIONALE FOR EXPANDED URP OUTREACH FOR TEAM-ADNI

Results from research and clinical trials including ADNI, have been limited in their interpretive power due to relative homogeneity in the study populations, which typically are dominated by college-educated non-Hispanic white individuals. To improve the generalizability of our data, ADNI4’s TEAM cohort will engage and recruit lower education/lower socioeconomic status/under or

uninsured participants recruited from health centers, community centers, older adult centers, or who are recruited by clinical site staff at community events, with the goal of enrolling up to 200 participants.

The TEAM-ADNI participants will complete a modified version of the ADNI4 clinical battery. This includes clinical/cognitive assessments, and collection of blood, plasma, and serum for genetics and biomarkers. When possible, participants will be offered the option to complete a 3T MRI as well as amyloid PET imaging, and tau PET imaging, with the study aiming for half of the TEAM-ADNI participants to complete these imaging procedures.

For those who do opt-in to complete the imaging procedures, the project will collect MRI (T1, FLAIR, T2*GRE, diffusion, and as much of the remainder of the ADNI4 MRI protocol as the site is able and the participant is willing); amyloid PET using the tracer florbetapir F18 (FBP); tau PET using the flortaucipir F18 PET (FTP) tracer.

TEAM-ADNI participants will have quarterly check-in calls with study staff to keep them engaged and check for any adverse events. Participants will be asked to complete an additional assessment 12 months after the baseline visit, which will repeat the same cognitive assessment battery (no blood collection or brain imaging).

2.2 BACKGROUND

Since its launch in 2004, the overarching aim of the Alzheimer’s Disease Neuroimaging Initiative (ADNI) has been to validate biomarkers for Alzheimer’s disease (AD) clinical trials. ADNI4 continues the previously funded ADNI1, ADNI-GO, ADNI2, and ADNI3 studies that have 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 AD.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Alzheimer’s disease (AD) is currently an irreversible neurodegenerative condition that over time causes progressive deterioration in a person’s cognitive, emotional, and behavioral functioning. In addition, AD is widely known as a highly disabling illness and a diagnosis can carry stigma affecting both the participant and family. Accordingly, participants who enroll in the study may be vulnerable to psychological reactions and issues if they receive results indicating increased risk for future dementia symptoms (e.g. amyloid PET results), or if they progress to varying and more advanced clinical symptoms of AD, and receive information about this progression. Such psychological reactions and issues may range from very mild symptoms of depression and anxiety to more serious psychopathology, including agitation, major depression, and suicidal ideation and actions.

2.3.1.1 STUDY PROCEDURES

2.3.1.1.1 Clinical, Cognitive, Neuropsychological Testing

Clinical, cognitive, and neuropsychological testing conducted in this study may cause some participants to become upset, frustrated, bored, or tired.

2.3.1.1.2 Biospecimens

Blood Draw

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

2.3.1.1.3 Imaging

Magnetic Resonance Imaging (MRI) – optional procedure (optional for all on in-clinic pathway; optional for remote pathway, if an imaging center is available)

There are no proven biological risks associated with MRI scanning. All participants will be screened for medical contraindications for MRI, which include metallic foreign bodies in the brain or eye, or cardiac pacemakers. However, there is a slight risk that a

participant may accidentally bring metal into the MR scanner room, which could be pulled into the MRI magnet and injure the participant. However, if standard safety precautions are followed this should never happen.

There is a slight risk of anxiety due to claustrophobia and noise. If a participant experiences anxiety when placed into the MR scanner, the participant may be removed from the scanner and offered the option of continuing or terminating the MRI and/or the study.

Positron Emission Tomography (PET) – optional procedure (optional for all on in-clinic pathway; no PET imaging for those on remote pathway, so if participant wants to complete PET imaging they must be on the in-clinic participant pathway)

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

The following [18F] labeled radiotracers will be utilized for PET imaging in this study:

- Florbetapir (FBP; Amyvid)
- Flortaucipir (FTP; Tauvid)

Information about safety and risk can be found in respective Investigator Brochures and/or Package Inserts. 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 exposure from background radiation sources.

More information about the known and expected benefits, risks, and reasonably anticipated adverse events (AEs) of these tracers can be found in their corresponding Investigator’s Brochures (IB) or package inserts.

Radiation exposure from the radiotracers used in ADNI can be found in relevant study manuals.

Other risks associated with PET scanning include fatigue and discomfort at having to remain in the scanner for up to 30 minutes, and the discomfort and possible bruising associated with intravenous injections. The lowest possible dose of radioactivity compatible with good image quality is used. All IV catheters are placed by medical professionals with extensive training and experience. Experimenters and study participants can communicate via intercom during the scan.

Participants in this study have the option to receive one amyloid PET scan (FBP) and one tau PET scan (FTP) at the baseline visit.

2.3.1.2 STUDY PARTICIPATION

2.3.1.2.1 Returning Results

All medically relevant results that might impact the future diagnosis or treatment of the participant will be provided to the participant and the responsible medical party at the site, or as identified by the participant. The site PI or primary physician or care provider’s discretion to disclose pertinent medical results (abnormal and normal) to participants is recommended, with medically relevant information being prioritized. For example, results from cognitive testing may be shared as part of a dementia diagnosis. Similarly, MRI scan findings of clinical significance, as determined by either the central read or local read, will be shared with the participant. Additionally, the responsible clinician/site PI may also return standard blood/urine lab results from the baseline visit (e.g. TSH, HbA1c, etc.).

In general, genetic and Alzheimer’s disease biomarker (including blood) samples are for research purposes only, not diagnostic, and will not be revealed to clinical staff or the participant. An exception will be allowed if the participant wishes to enroll in a treatment trial or requires the genetic or blood information to receive treatment.

Returning Amyloid Status:

Participants who opt to complete an amyloid PET scan will be given the option to learn the results (elevated or not elevated) from their amyloid PET imaging. If a participant so chooses, those results will be disclosed as described in the relevant study manual. Participants who receive a positive or elevated result may believe that the person is going to develop Alzheimer’s disease dementia, which, in turn, could cause psychological distress and an experience of stigma. In contrast, participants who received a negative or

non-elevated result may experience a mistaken belief that they will never develop AD, or they may develop concern born of the uncertainty that they have some but not enough amyloid. Sites will provide participants with handouts to review at home to help better understand their result.

2.3.1.2.2 Genetic

National Institutes of Health (NIH) policy requires that de-identified genomic data are uploaded to a secure government sponsored health research database for broad sharing with approved investigators. 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, genetic code is also shared with their children, parents, brothers, sisters, other blood relatives and other members of their ethnic group. 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 to attempt to identify any study participants.

2.3.1.2.3 Loss of Privacy

In this study, a great deal of information about participant health status will be collected. Study staff personnel will collect personal protected health information such as name, date of birth, address, phone number, and email. Each study staff will maintain the personal protected health information in a secure and locked location. All participants will be assigned a participant identifier (PTID) and all data collected under this protocol will be associated with that PTID. Data associated with the PTID will be shared widely, but it will not be possible to identify an individual participant from the data. However, there is a very unlikely possibility of a security failure, in which case 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).

To protect participant privacy from facial imaging identification, MRI and PET scans will undergo defacing prior to public release. Individuals could request access to non-defaced images but would need to justify the specific need and may need to sign a stronger data privacy agreement.

All deidentified data will be shared through the ADNI Laboratory of Neuro Imaging (LONI) website. In order to obtain ADNI data, investigators must sign a “Data Use Agreement” which prohibits any attempts to identify the study participants. The agreement also prohibits any subsequent transfer of ADNI data.

2.3.1.2.4 GUIDs

TEAM-ADNI will be incorporating Global Unique Identifiers (GUIDs) for all 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.

TEAM-ADNI study sites/staff 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 NIA, which will assign GUIDs and store them along with ADNI participant information in the clinical database. Sites will use the currently adopted GUID generator, known as the NINDS Centralized GUID solution, developed by The National Institute of Neurological Disorders & Stroke (NINDS), in conjunction with the National Institute on Aging (NIA), and the Parkinson’s Disease Biomarkers Program (PDBP) using the Biomedical Research Informatics Computer System (BRICS) platform.

3 OBJECTIVES AND ENDPOINTS

ADNI4 will continue to discover, optimize, standardize, and validate clinical trial measures and biomarkers used in AD research. ADNI4’s TEAM cohort will address low rates of engagement and inclusion of understudied participants from lower education, socioeconomic, and low/no health insurance backgrounds in AD clinical cohorts. The TEAM-ADNI cohort will include up to 200 participants.

Aim 1: Determining best methods for recruitment, enrollment, and assessment of lower education/lower SES understudied research populations (URPs) to improve generalizability of results and advance our understanding of Alzheimer’s Disease/Dementia.

TEAM-ADNI will recruit individuals from HCs and CCs, and clinical site staff may also directly recruit individuals for TEAM-ADNI. Participant enrollment metrics will help us understand recruitment barriers and facilitators and predictors of recruitment rates (including the different sources of participant recruitment, i.e. FQHCs vs RHCs; FQHCs vs OACs). Rates for participant consent and completion of the study activities, as well as the accrual index (AI) will provide important data about feasibility and scalability for future efforts to include individuals from these backgrounds in AD research studies.

Aim 2: Validation of biomarker measures.

Validate biomarker measures obtained at the baseline visit by correlating results with “gold standard” clinical measurements.

Aim 3: Inform clinical trial design.

If enrollment is successful, this study will produce more generalizable data concerning the relationships of biomarkers and pathology to cognitive decline and dementia. The TEAM-ADNI cohort helps to contribute to the larger goals of ADNI4 as well as contributing novel information about methods to include individuals from these varied backgrounds in clinical trials.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a non-randomized, natural history, non-treatment observational study. Cognitive testing, fluid biomarkers and genetics, and optional brain imaging will be assessed across participants recruited from Health Centers (FQHCs, RHCs, CHCs), CC/OACs, or participants who are recruited directly by clinical site staff (such as from recruitment events with community-based organizations and/or outreach events).

Options will exist for select individuals to complete cognitive testing and blood biomarker/genetics study activities remotely. Individuals who elect to do these study activities remotely must have a medical care team to receive disclosed medically relevant results, and as such remote study activities only exist for individuals recruited from FQHCs and RHCs, but not for individuals recruited from OAC/CCs or from community events.

Individuals recruited from HCs will be assessed for study eligibility by Clinical Directors Network (CDN), HC site staff, or ADNI study staff, and either referred to a nearby ADNI Clinical site (if one is in their area), or for those who are not near a clinic or who do not want to visit a clinical site, they can opt to complete cognitive tests and optional blood biomarker/genetics procedures using a remote/decentralized approach.

Individuals recruited from CC/OACs will be assessed for study eligibility by CDN, site staff, or ADNI study staff. Individuals recruited by ADNI site staff will be assessed for study eligibility by ADNI site staff. Participants recruited from CCs or by clinical site staff will complete study procedures at existing ADNI clinical sites.

At the baseline visit, all participants will undergo cognitive testing, collection of biomarker and genetics samples. Brain imaging will be completed on as many participants who are willing, with a goal of up to half of the TEAM-ADNI cohort getting an MRI and two PET scans (amyloid; tau). After the baseline visit, participants will have brief telephone checks every 3 months, followed by a one-year follow-up to repeat the cognitive assessment battery. No additional samples or brain imaging scans will be performed after the baseline visit.

