TRC-PAD Program: In-Clinic Trial-Ready Cohort

Short Title: TRC

Protocol Number: ATRI-004

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Funded by: National Institute on Aging

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SIGNATURE PAGE

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STATEMENT OF COMPLIANCE

This study will be conducted in compliance with the protocol, in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, and in full conformity with Regulations for the Protection of Human Participants of Research codified in 45 CFR Part 46 – Protections of Human Participants, 24 CFR Part 50 – Protection of Human Participants, 21 CFR Part 56 – IRBs, and/or the ICH E6, HIPAA, State and Federal regulations and all other applicable local regulatory requirements and laws.

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical studies are required to be qualified by education, training and experience and must have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (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. In addition, 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.

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

Only institutions holding a current Federal-Wide Assurance (FWA) issued by the Office of Human Research Protections (OHRP) may participate in the study. Refer to: http://www.hhs.gov/ohrp/assurances/.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	TRC-PAD Program: In-Clinic Trial-Ready Cohort (TRC)
Study Description:	Development of a large, well-characterized, biomarker-confirmed, trial-ready cohort to facilitate rapid enrollment into AD preclinical/prodomal trials utilizing feeder registries into the APT Webstudy and subsequent referral to in-clinic evaluation and biomarker confirmation. Participants with known biomarker status may have direct referral to the trial-ready cohort.
Objectives:	1. To build an efficient and sustainable recruitment system in order to enroll an initial TRC-PAD Cohort. 2. To optimize an innovative, adaptive risk algorithm to efficiently identify the most appropriate trial participants. 3. To develop and validate web-based cognitive and functional outcome measures for future clinical trials.
Study Population:	At least 2,000 (1,000 preclinical + 1,000 prodromal AD) trial-ready individuals aged 50-85
Description of Sites:	Approximately 60 AD clinical trials sites
Description of Study Intervention:	No intervention
Study Duration:	5 years
Participant Duration:	5 years