4.1.1 SAMPLE SIZE

Up to 200 participants will be enrolled in the TEAM-ADNI cohort in select regions of the United States.

4.2 END OF STUDY DEFINITION

A participant is considered to have completed the TEAM-ADNI study if they have completed the baseline visit (cognitive testing and biofluid sample collection; optional MRI/PET imaging) and the one year followup visit (cognitive testing) including the last visit or the last scheduled procedure shown in the SoE, Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoE in the study globally.

5 STUDY POPULATION

The study will enroll people aged 55-90 years 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 leadership.

Inclusion/Exclusion criteria for the TEAM-ADNI cohort are detailed in the lists below.

All individuals will complete a screening consent (consent #1) and then basic demographic data and inclusion/exclusion data will be collected. Those who are eligible to proceed based on inclusion/exclusion criteria will then be referred to an ADNI clinical site or to the ADNI 'remote' study arm to then review and provide consent to complete study procedures (consent #2).

There are three pathways for a participant to enter the TEAM-ADNI study:

1. For those participants recruited via HCs, the staff at those health centers and/or CDN or ADNI study staff will provide the screening consent, if the participant signs/agrees, the inclusion/exclusion criteria will be reviewed and documented to confirm eligibility prior to full study enrollment (secondary consent step).
2. Participants recruited via CC/OACs will be contacted by CDN, site staff, or ADNI study staff to complete the screening consent (in-person or over the phone) and then will review the inclusion/exclusion criteria to confirm eligibility prior to full study enrollment (secondary consent step).
3. Individuals recruited by clinical site staff at outreach/community events will be screening consented by ADNI clinical site staff who will then review the inclusion/exclusion criteria to confirm eligibility prior to full study enrollment (secondary consent step).

5.1 INCLUSION/EXCLUSION CRITERIA

5.1.1 INCLUSION CRITERIA FOR THE TEAM-ADNI COHORT

1. Age between 55-90 years (inclusive).
2. Study partner who has frequent contact with the participant (i.e., minimum average of 2 hours per week) and is able to accompany the participant to clinic visits (if applicable) or can provide information over the phone. Study partner will be contacted and verified as interested in participating before the participant will be considered eligible to move on to the second consent and baseline visit. This exclusion can be waived at the discretion of ADNI leadership.
3. Visual and auditory acuity adequate for neuropsychological testing.
4. No diseases expected to interfere with the study (see below exclusion list).
5. Participant is not pregnant, lactating, or of childbearing potential (i.e., women must be two years post-menopausal or surgically sterile).
6. Must understand and speak English or Spanish fluently.
7. Agrees to collection of blood for biomarker testing.
8. Agrees to collection of blood for Genome-Wide Association Studies (GWAS), APOE testing, DNA and RNA testing
9. Agrees to participate in the TEAM-ADNI study which includes cognitive evaluation.
10. Recruited from an FQHC/RHC/CHC, OAC/CC, or by ADNI clinical site study staff.
11. If the individual is not recruited from an HC (instead they are recruited from an OAC/CC or community event by clinical site study staff), then the individual must have 12 or fewer years of education (participants with more than 12 years of education will be excluded).

5.1.2 EXCLUSION CRITERIA FOR THE TEAM-ADNI COHORT

- 1) Any significant systemic illness or unstable medical condition that could lead to difficulty complying with the protocol or interfere with the study (such as neurologic conditions (i.e. Parkinson’s disease, multiple sclerosis, major depressive disorder, schizophrenia, bipolar disorder, obsessive compulsive disorder, brain tumor, aphasia), or other unstable conditions (i.e. uncontrolled congestive heart failure, advanced cancers, end-stage renal disease, post-transplant patients, uncontrolled seizure disorder, alcohol or substance disorder within past year)).
- 2) Current use of specific psychoactive medications (e.g. certain antidepressants, neuroleptics, chronic anxiolytics or sedative hypnotics, etc.).
- 3) Metal in the body such as pacemaker or other implanted metal which prevents MRI (even if participant opts not to complete imaging). History of working with metal grinding or other activities that might result in metal fragments in the eye.
- 4) Claustrophobia sufficient to prevent MRI or PET scanning (even if participant opts not to complete imaging).
- 5) Psychotic features, agitation or behavioral problems which study staff believe could lead to difficulty complying with the protocol.
- 6) Lack of a study partner. This exclusion can be waived at the discretion of ADNI leadership.
- 7) Investigational agents for the treatment of Alzheimer’s disease are prohibited for five half-lives or one month, whichever time period is longer, prior to entry and for the duration of the study.
- 8) Participation in other clinical studies involving neuropsychological measures being collected more than one time per year.
- 9) Female that is pregnant, lactating, or of childbearing potential.
- 10) Residence in skilled nursing facility.
- 11) If the individual was not recruited from an HC and has more than 12 years of education (i.e. some education post-high school).

5.2 LIFESTYLE CONSIDERATIONS

5.2.1 LIFESTYLE CONSIDERATIONS

During this study, participants in the TEAM-ADNI cohort are asked to:

- Fast for a minimum of six hours for a blood draw

5.3 SCREEN FAILURES

Screen failures are defined as participants who sign the screening consent (consent #1) but do not meet the inclusion/exclusion criteria and therefore do not move forward to sign the study procedures consent (consent #2). Individuals who do not meet the criteria for participation in the study (screen failure) because of transient issue(s) may be re-screened following resolution of previously identified transient issue(s). Re-screened participants will be assigned a new PTID if applicable (but will not be assigned a new Ebisu ID). The original PTID will be recorded in the Electronic Case Report Forms (eCRF). Reconsent will be required prior to re-screen. A minimum of 2 months will be required between the original screen and re-screen. Exceptions may be granted with ADNI leadership approval, and reasons for exceptions will be documented.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

5.4.1 IDENTIFYING POTENTIAL PARTICIPANTS AND RECRUITMENT EFFORTS:

HC recruitment will be as follows: Participating FQHC/RHC/CHC sites will conduct Electronic Health Record (EHR) queries, based on the above inclusion and exclusion criteria, to identify potentially eligible patients for participation in the TEAM-ADNI study. The lists of potentially eligible participants will be provided to Clinical Directors Network, Inc. (CDN) for patient outreach and recruitment.

HC/FQHC/RHCs that will conduct outreach and recruitment of their patients without CDN assistance will provide deidentified lists of potentially eligible participants to CDN for review. Older HC patients, who previously participated in CDN-conducted studies and indicated willingness to be referred to other studies, will also be contacted.

CC/OAC recruitment will be as follows: Older adults who visit participating OAC/CCs will learn about the TEAM-ADNI study from OAC/CC staff. Flyers and other materials might also be used to enhance outreach. Contact information for CDN and ADNI study staff may be listed, and individuals may provide their contact information to CDN if they are interested in being contacted to learn more about the study.

Clinical site recruitment: A clinical site may be involved in community events such as health fairs or other outreach and education opportunities where interested individuals may be identified. Flyers and other materials may be used to enhance outreach. Contact information for the ADNI clinical site may be listed, and individuals may provide their contact information to site staff if they are interested in being contacted to learn more about the study.

HC, CDN, or participating ADNI clinical site staff will contact potentially eligible patients for recruitment. To maximize patient response, HC/CDN will use a multimodal approach: via e-mail, mailed letter, and telephone, as well as direct referrals from their primary care clinicians. Individuals will receive a maximum of one mailed letter and up to 8 phone attempts. Subsequently, CDN or participating site staff will call potential participants to complete a screening consent and then complete screening questionnaires to assess eligibility, and interest and willingness to complete the TEAM-ADNI study assessments.

Individuals who begin the screening process and indicate they do not wish to participate, or participants who decide to stop participating will be asked to take an anonymous survey to help identify barriers and motivators for participating in AD clinical research.

5.4.2 ENROLLMENT OF ELIGIBLE PARTICIPANTS

All participants meeting the inclusion and exclusion criteria will be enrolled, regardless of gender, ethnicity, or race. Based on the current ADNI4 study, we anticipate that over 50% of the participants will be women. Individuals of child-bearing potential are not eligible for this study.

6 DISCONTINUATIONS AND WITHDRAWALS

6.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

Study staff may discontinue or withdraw a participant from the study for safety or administrative reasons, including but not limited to the following:

- Ability to become pregnant or pregnancy.
- Significant study non-compliance.
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- If the participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Administration of an investigational treatment to the participant. Participants who decide to enroll in a treatment trial will be withdrawn from the TEAM-ADNI study.

The reason for participant discontinuation or withdrawal from the study (if reason was provided) will be recorded on a Case Report Form (CRF).

6.2 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if they are unable to be contacted by the study staff.

The following actions must be taken if a participant fails to be available for a required study visit:

- The site or project staff will attempt to contact the participant and reschedule the visit, and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, e.g., 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

The reason for Lost to follow-up from the study will be recorded on a CRF.

7 STUDY ASSESSMENTS AND PROCEDURES

7.1 VISITS

7.1.1 DESCRIPTION OF STUDY VISITS

Health Center (HC) recruited participants:

HC staff or CDN staff will screen potential participants who they believe can provide consent. Where possible, participants recruited from HCs will be offered two study visit pathways:

- (1) all recruited will complete a screening call/visit including consent # 1 (screening consent) to review study components and inclusion/exclusion criteria
- (2a) participant is eligible and wants to complete TEAM-ADNI study at an existing ADNI clinical site
 - i. consent #2 (study procedures) at clinical site
 - ii. demographics, questionnaires, cognitive testing (*note these could be completed over the phone)
 - iii. provide blood/urine samples (*note this will likely happen on separate day because of fasting requirement)
 - iv. optional brain imaging MRI/PET scans
- (2b) participant is eligible and wants to complete TEAM-ADNI study as a 'remote' participant including:
 - i. consent #2 (study procedures) over phone/video call
 - ii. phone/video call to complete demographics, questionnaires, cognitive testing
 - iii. blood/urine samples collected at a Quest Diagnostics or similar facility
 - iv. optional MRI at an imaging facility (select locations only)

OAC/CC/Clinical Site staff recruited participants:

Participants recruited from OAC/CCs or by ADNI clinical site staff will only be offered the option to complete TEAM-ADNI study procedures at an ADNI clinical site:

- (1) all recruited will complete a screening call/visit including consent #1 (screening consent) with CDN team or ADNI study staff if recruited via OAC/CC or with ADNI clinical site staff if site recruited, to review study components and inclusion/exclusion criteria
- (2) participant is eligible and will complete TEAM-ADNI study procedures at an ADNI clinical site
 - i. consent to study procedures at clinical site
 - ii. demographics, questionnaires, cognitive testing (*note these could be completed over the phone)
 - iii. provide blood/urine samples (*note this will likely happen on separate day because of fasting requirement)
 - iv. optional brain imaging MRI/PET scans

Study visit procedures in TEAM-ADNI will be very similar to ADNI4 to maximize the value of the comparative and longitudinal data. The estimated time for an ADNI4 participant to complete all cognitive assessments is approximately one hour, with optional assessments/questionnaires that could be completed after the core assessments (CDR, MoCA, RAVLT, Category Fluency, GDS) or on another day, if the participant is willing.