1.2 SCHEMA

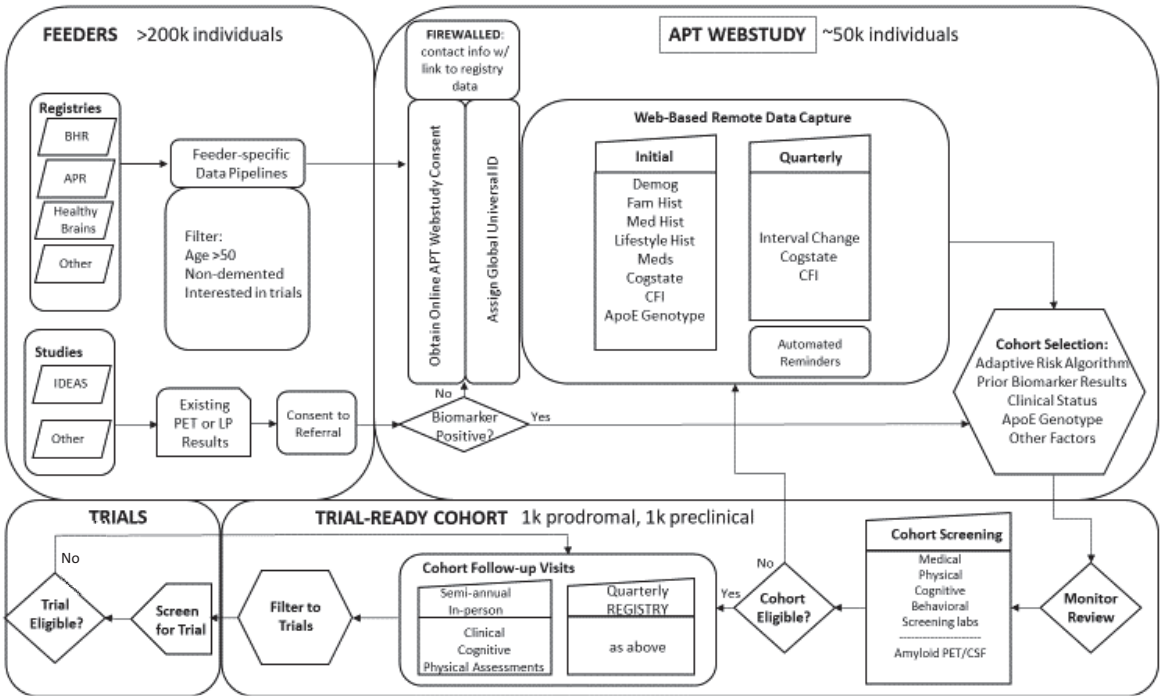

Figure 1 Overall Schema of TRC-PAD Program (Feeder Registries, APT Webstudy and In-clinic TRC)