- Consent – approximately 15-20 minutes.
- Demographic and background information – approximately 20-30 minutes.
- Medical history, height, weight, blood pressure – approximately 10 minutes.
- Cognitive, mood, behavioral and functional assessment battery – approximately 1 hour; additional optional questionnaires/assessments if participant agrees (up to 1 additional hour, indicated as optional on SoE).
- Biospecimen collection, including blood and urine, for APOE genotyping, genetic and biomarker research and sample storage – approximately 10 minutes (does not include travel time or wait time, if visiting Quest Diagnostics).
- MRI and PET (amyloid and tau) brain scans (optional) – approximately 1 hour for the MRI; approximately 2 hours each for amyloid and tau PET scans, which are carried out on separate days (but one PET scan can be carried out on the same day as the MRI scan). These are optional procedures for participants who can visit an ADNI clinical site (MRI and PET) or, for select remote/decentralized participants who can visit a designated MRI facility.
- Disclosure of basic clinical labs/vitals, any clinically significant or relevant results, and amyloid PET (if opted-in), if requested by the participant – approximately 15-30 minutes.

Visits have a desired scheduling window of 8 weeks before and after the target date. Once the visit begins, all imaging, biofluid collection, and clinical/cognitive assessments will ideally take place within the next 8 weeks. However, to accommodate the scheduling of participants and ADNI study staff, exceptions can be provided to extend the window by ADNI leadership.

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

1. Adverse Events
2. Montreal Cognitive Assessment (MoCA)
3. Clinical Dementia Rating (CDR) scale, or Quick Dementia Rating Scale (QDRS) if CDR not completed
4. Rey Auditory Verbal Learning Test (RAVLT)
5. Category Fluency (Animals)
6. Geriatric Depression Scale (GDS)

Participants should be encouraged to undergo all procedures. Where participants do not wish to undergo all of the procedures, the order of priority for procedures is as follows:

1. Blood draw and urine collection
2. MRI (optional, only available to participants completing study procedures at a clinical site or select imaging facilities for those participants recruited via FQHCs who select the 'remote' participation pathway)
3. Amyloid PET scan (optional, only available to participants completing study procedures at a clinical site)
4. Tau PET scan (optional, only available to participants completing study procedures at a clinical site)

Participants will be followed for one year (quarterly phone check-in visits after the baseline visit and then a one-year follow-up visit with the cognitive assessment battery only). Depending on funding, this protocol may be amended to ask participants to consent to a longer follow-up study.

7.1.2 VISIT SCHEDULING

Participants will go through screening consent and basic data collection to establish eligibility for full study participation based on the inclusion/exclusion criteria. Those eligible will then be consented for the study procedures (consent #2, at a clinical site if on the clinical-pathway, or remotely over the phone if remote-pathway). The participant must have a study partner who must participate either in-person or remotely (study partner signs a separate informed consent), this criterion can be waived by ADNI study leadership.

7.1.3 SCREENING

Participating HC sites will conduct Electronic Health Record (EHR) queries, based on the above inclusion and exclusion criteria. They will identify potentially eligible patients for participation in the TEAM-ADNI study. The lists of potentially eligible participants will be provided to Clinical Directors Network, Inc. (CDN) for patient outreach and recruitment. HCs that will conduct outreach and recruitment of their patients without CDN assistance will provide deidentified lists of potentially eligible participants to CDN for

review. HC patients, who previously participated in CDN-conducted studies and indicated willingness to be referred to other studies, will also be contacted.

Older adults who visit participating OAC/CCs will learn about the TEAM-ADNI study from OAC/CC staff. For referrals who do not have EHR review (such as recruited via OACs or by ADNI clinical site staff such as at a community/outreach event), CDN or ADNI clinical site staff will call potential participants to complete a screening consent and then complete screening questionnaires to assess eligibility and interest and willingness to complete the TEAM-ADNI study assessments.

Individuals will sign a screening consent form (consent #1) that outlines the TEAM-ADNI study procedures (to ensure individual understands the different components and is interested in completing study activities) and explains that the screening data collection is the first step towards participation in the larger study. If individual signs the screening consent, the HC/CDN/ADNI study staff will collect basic demographic data and review all inclusion and exclusion criteria with the individual to ensure eligibility. The staff member will also have the authority to determine whether the participant is motivated and capable to complete the study and decide if the individual should be moved forward to participate in the full study (move to baseline visit) or if the individual should be screen-failed due to concerns over compliance and ability to continue. If screening informed consent (consent #1) is not obtained, the participant is not considered enrolled and the visit is discontinued.

7.1.4 BASELINE VISIT

The baseline visit may only be initiated following completion of the study procedures informed consent (consent #2).

When possible, participants recruited from HCs will be given the option to complete the study tasks at a clinical site or to complete study tasks remotely. Participants recruited from HCs who do not live near an ADNI clinical site will be given the option to complete study tasks remotely.

Participants recruited from CC/OACs/community events will be given the option to complete the study tasks at their local ADNI clinical site (no remote participation option, though questionnaires and cognitive assessments may be completed by phone with study staff).

Ideally, the baseline visit would occur within 90 days of participant providing consent to enroll (that is the desired but not required time frame). Ideally, once initiated, all baseline visit procedures (except imaging) would be completed within 8 weeks, if possible (this is the desired but not required time frame). If participant opts to have imaging, it is desirable that the scans should be completed within 8 weeks of baseline visit initiation, if possible. The highest priority is to collect as much data as the participant is willing, even if it takes longer than the desired time frames noted here.

Baseline visit procedures include: 1) cognitive, functional, and behavioral assessments, 2) review of current medications and adverse events, 3) biofluid collection (blood and urine). Imaging scans (MRI, amyloid PET, and tau PET) are optional for the participant to complete at the baseline visit, with the study aiming for half of all participants to complete the imaging. The complete list of all baseline visit procedures is provided in the SoE.

In no instance should cognitive assessments be performed while the participant is in a fasting state. Procedures that require fasting are the blood draw, which should be scheduled to occur separately from cognitive testing.

7.1.5 ONGOING LONGITUDINAL VISITS

Quarterly Telephone Checks:

Every 3 months participants will be contacted by phone for a brief check-in with study staff, primarily to enhance retention and long-term follow-up by keeping them engaged in the study. Study staff will ask participants if there has been any change in their memory, thinking, or activities of daily living, and report any adverse medical events have happened within the previous 3 months or since last contact. If participants do not complete the quarterly phone calls this will not be considered a protocol deviation. Participants are not considered lost to follow-up if they do not complete the phone check-ins.

One-year Follow-up Visit: The one-year follow-up visit will be timed for 12 months from Baseline Visit Day 1. The visit will repeat the same cognitive, functional, and behavioral assessments that were completed at baseline visit, and review of concurrent medications and adverse events. Once initiated, ideally all one-year follow-up visit procedures would be completed within 4 weeks (that is the desired but not required time frame).

7.1.6 OTHER TYPES OF STUDY VISITS

7.1.6.1 RESULTS DISCLOSURE VISIT(S)

Participants will be given option to learn all results of their clinical (blood/urine) labs (such as HbA1c, TSH, B12, etc.) Participants will also be given the option of learning all clinically significant results from their cognitive assessments, MRI, and amyloid PET imaging (if completed). If a participant so chooses, those results will be disclosed either in-clinic (whenever feasible) or over the phone by qualified staff. A qualified staff member will disclose results from cognitive testing when the participant opts to learn about their results from those assessments.

Participants who opt for an amyloid PET scan are eligible to receive their amyloid PET results once they have provided amyloid disclosure consent (included in consent #2, study procedures consent, if relevant). At the time of consent and at the future disclosure visit, the site will provide the participant with educational materials. Sites will collect information on all eligible participants prior to the PET scan visit, at the time of the disclosure visit, after the disclosure visit, and longitudinally (at the 12-month visit if previous disclosure event had occurred). If the participant has decided not to receive their results, this information will not be collected.

After the participant completes their Amyloid PET scan, study staff complete data entry necessary for the PET Core team to conduct a clinical read on the scan. Once results are available, study staff are to disclose the results to eligible participants within 3 months of completed data entry. Disclosure may be delayed if data entry is delayed. It is suggested that the participant's study partner, or someone who is available and has a personal, supportive relationship with the participant, attends the disclosure visit. At the site PI/clinician's discretion, the results should not be disclosed if the participant appears psychologically distressed. The site will collect information during the visit. Additional optional assessments of well-being may be administered based on the site PI/clinician's discretion. These additional optional assessments include: STAI-AD and questions related to suicide ideation.

Study staff are to meet with the eligible participants 1 week after the disclosure visit remotely. At the site PI/clinician's discretion, the post-disclosure visit can be completed by a study coordinator who has completed amyloid disclosure training. The study staff will collect information about the participant's recall and understanding of their result as well as any post-disclosure behavior changes.

7.2 ASSESSMENTS

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 relevant study manual. Participants recruited from HCs who opt to complete the TEAM-ADNI study as a 'remote' participant will be assigned to a centralized 'remote' site, similarly overseen by a site PI and supported by ADNI staff in analogous roles to traditional, clinic-based research settings.

7.2.1.1 ABBREVIATED MULTIDIMENSIONAL ACCULTURATION SCALE (AMAS) – OPTIONAL AND ONLY FOR LATINO PARTICIPANTS

The AMAS is a self-report, bidirectional measure that assesses acculturation levels to both the US and Latina/o background. It includes six subscales (three for each background) related to language competence, social competency, and identity, producing two summary scores: 1) Total US Acculturation Score and 2) Total Latina/o Acculturation Score (scores range from 1 to 4; higher scores indicate higher acculturation levels). The AMAS has excellent psychometric characteristics and has been validated with populations similar to the Latina/o participants likely to be included in this sample. For this study, the AMAS Total US Acculturation and Total Latina/o Acculturation Scores will be used⁴³. This measure will only be administered to participants who self-identify as Latina/o.

7.2.1.2 AMERICAN NATIONAL ADULT READING TEST (AMNART) – OPTIONAL

The AMNART estimates premorbid verbal intelligence (VIQ) in patients with dementia^{20, 21} and quality of education. The test requires patients to read and correctly pronounce 50 “irregular” words that do not follow common rules of phonography and orthography. This is an optional assessment for participants to complete after the core cognitive assessment battery is completed.

7.2.1.3 AREA DEPRIVATION INDEX (ADI)

The ADI is a composite measure of socioeconomic disadvantage for the United States. Using United States Census indicators of poverty, education, housing, and employment, neighborhood socioeconomic status is ranked by disadvantage at the state and national level. Each census block/neighborhood is split into state deciles and national percentiles, with lower percentile scores indicating less socioeconomic disadvantage^{45, 46}.

7.2.1.4 BRIEF PERCEIVED ETHNIC DISCRIMINATION QUESTIONNAIRE-COMMUNITY VERSION (BRIEF PEDQ-CV) – OPTIONAL

The Brief PEDQ-CV⁴² is a 17-item questionnaire assessing the frequency & intensity of instances when the participant felt discriminated against based upon his or her URP status. The questionnaire includes four subscales: social exclusion, stigmatization, workplace discrimination, and threat/harassment. The Brief PEDQ-CV has demonstrated high reliability (Cronbach’s $\alpha = 0.87$) and is considered a valid measure of perceived discrimination. This is an optional assessment for participants to complete after the core cognitive assessment battery is completed.

7.2.1.5 CATEGORY FLUENCY TEST (CFT)

The Category Fluency Test (CFT) is a neuropsychological task that assesses semantic memory and involves planning, organization, and cognitive flexibility. Participants may be asked to generate as many examples as possible in 60 seconds from a semantic category ANIMALS²². Total score is the number of correct exemplars generated across the three trials, where higher scores indicate better performance.

7.2.1.6 CLINICAL DEMENTIA RATING (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^{32, 33}.

7.2.1.7 FUNCTIONAL ACTIVITIES QUESTIONNAIRE (FAQ) – FOR STUDY PARTNERS ONLY

The 10-item Functional Activities Questionnaire (FAQ)³⁴ is a subjective, informant-based rating of a study participant’s ability to carry out 10 complex activities of daily living (e.g. managing finances, driving, and preparing meals) over the past 4 weeks. FAQ total scores range from 0-30, with higher scores indicating greater functional impairment or dependency.

7.2.1.8 GERIATRIC DEPRESSION SCALE (GDS) SHORT FORM

The Geriatric Depression Scale (GDS) is a self-report assessment used to identify depression in the elderly^{68, 69}. The original scale is composed of 30 questions in a yes/no response format that assesses affective and behavioral symptoms in the past week that may be associated with depression. The 15-item short form (GDS-15) has been shown to correlate highly with the 30-item version³⁴⁰. GDS-15 may be included as a screening measure in clinical studies to assess psychological stability of a trial candidate for full study participation, with scores of > 6 warranting further clinical consideration of endorsed symptoms.

7.2.1.9 HOLLINGSHEAD INDEX SCORE

The Hollingshead Two Factor Index of Social Position was developed by August B. Hollingshead in 1965 at Yale University to estimate social positions that individuals occupy in society⁴⁹. The scale comprises a combination of educational attainment and occupational role. It outlines 7 strata of occupations from professionals/ executives to lesser professions, administrators and skilled labor employees and calculates a Hollingshead score based on education and occupation. This allows for a single score to rate social position rather than using education alone. Since the development of the Hollingshead, occupations have changed in society. The ACTC, under the leadership of Dorene Rentz, PsyD and Rema Raman, PhD, modernized the Hollingshead Educational Strata with the

2017 Occupational Employment Statistics table of profiles. TEAM-ADNI will utilize this modernized Hollingshead scale and this is integrated into the demographics collection at baseline visit.

7.2.1.10 IMPACT OF EVENTS SCALE – INTRUSION + AVOIDANCE – ONLY FOR PARTICIPANTS WHO OPT-IN TO AMYLOID PET DISCLOSURE

The Impact of Events Scale (IES)⁵⁷ is a 15-item self-report measure that assesses 2 common responses related to a specific stressful life event: intrusion and avoidance. It is a reliable scale that can be anchored to any specific life event and permits the assessment of subjects over time, comparison of the degree of distress among subgroups, and comparison of the impact of various events. The IES has been anchored to test-related distress in previous genetic testing studies and has been adapted for amyloid imaging related distress.

7.2.1.11 MONTREAL COGNITIVE ASSESSMENT BLIND/TELEPHONE (MOCA BLIND/TELEPHONE)

The MoCA-Blind⁶³⁻⁶⁵ is an adapted version of the original MoCA, used as a rapid screening tool to detect mild cognitive dysfunction, and administered by phone rather than in-person interview. It contains the same items as the original MoCA except items requiring visual abilities have been removed. MoCA-Blind assess the cognitive domains of attention and concentration, memory, language, conceptual thinking, calculations, and orientation. The time to administer MoCA-Blind is approximately 5-10 minutes and the total possible score is 22.

7.2.1.12 NEUROPSYCHIATRIC INVENTORY (NPI) – FOR STUDY PARTNERS ONLY; OPTIONAL

The Neuropsychiatric Inventory (NPI) is a well-validated, reliable, multi-item instrument that assesses the presence of psychopathology in individuals with brain disorders, specifically AD and other dementias³⁸. NPI ratings are based on interview with a knowledgeable study partner who can provide information about the frequency and severity of up to 12 neuropsychiatric features observed/present since the participant began experiencing memory problems (or other specified period of time). Frequency assessments range from 1 (occasionally, less than once per week) to 4 (very frequently, once or more per day or continuously). Severity is rated as 1 (mild), 2 (moderate), or 3 (severe). Total NPI scores range from 0-144.

7.2.1.13 NEUROPSYCHIATRIC INVENTORY-QUESTIONNAIRE (NPI-Q) – FOR STUDY PARTNERS ONLY; OPTIONAL

The Neuropsychiatric Inventory – Questionnaire (NPI-Q) was developed and cross-validated with the standard NPI to provide a brief assessment of neuropsychiatric symptomatology^{38,39}. The NPI-Q evaluates the presence and severity of 12 neuropsychiatric features that may have been observed/present over a specified period of time. In the current study, the informed caregiver/qualified study partner evaluates the frequency and severity of participant symptoms in the previous 4 weeks. Symptom severity is rated by the study partner as 1 (mild), 2 (moderate), or 3 (severe). The NPI-Q provides a severity rating for each feature as well as a total severity score that reflects the sum of individual domain scores. Total NP-Q scores range from 0-36.

7.2.1.14 PERCEIVED STRESS SCALE 10-ITEM (PSS-10) – OPTIONAL

An important consideration in measuring cognition is current stress. Research suggests that current perceived stress can affect neurocognitive functioning⁷². Thus, measuring current stress in the present study is an important element of study procedures. The PSS measures current stress levels and stressful experiences in the last month. It asks about experiences such as feeling in control of one's life, feeling the ability to be productive, feeling overwhelmed, and being upset by unexpected events⁴¹. These items are rated on a Likert scale of 1-5, with 1 representing "Almost Always" and 5 representing "Almost Never." In scoring, the scale is reverse coded where appropriate, such that a low score is indicative of a lower level of perceived stress. This is an optional assessment for participants to complete after the core cognitive assessment battery is completed.

7.2.1.15 QUICK DEMENTIA RATING SCALE (QDRS) – FOR PARTICIPANT AND STUDY PARTNER ONLY IF THE CLINICAL DEMENTIA RATING SCALE (CDR) WAS NOT USED

The Quick Dementia Rating System (QDRS)^{61,62} is a 10-item questionnaire that stages dementia similar to the Clinical Dementia Rating Scale (CDR)⁶². The QDRS takes just 3-5 minutes and is completed by the participant and/or study partner. It does not require interview of the participant or study partner by a clinician. The first 6 QDRS items address observed changes in memory, orientation, decision making/problem solving abilities, activities outside the home, function at home and hobby activities, and toileting/personal hygiene. The remaining 4 items address behavior and personality changes, language and communication abilities, mood, and

attention and concentration. Ratings of change in participant’s current cognitive and functional abilities are made in comparison to ‘how they used to be’. QDRS scores range from 0-30, with higher scores reflecting greater cognitive impairment.

7.2.1.16 REY AUDITORY VERBAL LEARNING TEST (RAVLT)

The RAVLT is a list-learning task, which assesses multiple cognitive parameters associated with learning and memory²⁷.

7.2.1.17 RURAL-URBAN COMMUTING AREA (RUCA) AND THE RURAL-URBAN CONTINUUM CODES (RUCC)

Rurality will be measured by two well-validated measures, both the Rural-Urban Commuting Area (RUCA) and the Rural-Urban Continuum Codes (RUCC). RUCA codes use measures of population density, urbanization, and daily commuting to classify US census tracts and is one of the most commonly-used measures of rurality in the research literature. RUCC is another popular measure of rurality. It provides distinctions between metropolitan (by the population size of their metro area) and nonmetropolitan counties (by the degree of urbanization and adjacency to a metro area), based on Office of Management and Budget definitions⁵¹⁻⁵⁵.

7.2.1.18 RYFF SCALES OF PSYCHOLOGICAL WELL-BEING: PURPOSE IN LIFE SUBSCALE – ONLY FOR PARTICIPANTS WHO OPT-IN TO AMYLOID PET DISCLOSURE

TEAM-ADNI will use the Purpose in Life measure of Ryff Psychological Well-being Scales and Scoring model. This measure reviews the extent to which participants felt their lives had meaning, purpose, and direction⁵⁹.

7.2.1.19 STATE-TRAIT ANXIETY INVENTORY FOR ADULTS (STAI-AD) AND SUICIDE IDEATION QUESTIONNAIRE – ONLY FOR PARTICIPANTS WHO OPT-IN TO AMYLOID PET DISCLOSURE

The 6-item STAI-AD assessment is used in studies to identify current symptoms of anxiety in older adults⁶⁶. It is a validated⁶⁷, shortened version of the ‘state anxiety’ portion of the State-Trait Anxiety Inventory⁵⁶. For each of six items, individuals select one of four options (‘Not at all’, ‘Somewhat’, ‘Moderately so’, or ‘Very much’) that best described their feelings over the past 7 days.

The suicide ideation questionnaire captures the occurrence, frequency, and severity of suicide related thoughts and behaviors.

7.2.1.20 THE WORD ACCENTUATION TEST – CHICAGO (WAT-C)

The WORD ACCENTUATION TEST- CHICAGO (WAT-C) is a psychometrically robust measure of Spanish reading proficiency, demonstrating strong correlations with cognitive aptitude, estimated premorbid intellectual ability, and quality of education⁶⁰.

7.3 IMAGING (OPTIONAL BUT AIMING FOR HALF OF PARTICIPANTS TO COMPLETE)

7.3.1 PET SCANNING: AMYLOID – FLORBETAPIR (FBP); TAU – FLORTAUCIPIR (FTP)

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

7.3.1.1 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 all scan imaging protocols; a scanner requires qualification only once for all tracer studies. Qualification will employ the same methods utilized for site qualification in ADNI3/4, which entails scanning a Hoffman brain phantom. This phantom will be supplied to ADNI sites that do not have their own. Details of the phantom imaging protocol will be provided in a technical manual.

7.3.1.2 DATA ACQUISITION FOR PET SCANS

TEAM-ADNI participants who enroll in the clinic-based study pathway have the option to complete one amyloid PET scan and one tau PET scan at the baseline visit.

Each participant will receive one amyloid tracer (florbetapir) and one tau tracer (flortaucipir). In the United States, florbetapir and flortaucipir are all FDA approved tracers for PET imaging.

Scan protocols differ for each tracer. The injected doses for each tracer are listed in the table to the right. After insertion of an intravenous line, the tracer is injected outside the scanner. Following injection, participants remain in a comfortable state, usually in a chair but not in the scanner, for a period of time. Imaging times after injection are listed in the table for each tracer. Prior to each scan, an x-ray CT (for PET/CT systems), or positron transmission scan (for PET-only systems) is obtained for attenuation correction of the image; an MRI scan (for PET/MRI systems) may be obtained before, after or during the PET scan. Technical details for scan acquisition will be provided in a technical manual and radiation dose exposure is provided in the technical manual. The total time commitment for a PET scan may range from about 1.5 hours to 2.5 hours.

Tracer	Injected Dose	Imaging Time (post-injection)
Florbetapir	10 mCi	50-70 min
Flortaucipir	10 mCi	75-105 min

7.3.1.3 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 adequate, 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.

7.3.2 MRI

Participants will have the option to complete a brain MRI scan as part of the baseline visit.

7.3.2.1 SITE QUALIFICATION

Each site must be qualified for MRI. The ADNI4: TEAM MRI protocol uses the ADNI4 MRI protocol, and allows for slight variation depending on scanner capabilities and length of MRI allotted at the imaging location. All scanners not currently operating the ADNI4 MRI protocol will have to be qualified for the TEAM-ADNI study.

If the scanner to be used in TEAM-ADNI is currently qualified for ADNI4, then no further qualification/certification is required.

For imaging sites not qualified under ADNI4, the site will be sent an electronic file containing the TEAM-ADNI imaging protocol that has been ported to the site’s scanner make/model/operating system. The site will load the file onto the scanner to be qualified, and then image a phantom 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. If the scan has not been performed according to protocol, the site will be asked to perform another qualification scan. This will be repeated as many times as necessary until the site has demonstrated exact execution of the MR protocol, at which point the scanner will be qualified for TEAM-ADNI. 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.

7.3.2.2 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. All sequences will be vendor product (FDA approved). The full MRI protocol includes: a scout, structural T1-weighted MRI, FLAIR, T2 GRE, T2, diffusion tensor imaging, ASL perfusion MRI, task free resting state functional MRI, and high resolution hippocampal subfield imaging. The core ADNI series (T1, FLAIR, T2*GRE, and diffusion MRI) should be performed on all participants who opted to undergo imaging. The site may perform as much of the remaining ADNI MRI protocol as possible. The total scan time will vary but is expected to last between 25 minutes and one hour but may be slightly longer depending on technical factors. If the subject becomes uncomfortable, they can ask to be removed from the scanner at any time.

7.3.2.3 CLINICAL READ OF MRIS

The research site or scanning center (for any remotely assessed participants who complete an MRI at a non-ADNI site) will provide a read of the MRI by a local radiologist following local standards of care for each MRI completed in the ADNI protocol.

7.3.2.4 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 (QC) review on each MRI scan. Quality control for MRI will result in failure of some scans, which may need to be repeated, if the participant is willing. Repeat scans must be scheduled as soon as possible and no later than four weeks of the notification of failed QC.

7.4 BIOSPECIMENS

University of Rochester Medicine Central Lab (URMC), National Centralized Repository for Alzheimer’s Disease and Related Dementias (NCRAD), University of Pennsylvania (UPENN), and Quest Diagnostics will analyze laboratory samples.

7.4.1 BLOOD DRAW & URINE COLLECTION

The relevant study manual will provide detailed instructions for the collection, processing and shipment of all biofluid samples. Plasma and serum 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 some clinical labs. Only water is permitted (no food but water is encouraged) until blood draws are completed.

Methods used for blood draw will continue as in ADNI4.

7.4.1.1 CLINICAL LABS (BLOOD AND URINE)

Clinical labs are collected at the baseline visit. 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. Labs to be collected include Hematology, Chemistry Panel (includes Creatinine and BUN), TSH, Vitamin B12, Urinalysis, HgbA1c, Cystatin C, lipid panel, high sensitivity CRP and Lipoprotein A. All baseline clinical labs will be sent to URMC if collected in the in-clinic setting, or to Quest Diagnostics if collected in remote setting.

7.4.1.2 BASELINE BLOOD SAMPLES FOR PBMC AND LONG READ SEQUENCING

Whole blood samples will be collected at the baseline visit for all participants and used for extraction of peripheral blood mononuclear cells (PBMCs). An additional blood sample will also be used for long read sequencing. 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 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.

7.4.1.3 BLOOD SAMPLES FOR GENOMIC ANALYSIS AND RELATED BIOASSAYS

At baseline visit, blood will be collected for extraction of DNA and RNA at NCRAD and to provide plasma and serum for the Biomarker Core. Whole blood is processed at each site to separate plasma, serum, and buffy coat (white blood cells). The buffy coat components are aliquoted at the sites and shipped overnight under ambient conditions to NCRAD where DNA will be extracted, aliquoted and banked. If RNA or Buffy Coats are collected on a Friday, they are to be frozen and shipped frozen the following Monday. 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.

7.4.1.4 GENETIC AND GENOMIC ANALYSES

APOE and genome-wide genotyping will be completed for all TEAM-ADNI participants.

7.4.1.5 PLASMA AND SERUM COLLECTION FOR BIOMARKERS

Plasma, serum, and buffy coat will be collected at the baseline visit 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 overnight on dry ice to the Biomarker Core at the UPENN. As above, buffy coat will be extracted from blood at the site and shipped overnight under ambient conditions to NCRAD. If buffy coat is collected on a Friday, it is to be frozen and shipped frozen on following Monday.

7.5 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.5.1 ADVERSE EVENT (AE) DEFINITION

An Adverse Event (AE) is defined as any untoward medical occurrence including 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.

All AEs are to be documented, regardless of relationship to study procedures, commercial, or investigational products used in this study (amyloid [Florbetapir] or tau [Flortaucipir] PET tracers), beginning from the time the participant signs the Informed Consent Form (ICF) through the last study visit or last assessment.

All research team members will be participating in ensuring subject safety. All participants will be evaluated for adverse events at each visit and telephone check.

The investigator is obliged to follow participants with AEs 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.

AEs the site PI (or medically qualified designee) deems related to study procedures or investigational products used in this study and serious adverse events (SAEs) occurring within 72 hours of PET tracer administration, regardless of causality, are to be documented beginning from the time the participant signs the ICF through the last study visit or last assessment.

AE identification criteria and reporting requirements will be provided in the relevant study manual and must be followed regardless of applicable regulatory requirements that may be less stringent.

7.5.2 SERIOUS ADVERSE EVENT (SAE) DEFINITION

A serious adverse event (SAE) is defined as an adverse event or suspected adverse reaction that results in any of the following outcomes:

- death;
- a life-threatening adverse event (i.e., the participant was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death);
- in-patient hospitalization (>24 hours) or prolongation of existing hospitalization including emergency department visits (see the relevant study manual for more information regarding hospitalizations);
- a persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- or a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant or may require intervention to prevent one of the outcomes listed in the definition above.

7.5.3 EVENT ASSESSMENT, REPORTING, AND FOLLOW-UP

The occurrence of an AE or SAE may come to the attention of study personnel during study visits; as a result of laboratory report and/or imaging read findings; through other interactions with the participant, caregiver, and/or study partner/knowledgeable

informant. Solicitation of specific events will not be required (i.e., the participant will not be asked if they have experienced any specific adverse events).

All AEs and SAEs will be captured on the CRF as described in Section 7.5 and in the relevant study manual. All AEs and SAEs that occur during study participation (i.e., after consent is signed and through the last study visit or assessment) must be documented, regardless of relationship to study procedures or investigational products used in this study (e.g., PET tracers), and must be followed to adequate resolution.

7.5.4 SERIOUS ADVERSE EVENT REPORTING AND FOLLOW-UP

Any such experience, due to any cause, that occurs during the course of the investigation or within 30 days of the last study visit must be reported to the ATRI Coordinating Center via EDC 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. Sites will report SAEs based on the IRB and local institutional requirements.

A SAE reported to have occurred within 72 hours of amyloid (FBP) or tau (FTP) PET tracer administration 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 also be reported to Avid/Lilly, and PET Net for events related to florbetapir and flortaucipir.

All available information, including the site PI's assessment of causality, must be provided at the time the initial SAE is reported via the eCRF. The baseline SAE report is to be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documentation requested by the Data and Coordinating Center and/or the IRB.

Any relevant follow-up information received on SAEs should be reported within 24 hours of its receipt. If the relevant follow-up information changes the site PI's assessment of causality, this should also be noted on the follow-up SAE form.

The site PI is responsible to notify their IRB of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the Data and Coordinating Center, the IRB, or delegate(s) to be filed in the TMF.

The detailed contact information for reporting of SAEs is on the Study Contact Sheet made available to all sites.

For urgent safety issues, please ensure all appropriate medical care is administered to the participant and contact the appropriate study team member listed on the Study Contact Sheet.

7.5.4.1 EXPEDITED REPORTING

The Coordinating Center must inform site PIs (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (i.e., within specific time frames). For this reason, it is imperative that clinical sites provide complete SAE information in the manner described in this protocol and the relevant study manual.

7.5.5 EVENT CLASSIFICATION

Every effort must be made by the site PI (or medically qualified designee) to categorize each AE according to its severity and its relationship to the investigational PET tracer products.

7.5.5.1 SEVERITY

The site PI (or medically qualified designee) will assess adverse event (AE) severity using the protocol defined grading system described below and recorded in the CRF.

- Mild – Discomfort noticed, but events require minimal or no treatment and do not interfere with the participant's daily activities.
- Moderate – Discomfort sufficient to reduce or affect normal daily activity. Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

7.5.5.2 EXPECTEDNESS

Site PIs are responsible for determining if an adverse event (AE) is expected or unexpected and the medical monitoring team will work with them if there are any questions. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

7.5.6 REPORTING EVENTS TO PARTICIPANTS

The consent form explicitly states that if an incidental finding is detected on a study scan or laboratory that may have clinical significance, the information will be provided to the research site and then the participant will be contacted by the research site and a plan will be made for medical follow-up.

MRI Clinical Read – The MRI will be read by a radiologist associated with each MRI scanning site. The report will be entered into the data collection system. The results will be made available to the study staff, the clinicians involved with patient care through the Electronic Health Record if participant requested (and consented to share with their primary care provider), and to the patient if desired or requested.

PET Clinical Read – Amyloid PET scans will be read by the PET Core; results will be available to study staff, which in turn can be provided to the participant if the participant requests the result and to support clinical decision-making with regard to approved therapeutics such as lecanemab or donanemab for patients with clinical impairment.

8 STATISTICAL CONSIDERATIONS

8.1 POPULATIONS FOR ANALYSES

The Biostatistics Core, Project1 Core, and other Cores will carry out interim and final analyses of TEAM-ADNI study data, separately and in combination with previous phases, for the primary aims and hypotheses. Strategies for analysis goals are summarized briefly below.

The first goal will be to monitor progress of enrollment, completeness of data capture, and adverse events. The second goal will be to determine the demographic composition of the group: age, gender, race, ethnicity, medical comorbidities, and socioeconomic status. These results will be compared with the current ADNI 4 participants. The third goal will be to determine the results of the cognitive assessment battery, and to compare these results with ADNI4 participant results, accounting for demographic variables. The fourth goal will be to determine the results of the fluid and genetic biomarkers, assess associations with cognitive and functional measures and to compare these results with ADNI4 participant results, accounting for demographic variables. The fifth goal is to determine the results of the MRI and PET biomarkers, assess associations with fluid biomarkers and cognitive and functional measures, and to compare these results with ADNI4 participant results, accounting for demographic variables.

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

9 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1 KEY ROLES AND STUDY GOVERNANCE

The ADNI4 Study is funded by a grant to the Northern California Institute for Research and Education (NCIRE) and will utilize the Alzheimer's Therapeutic Research Institute (ATRI) as the Data and Coordinating Center.

The name and contact information for the Medical Monitor and other personnel from ADNI Cores, described in 9.1.1, and ATRI are listed on the Study Contact Sheet made available to all clinical sites.

9.1.1 ADNI CORES

The ADNI study has developed ten Cores who work collaboratively to ensure the success of this study.

9.1.1.1 ADMINISTRATIVE CORE

The overall goal of the Administrative (Admin) Core is to ensure the success and impact of the entire ADNI study. The Administrative Core developed and oversees the Ebusu platform used for data collection on the TEAM-ADNI remote participants. The Admin Core will collaborate with leadership from all Cores and Clinical Directors Network to review the data from the remote TEAM-ADNI participants. The Administrative Core will work closely with the Clinical Directors Network, Engagement Core, and Clinical Core on tailored marketing and other CER-based recruitment strategies to attract a wide variety of participants to join the TEAM-ADNI study.

9.1.1.2 CLINICAL CORE

The Clinical Core (including the Coordinating Center at the USC Alzheimer’s Therapeutic Research Institute (ATRI)) will continue to oversee all in-clinic participant activities, including clinical site start-up and monitoring, regulatory oversight and data management. Safety oversight and reporting to the ATRI Data and Safety Monitoring Board (DSMB) will be managed by the ATRI Medical Safety section. TEAM-ADNI will utilize the ATRI Electronic Data Capture (EDC) System⁴⁸ for in-person and remote data collection (via eCRFs), with nightly uploads to LONI for sharing. The Clinical Core will collaborate closely with the Engagement Core, Admin Core, and Clinical Directors Network on all recruitment and retention activities. Further, the Clinical Core will continue its investigations of the relationship among biomarker and cognitive/clinical data in the progression along the AD continuum, supporting therapeutic trial design.

9.1.1.3 ENGAGEMENT CORE

The Engagement Core will help lead TEAM-ADNI’s effort to increase the representation and engagement of participants from lower socioeconomic and education backgrounds into TEAM-ADNI and other Alzheimer’s disease and related dementias (ADRD) clinical trials more broadly. The Engagement Core will work closely with the Admin and Clinical Cores, and Clinical Directors Network to deploy an evidence-based, community-engaged research (CER) approach to recruitment and retention. Critical, to this effort, the Engagement Core may hire Clinical Research Liaisons (CRLs) and Community Research Navigators (CRNs). The CRLs will promote recruitment by liaising with Community-Based Organizations and community members; and conducting eligibility screenings and facilitating the referral process. The CRNs will promote continuous engagement, aimed at high retention of enrolled participants. They will serve as guides, including a “help desk” function, to support participants and study partners. Engagement Core also has trained staff, both English- and Spanish-speaking, who may serve as raters/assessors (i.e. certified to administer CDR, cognitive assessments, etc.) for TEAM-ADNI participants who choose the ‘remote’ participation option. Additionally, the Engagement Core will deliver an array of training opportunities for ADNI personnel and investigate the biological, psychological, and contextual factors that contribute to ADRD outcomes and utilizing CER-based methods.

9.1.1.4 MRI CORE

The overall mission is to optimize and standardize MRI for AD clinical trials providing curated images and numeric summary values from a variety of multisite MRI modalities. Numeric summary values will be created by ADNI Core PIs for each sequence in each exam at every time point. We anticipate that the emphasis on recruiting individuals from lower socioeconomic backgrounds will result in a higher prevalence of cerebral vascular disease (CVD) in comparison to prior ADNI cycles. The MRI Core will make a significant contribution in support of this new direction by greatly increasing emphasis on MRI measures of CVD.

9.1.1.5 PET CORE

The overall mission of the ADNI PET Core is to standardize the acquisition, quality control, processing, and analysis of multicenter PET data to provide a flexible dataset for analysis of measurement of A β and pathological tau in the brain that can be used in conjunction with other ADNI variables to model clinical trials and longitudinal change.

9.1.1.6 BIOMARKER CORE

The overall mission of the Biomarker Core is 24/7 management of the ADNI fluid repository and providing highly standardized analyses of AD biomarker analytes in CSF and plasma. The Biomarker Core will oversee the plasma analyses of the TEAM-ADNI participants. The Biomarker Core will continue to provide biofluid aliquot samples to investigators following review and approval of their study by the RARC as described in the guidelines documents on the ADNI/LONI website.

9.1.1.7 GENETICS CORE

The mission of the Genetics Core is to identify and validate genetic markers for use in drug discovery and clinical trials. APOE genotype contributes to clinical trial stratification and enrichment as it influences onset age, A β deposition/clearance, and susceptibility to adverse effects of anti-amyloid treatment. The Core will continue its focus on advances in genetics and related omics to discover, validate, and implement novel genetic markers that can improve the precision and power of AD clinical trials. The Core will provide APOE genotype, polygenic risk scores, increase statistical power for all analyses, and include new phenotypes to enable novel questions. New bioinformatics strategies will be used to analyze the growing multi-omics and multimodal endophenotype data. Enhanced recruitment of generalizable populations will foster discovery of novel variants beyond those historically observed in participants of European ancestry.

9.1.1.8 NEUROPATHOLOGY CORE

The overall mission of the Neuropathology Core is to maximize brain donations across all ADNI sites, provide uniform comprehensive neuropathological assessments of all brain donations to inform biomarker discovery and validation studies, share digitized histology slides of all ADNI cases, and provide tissue specimens (governed by the Neuropathology RARC and NIA) for use in approved ADNI and non-ADNI studies of ADRD.

For this TEAM-ADNI study, the Neuropathology core will collaborate with the Administrative, Clinical, and Engagement Cores to create a new optional questionnaire to help us learn TEAM-ADNI participant's and their study partner's knowledge, attitudes, motivators, and barriers to brain donation. Information learned will provide important insights for how ADNI may include brain donation as part of future research efforts with these understudied research populations.

9.1.1.9 BIOSTATISTICS CORE

The goal of the Biostatistics Core is to ensure that sound designs and statistical analyses are used to address the overall goal of ADNI, which is to validate biomarkers for clinical trials. As ADNI's experts in biostatistical methods and the data across cores, we collaborate with all Cores/Project on design and analyses for each research theme and specific aim: harmonizing data across ADNI phases and technologies, characterizing change, identifying predictors, improving clinical trial design, and discovery.

9.1.1.10 INFORMATICS CORE

The mission of the Informatics Core is to provide an information infrastructure to support the operational and research aims of each of the ADNI cores and to provide data access and information resources for the wider ADNI research community.

9.1.1.11 CLINICAL DIRECTORS NETWORK –

Clinical Directors Network (CDN) is a primary care practice-based research network (PBRN), clinician training organization and Agency for Healthcare Quality and Research (AHRQ)-designated Center of Excellence (P30) for practice-based research and learning. CDN partners with HCs including FQHCs, other safety-net primary care and public health practices, as well as community-based organizations (CBOs) including OACs to engage individuals from these centers in clinical research. For the TEAM-ADNI study protocol, CDN will identify HCs and CC/OACs from its network that are most suitable for participation in the TEAM-ADNI study and will work with personnel at those sites for study recruitment and enrollment. Participating HC/CC/OAC sites will provide lists of potentially eligible individuals who will be contacted by CDN or staff from those sites for screening. CDN or HC/CC/OAC site staff may consent interested individuals (screening consent) and collect screening visit data via the Administrative Core's Ebusu online study platform. If the participant is eligible for full study, CDN or HC/CC/OAC site staff may assist with baseline visit scheduling and accompany participants to study visits if desired by participant (including to in-clinic visits if participant requests). If participant opts for the 'remote' participant pathway, CDN or ADNI study staff may assist with consenting (consent #2 remote study procedures), and may assist in remote data collection, scheduling cognitive data collection by ADNI remote site staff, scheduling blood draw at Quest Diagnostics, or at an MRI facility, if applicable. CDN or HC/CC/OAC site staff may also accompany remote participants to Quest Diagnostics visit or for optional MRI, if desired by participant. CDN or HC/CC/OAC staff may continue communication with enrolled

participants throughout the study to facilitate scheduling follow-up visits/calls, and may also be involved in facilitating return of results process (such as for standard blood/urine labs; but will not be involved in amyloid PET disclosure though).

9.1.2 DATA AND COORDINATING CENTER

The USC Alzheimer’s Therapeutic Research Institute (ATRI) will serve as the Data and Coordinating Center. No human subjects will be enrolled at USC ATRI. Under the direction of Dr. Paul Aisen, ATRI will provide comprehensive, (e.g.: data management, clinical operations, and regulatory) oversight for this study.

All user and study data are stored and maintained on servers hosted on Amazon Web Services (AWS) under an Enterprise Agreement with USC, which stipulates rights and responsibilities between both parties. AWS implements sophisticated technical and physical controls designed to prevent unauthorized access to or disclosure of customer content which have been independently validated to meet or exceed ISO 27018 (Information technology – Security techniques – Code of practice for protection of personally identifiable information (PII) in public clouds acting as PII processors).

All communication to and from the data system is encrypted. All user and study data transmissions occur through a secure internet connection-HTTPS over TLS 1.2 and higher (Hypertext Transfer Protocol within a connection encrypted by Transport Layer Security) using secure 256 bit and stronger ciphers. All study data stored are encrypted at rest. 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. Each user of the system has an individual account with a password which is required to be reset at set intervals to comply with USC ATRI password requirements. Users are logged out of the system after a period of inactivity.

9.2 REGULATORY CONSIDERATIONS

This study will be conducted in accordance with GCP guidelines as required by the following:

- Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- The ICH GCP Guideline [E6].
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed consent and IRB regulations and applicable sections of US 21 CFR Part 312.
- Other applicable laws and regulatory authority requirements or directives.

9.3 INFORMED CONSENT

As used in this protocol, the term “informed consent” includes all consent and assent given by participants (or surrogate/Legally Authorized Representative [LAR]) and study partners.

Informed consent will be obtained and documented in accordance with applicable local and regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and in adherence to ICH GCP. Informed consent is a process that is initiated prior to an individual agreeing to participate in the study and it continues throughout an individual’s study participation. The informed consent process will be documented in the source document (including the date, person obtaining informed consent, and any relevant discussion notes).

The investigator (or designee) is responsible for ensuring that the participant/LAR and the study partner understand the nature of the study, the procedures involved, the expected duration, the potential risks and benefits, confidentiality of study records, and their rights as research participants. The investigator (or designee) will answer any questions the participant/LAR and study partner have throughout the study and will share, in a timely manner, any new information that may be relevant to their willingness to continue their participation. Participants/LARs and study partners will be informed that participation in the study is voluntary, that they may withdraw from the study at any time, and that withdrawal of consent will not affect their access to medical treatment or their relationship with the institution. Participants/LARs and study partners will be given the adequate time to review the consent forms and ask questions.

The informed consent will also cover the broad sharing of all study data as well as storage of biological samples for future research. Consent forms will specify that samples for genetic and biomarker research are for research purposes only and are not diagnostic in nature and participants will not receive results.

Documentation of informed consent from the participant/LAR and study partner will be obtained prior to initiating and research activities.

9.3.1 OVERVIEW OF INFORMED CONSENT

Three types of consent forms will be used in this study:

- **Consent #1: Screening Consent (Participant/LAR)**

Used to explain the study purpose, risks, and procedures in broad terms, and will assess willingness to participate in the overall study. It will include data collection related to demographics and study inclusion/exclusion criteria to be used for determining enrollment eligibility.

Participants who are ineligible due to inclusion/exclusion criteria will be screen failed and will not proceed to consent #2.

Participants who are determined eligible will be moved to the baseline visit step (consent #2).

- **Consent #2: Study Procedures Consent (Participant/LAR)**

For participants who meet eligibility criteria, this form describes the full study procedures (e.g. questionnaires, cognitive testing, blood draw, optional imaging, and data/biospecimen sharing).

- Participants who are referred to an ADNI clinical site will review consent #2 with clinical site staff.
- Participants who want to complete study tasks remotely will have a phone/video call with CDN or ADNI study staff to review consent #2 in detail prior to verbally consenting (remote participants will also be mailed printed copies of both ICFs).

- **Consent #3: Study Partner Consent**

A separate consent form (or information sheet) will be reviewed and completed by the study partner prior to their participation in study procedures (e.g. informant interviews, assessments).

The signed consent forms (or equivalent) from participant/LAR and study partner will be filed in accordance with local SOPs and regulatory requirements. Copies of the signed/completed consent forms will be provided to participants/LARs and study partners, either in person, by mail, or electronically (e.g. email).

9.4 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

The protocol, informed consent form(s), and appropriate related documents require review and approval by the IRB prior to implementation, in accordance with applicable regulations, including 45 CFR 46, 21 CFR 56, and ICH E6 (GCP) Section 3, and all relevant local laws or institutional policies.

Any amendment to the protocol or revisions to the consent form(s) will be submitted to the IRB for review and approval.

Documentation of approval is required prior to implementation, unless necessary to eliminate an immediate risk to participants.

9.5 SAFETY OVERSIGHT

The Data and Safety Monitoring Board (DSMB) is an independent group, appointed by the NIA, providing recommendations and safety oversight to the ATRI Director, study leadership, and the NIA. The DSMB is composed of individuals with expertise in AD. Members of the DSMB will be independent from the study conduct and free of conflict of interest, or measures will be in place to minimize perceived conflict of interest. The DSMB will meet on an ongoing basis to assess safety and efficacy data on all participants. The DSMB will review Serious Adverse Event reports on a yearly basis. The DSMB will operate under the rules of an approved charter and each data element that the DSMB needs to assess will be clearly defined.

The ATRI Medical and Safety Unit director will oversee the medical and safety operations for the study. The Medical Director, Dr. Michael Rafii, will be responsible for medical management of the study including standardized coding of AEs and central medical monitoring. The lead safety biostatistician, Dr. Michael Donohue, will be responsible for statistical safety review and reporting for the study. Under Dr. Donohue's direction, the safety Biostatistics personnel will create open and closed session safety reports for the PI, the DSMB, and the clinical sites in fulfilling their regulatory/reporting obligations to applicable health authorities (FDA/HCa), central and local IRBs/IECs, as well as to the NIA, and other oversight and regulatory agencies. All AE will be recorded in a secure web-based electronic data capture (EDC) system. SAEs must be reported on a SAE report form and on the AE pages in the CRF. Any SAE must be reported immediately by the investigator, within one calendar day (24 hours) from time of awareness by telephone or fax to the medical monitor, who in turn will notify the Sponsor. This reporting routine will be described in a written procedure prior to start of screening. All safety related information will be collected and processed promptly, to comply with regulatory requirements. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be reported according to regulatory guidelines and regulations.

9.6 CLINICAL MONITORING

Monitoring of clinical sites is conducted to ensure that the rights and well-being of study participants are protected and that the conduct of the study is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study performed by the Data and Coordinating Center will be limited to review of participant Informed Consent Forms as described in the Clinical Monitoring Plan (CMP).
- Details of clinical site monitoring will be documented in the CMP. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the method for documenting review of the informed consent process.
- Site PIs are expected to cooperate in the monitoring process. Site PIs will be required to ensure the availability of source documents (as defined by ICH E6, Section 1.52) and other study records (including participants' corresponding medical records) as requested, promptly address any matters brought to their attention by the Clinical Monitor, and meet in-person with the Clinical Monitor during certain site visits when requested.
- Audits may be conducted by the Data and Coordinating Center (or designee) to ensure monitoring practices are performed consistently across all participating clinical sites and that Clinical Monitors are following the CMP.

9.7 QA/QC

Data collected remotely via the Ebisu platform will be overseen and managed by the ADNI Administrative Core. The Admin Core will perform internal quality assurance including documentation review and completion, internal quality management of study data collection, and personnel training and documentation. The Admin Core will implement QC procedures that cover the data entry system and include data QC checks to be run on the database. Admin Core personnel are responsible for maintaining the Ebisu platform and database in compliance with the protocol.

Each clinical site is responsible to have a documented process and/or plan to perform internal quality management of study conduct that describes (at a minimum): data and biological specimen collection, documentation review and completion, responsibility for addressing Quality Assurance (QA) issues, and site personnel training and related documentation (including maintenance of intra- and inter-examiner agreement).

The Data and Coordinating Center will implement QC procedures that cover the data entry system and include data QC checks to be run on the database. Any missing data or data anomalies will be communicated to the clinical sites for clarification and/or resolution.

The clinical site will provide direct access to all study related locations and systems, source data/documents, and reports for the purpose of monitoring and auditing by the Data and Coordinating Center (or delegate) and inspection by local and regulatory authorities.

The Site Investigator and site personnel are responsible for maintaining the site master file containing all study-related regulatory documents as outlined by the Data and Coordinating Center. The site master file will be suitable for inspection at any time by the

Data and Coordinating Center, its designees, and/or regulatory agencies. Inspections of site facilities (e.g., pharmacy, laboratories) may occur to evaluate study conduct and compliance with the protocol.

If a health authority requests an inspection during the study or after its completion, the site PI (or designee) is responsible to inform the Data and Coordinating Center immediately.

9.8 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the study protocol, ICH GCP. The noncompliance may be either on the part of the participant, the site PI, or the clinical site personnel. As a result of deviations, corrective actions are to be developed by the clinical site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site PI to use continuous vigilance to identify and report deviations, refer to relevant study manuals for details on reporting protocol deviations. All deviations must be addressed in study source documents and reported to Data and Coordinating Center in the CRF. Protocol deviations must be sent to the IRB per their policies. The site PI is responsible for knowing and adhering to the IRB requirements. Further details about the handling of protocol deviations will be included in the relevant study manual and made available to site staff for reference.

9.9 DATA HANDLING AND RECORD KEEPING

9.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES – EBISU (ADMIN CORE)

Some data collected for those participants on the ‘remote/decentralized’ pathway will be the responsibility of the ADNI Admin Core. The Admin Core will oversee remote data collection via Ebisu, including data standardization, data management, data transfer, and quality control.

9.9.1.1 DATA COLLECTION AND STORAGE

Study data will be collected remotely via Ebisu. The Ebisu software platform (Ebisu) is developed and operated by the University of California, San Francisco, and takes security and data security very seriously. Ebisu uses a cloud provider, Microsoft Azure, to assure that all servers and infrastructure used are in professionally-managed data centers with sophisticated intrusion detection, security perimeter management and robust firewalls. All data collected through this web-based platform including audio recordings will be stored on secure servers. While participating in research lends itself to a loss of privacy, every effort will be made to avoid this. Ebisu data system for TEAM-ADNI includes password protection and internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate. The data system will utilize HIPAA compliant applications. Further, all software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data and communications are encrypted on the wire when transmitted over any network. All data stored are encrypted at rest. All Ebisu staff desktops and laptops make use of full disk encryption, virus scanner, and intrusion detection software. Participant information will be available only to the study PI and ADNI4 research staff, including Admin Core, Clinical Directors Network, and Engagement Core staff.

9.9.1.1.1 Remotely Collected Data: Ebisu

In order to provide the data generated 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), any remotely collected applicable data will be linked to the database at LONI. The LONI database will be frequently updated, and all data acquired by the ADNI Ebisu platform will be provided to LONI at regular intervals. No personal identifying data will be in this database. All the personal identifying data will be kept in a secure location (via secured servers for remotely collected data).

All study data collected by Ebisu are stored and maintained on servers hosted on Microsoft Azure and Amazon Web Services under Enterprise Agreements with University of California Office of the President (UCOP). Study data are not stored at NCIRE or UCSF

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 system resulting in the access of information. However, safeguards are in place to minimize this risk.

All participants will be assigned a code, and this will be used for all data storage and communication between study staff and sites. PII 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. The ADNI ATRI Coordinating Center does not have access to these keys. Electronic data are password protected and maintained on secure networks.

All data for remote components of TEAM-ADNI will be transmitted securely via the Internet to ADNI Admin Core. Access to the Ebisu system is role-based and will be limited to key personnel in the Admin Core (NCIRE and UCSF), Clinical Directors Network, and Engagement Core (University of Wisconsin, Fordham University, and Icahn School of Medicine at Mt. Sinai). Access is granted to study team members based on role. Each user of the system has an individual account with a password that meets UCSF requirements. Users are logged out of the system after a period of inactivity. All communication to and from the data system is encrypted. Data security and redundant data backups are monitored by the Admin Core staff.

9.9.2 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES – IN-CLINIC AND REMOTELY DERIVED DATA

The Data and Coordinating Center is responsible for overseeing participant data collection, standardization, data management, data transfer, and quality control, with data collected for participants seen in a clinical setting or as ‘remote/decentralized’ participants. In the ‘remote’ participant group, study staff will use the same data capture system and case report forms so as to maintain data harmonization for the study.

Data collection for the TEAM-ADNI cohort is the responsibility of the site PI and clinical site personnel under the supervision of and as delegated by the site PI. The site PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of all data recorded and reported and must acknowledge as such by signature.

9.9.2.1 DATA COLLECTION AND STORAGE

Study data will be collected in the following ways:

- the site PI (or designee) will record data collected (either written or electronic record of data).
- the participant or study partner will complete assessments on paper or electronically.

As defined by ICH guidelines, a CRF is a printed, optical, or electronic document designed to record all the protocol-required information to be reported to the Data and Coordinating Center on each study participant.

All source documents are to be completed in a neat, legible manner to ensure accurate interpretation of data. Data recorded in the CRF/eCRF must be consistent with the data recorded on the source documents. Source documentation must exist to verify and support data reported and to ensure the accurate interpretation of data.

Except where otherwise specified in the relevant study manual, data will be collected on the CRFs and entered into ATRI EDC, a 21 CFR Part 11 compliant data management system provided by the ATRI Data and Coordinating Center. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements.

Written or electronic data must be entered on the eCRF provided for that purpose, except where instruction to use only the computerized system for capture of a particular assessment. In some instances, no prior written or electronic record of data may exist, and data reported directly on the eCRF is considered source data. The clinical site will be trained on the use of CRFs, eCRFs, and computerized systems for data collection and will administer and submit data from computerized assessments according to instructions from the Data and Coordinating Center.

If necessary, data correction requests will be generated for resolution by the clinical site. If corrections are necessary to the eCRFs or data collected via other systems, the site PI (or designee) will correct the data and provide documentation for the reason for change.

Details about data entry, CRFs, and source documentation (including which electronic systems support eSource) will be found in the relevant study manual. Defer to the relevant study manual for information about source data that is expected to exist only electronically and which electronic systems support eSource.

9.9.2.1.1 TEAM-ADNI Cohort 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), these data 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 daily. 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 are stored and maintained on servers hosted on Amazon Web Services under an Enterprise Agreement with USC. Study data are not stored at USC facilities. All communication with the servers is encrypted. All study data stored are encrypted at rest. 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.

Every participant will be assigned a unique 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.

9.9.2.1.2 Research Biospecimens and Genetic Material Storage: NIH/NIA & NCRAD

Blood samples from the TEAM-ADNI cohort will be maintained as described in this section.

All coded samples will be inventoried and tracked using commercially available software by the Genetics Core at Indiana University. A database will be created and used for the inventory of stored samples in conjunction with a bar code reading system. Bar code labels affixed to each sample vial will contain the following information: sample ID# (to preserve confidentiality), study name, kit number and specimen type. The sample form that accompanies the sample will contain the date of collection and processing, total initial volume collected, sample type (e.g., DNA, RNA, PBMCs, etc.), kit number, gender, and YOB. The database will also include specimen specific details such as volume, aliquot number, freezer, shelf, rack, box, and location of the specimen in the box. Cell lines (immortalized and non-immortalized), RNA and DNA will be processed and stored at Indiana University. The study databases (ATRI, LONI, IU) will not have any record of the names of the study participants, or of specific medical identifiers such as clinical medical record numbers. While biomarker and genetic test results can be linked to clinical research data for purposes of analyses, there is no way to achieve linkage of test results to names of participants.

The procedures for patient confidentiality will be approved by the IRB of the Indiana University. The protection of patient confidentiality and the use of stored specimens will be in accordance with the rules and procedures established by the Indiana University IRB. The specimens are banked in a secure sample storage facility at Indiana University. Only trained staff will have access to the freezers. The samples are without a link to identity of the participant from whom the sample came. All samples are bar coded and identified by a bar code.

Specific procedures for requesting and accessing specimens will be created by the Resource Allocation Review Committee (RARC) of ADNI, as well as the Biospecimen Review Committee (BRC) at Indiana University, in accordance with recommendations proposed in

the NBAC Human Biological Materials Report. These specimen guidelines have also been developed in accordance with the American Society for Human Genetics' position paper on the NBAC report and the Ad Hoc Committee on Stored Tissue of the College of American Pathologists

9.9.2.1.3 Cohort Biomarker Data and Material Storage: UPENN

Blood samples from the TEAM-ADNI cohort will be maintained in the same ways as described in this section.

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 a Global Specimen Number which is a unique number that when used with the Laboratory Data Management System (LDMS) sample tracking system provides the following information: sample ID# (to preserve confidentiality), date of collection and processing, total initial volume collected, sample type (plasma, serum), volume, aliquot number, freezer, shelf, rack, box, and location in the box. A bar code label will be used on the sample tracking form. The LDMS is powered by Oracle and 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 are available only locally. The data are 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.

9.9.2.1.4 TEAM-ADNI Cohort Imaging Data Storage: LONI

PET and MRI scans will be labeled according to each imaging site's imaging machine capabilities using PTID and scanner specific series descriptions as detailed in the relevant study manual. All MRI and PET scans will undergo de-identification, which is embedded within the LONI Image Upload process, as well as defacing, to ensure that no participant identification information is present in the image files.

9.9.3 STUDY RECORDS RETENTION

Clinical sites will maintain study documents in an organized and accessible manner to facilitate study management and for audit and inspection purposes.

Clinical sites will follow minimum requirements for record retention as specified in study contract(s).

Clinical sites are considered covered entities and as such must comply with the HIPAA Privacy Rule which stipulates that HIPAA covered documents must be retained for a minimum of six (6) years from when the document was created, or – in the event of a policy – from when it was last in effect (45 CFR 164.316(b)(2)(i)). Record retention requirements of 45 CFR 164 (HIPAA) are in addition to HHS and FDA requirements.

Clinical sites may be required to comply with additional regulations and policies (e.g., NIH, HHS, FDA, CFR, HIPAA) and should follow the rule that has the longest period for document retention. It is advised that institutions and site PIs consult their institution's policies and procedures, HIPAA Privacy and Security officials, and legal counsel and/or risk management personnel to determine record retention requirements.

The site PI (or if regionally required, the head of the medical institution or designated representative) is responsible for retaining all study documents, including, but not limited to the protocol, copies of CRFs, the IB, regulatory agency registration documents (Form FDA 1572 for US clinical sites, or equivalent for non-US sites), ICFs, IRB correspondence, and all other essential documents and study records. Approval is required from the Data and Coordinating Center prior to destruction of study documents or offsite storage of study documents.

9.10 CONFIDENTIALITY AND PRIVACY

The contents of this protocol and any amendments and results obtained during the study are to be kept confidential by the study staff, site PI, clinical site staff, and IRB and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the Data and Coordinating Center. Data and biospecimens

collected as part of the study shall only be used in accordance with the terms and conditions set forth in the Clinical Trial Agreement executed between the institution/site PI and the Data and Coordinating Center.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/site PI and the Data and Coordinating Center.

Participant confidentiality and privacy is strictly held in trust by all participating investigators, site PIs, clinical site personnel, Data and Coordinating Center staff, and their designees. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Data and Coordinating Center.

All research activities will be conducted in as private a setting as possible.

Clinical Monitors, other authorized representatives of the Data and Coordinating Center and/or the regulatory sponsor representatives of the IRB, 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 site will permit access to such records.

Any data, specimens, forms, reports, and other records that leave the clinical site will be identified by a PTID to maintain confidentiality. All physical 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 the IRB, applicable health authority (FDA), NIA, and Office for Human Research Protections (OHRP).

At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the IRB, institutional policies, or Data and Coordinating Center and/or the regulatory sponsor requirements.

Study participant research data, which are for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Data and Coordinating Center. These data will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique participant identification number. The study data entry and study management systems used by clinical sites and by Data and Coordinating Center research staff will be secured and password protected. At the end of the study, all study databases will be archived at the Data and Coordinating Center.

9.10.1 HIPAA

Information about study participants will be kept confidential and managed according to the requirements of 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 the 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 investigator, 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.

9.10.2 CERTIFICATE OF CONFIDENTIALITY

To further protect the privacy of participants, this research is covered by a Certificate of Confidentiality (COC) from the NIH. This certificate protects identifiable research information from forced disclosure. It allows the site PI 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.

9.11 FUTURE USE OF STORED SPECIMENS AND DATA

After the study is completed, the archived data will continue to be stored at the Admin Core (for data collected via Ebusu), and the Data and Coordinating Center (for data collected in-clinic) and de-identified and/or limited datasets may be made available for use by other researchers including those outside of the study. Transmission and storage of data via Ebusu/the Admin Core and at the Data and Coordinating Center will be described in the informed consent. In addition, all data displayed at LONI will continue to be available.

De-identified biological samples will be stored at the respective labs, see section 9.9.2 for more details, and may be made available for use by other researchers including those outside of the study. These samples could be used to research the causes of AD and related neurodegenerative diseases, its complications and other conditions for which individuals with increased $A\beta$ in brain and/or autosomal dominant AD are at increased risk, and to improve treatment. The respective labs will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed or if the biological specimen has already been shared.

When the study is completed, access to study data and/or samples will be provided through the Data and Coordinating Center.

9.12 PUBLICATION AND DATA SHARING POLICY

9.12.1 PUBLICATION OF RESULTS

The results of this study will be published in accordance with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

9.12.2 SHARING OF STUDY DATA, BIOSPECIMENS, AND GENETIC MATERIAL

All ADNI data will be shared on the USC LONI ADNI website to all qualified scientists who complete the Data Use Agreement and are approved by the ADNI Data and Publications Committee. All ADNI biospecimens will be shared, pending NIA review. NIA determines distribution of biospecimens.

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 research data to serve these and other important scientific goals. To protect participant's rights and confidentiality, only de-identified data will be shared.

Because this is an NIH-funded study, data and biospecimens will be shared with other researchers pursuant to the NIH Data Sharing Policy on Data, Imaging, and Biospecimen Sharing, in accordance with any local or country legal or regulatory restrictions.

To facilitate future research, research biospecimens and DNA from participants will be banked and may be shared with other researchers studying AD, aging, or other health conditions. Banking of these samples will permit qualified investigators to probe candidate biomarkers and genetic polymorphisms as predictors of outcome in future studies.

This study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

Genetics, genomics, and related data will be shared with other researchers pursuant to the NIA Alzheimer's Disease Genetics sharing policy. National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site (NIAGADS), along with other NIA-approved sites, will make genetic, genomic, and related data and associated phenotypic data available to qualified investigators in the scientific community for secondary analysis in accordance with standards established by the 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. Investigators are approved by a Data Access Committee for access to specific datasets for a specific use(s).

9.13 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this study. The study leadership in conjunction with the NIA has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

9.14 STUDY DISCONTINUATION AND CLOSURE

The study may be temporarily suspended or prematurely terminated at a clinical site, a subset of clinical sites, or at all clinical sites if there is sufficient reasonable cause. Clinical site participation may be suspended or discontinued if the Data and Coordinating Center, the site PI, or the IRB of the study, judges it necessary for medical, safety, regulator, or other reasons consistent with applicable laws, regulations, and GCP. The study may be suspended or terminated if the Data and Coordinating Center judges it necessary for medical, safety, regulatory, other reasons consistent with applicable laws, regulations, and GCP.

If the IRB decides to suspend or terminate the study at a clinical site prior to the intended end of study as defined above, the site PI will immediately send the notice of study suspension or termination by the IRB to the Data and Coordinating Center.

If the Data and Coordinating Center decides to suspend or terminate the study, written notification, documenting the reason for study suspension or termination, will be provided by the Data and Coordinating Center or suspending or terminating party to site PIs and regulatory authorities. If the study is suspended or prematurely terminated, the site PI will promptly inform study participants and the IRB and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

For temporary suspensions, the study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Data and Coordinating Center and/or the IRB/.

10 ABBREVIATIONS

AE	Adverse Event
CC	Community Center
CDN	Clinical Directors Network, Inc.
CFR	Code of Federal Regulations
CHC	Community Health Clinic/Center
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRLs	Community Research Liaisons
CRNs	Community Research Navigators
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration

FQHC	Federally Qualified Health Center
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HCS	Health Centers
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ISO	International Organization for Standardization
LDMS	Laboratory Data Management System
NCT	National Clinical Trial
NIH	National Institutes of Health
OAC	Older Adult Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
RHC	Rural Health Clinic
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOE	Schedule of Events
SOP	Standard Operating Procedure(s)
UP	Unanticipated Problem
US	United States

11 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0		N/A	Initial
1.1	01Dec2025	Updated Schedule of Events (removed recollection of medical history at m12, changed optional participant feedback questionnaire to required at baseline, etc.) and clarified measured used in the amyloid PET disclosure process.	Modifications needed to help meet study goals prior to beginning recruitment and enrollment.

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