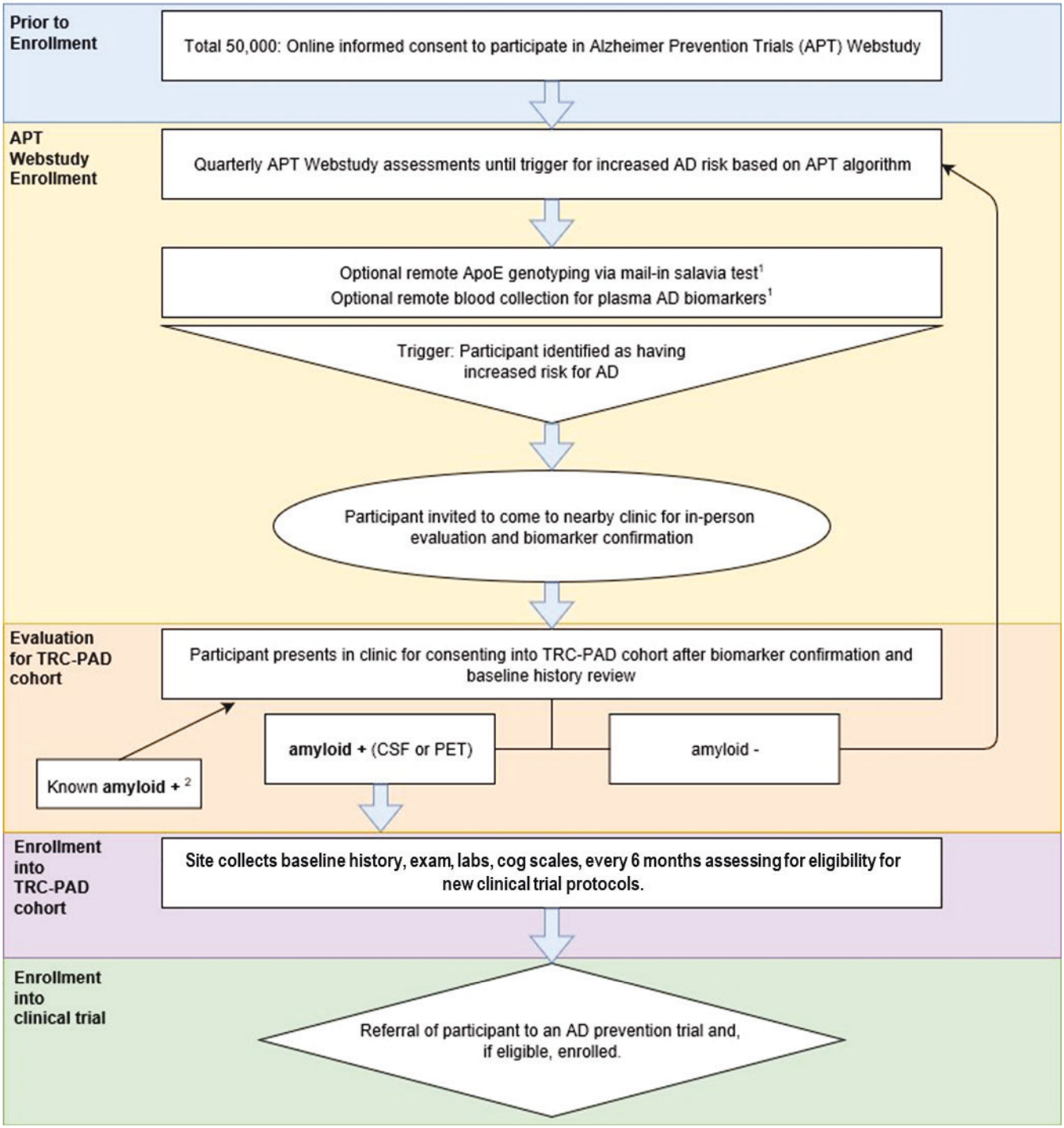

Figure 2 Participant Flow diagram: APT Webstudy and In-clinic TRC

[1] Optional remote APOE genotyping via mail-in saliva test and optional remote blood collection for plasma AD biomarkers subject to availability.

[2] **'Known Amyloid +'** indicates prior confirmed biomarkers (PET or CSF) consistent with disease pathology or elevated or intermediate brain amyloid.

1.3 SCHEDULE OF ACTIVITIES (SOA)

The schedule below is for the In-Clinic TRC

Procedures	Screening (Stage 1-2 complete within 60-day window; Stage 3 complete within 84-day window)			Follow-up Visits[8] Every 6 months +/-21 days
	Stage 1	Stage 2[3]	Stage 3	
Informed consent	X			
Demographics	X			
Medical history	X			X
Concomitant Medication	X			X
Adverse events		X		X
Vital Signs[1]	X			X
Physical and Neurological exam	X			X
PACC	X			X
CFI	X*			X*
CDR-SB	X*			X*
STAI and GDS	X*			X*
Concerns about AD, Future Time Perspective Scale	X*		X[6]	X*
Blood and urine for clinical labs	X			
Blood for Genomics[2] and AD Biomarkers (fasted)[10]	X			
Amyloid testing[3] by CSF[4,10] or PET		X		
Wellness Telephone Check[5]		X	X	
Eligibility Discussion			X	
Impact of Events Scale			X[7]	
Global Unique Identifier (GUID) generation	X[9]			

[1] Vital signs include weight, plus height at screening visit only.
[2] DNA collection performed for APOE Genotyping and banking/future analyses.
[3] Previous amyloid testing from external study may be used with approval from the Coordinating Center and screening stage 2 may be skipped.
[4] A coagulation panel and platelet count will be obtained either locally or centrally prior to the LP (within 3 months), in order to rule out a clotting disorder. Participants on anticoagulation are not eligible for LP.
[5] Post-LP/ post-PET, post-eligibility discussion telephone follow-up within 72 hours after procedure.
[6] Administered in-person after eligibility discussion.
[7] Administered by phone at the wellness telephone check following eligibility discussion.
[8] Screening visit procedures may be repeated at follow-up visits, with approval from the Coordinating Center, if needed to assess potential changes in eligibility for clinical trials, e.g. after participation in a clinical trial or prolonged enrollment in TRC without successful enrollment in a trial.
[9] GUID generation will occur at screening visit or at any visit thereafter once consent has been obtained
[10] CSF and Blood biomarker collection should occur after a minimum 8-hour fast

*At the discretion of the PI, these assessments may be conducted over the phone.

For those participants who are enrolled in the APT Webstudy, quarterly online participation will continue while screening for and enrolled in TRC.

2 INTRODUCTION

2.1 STUDY RATIONALE AND BACKGROUND

Alzheimer's disease (AD) remains one of our greatest unmet medical needs, without any approved disease-modifying therapies. Both animal data and recent clinical trial results with anti-amyloid agents suggest that our previous attempts to intervene may have been "too little, too late." Fortunately, a number of trials in both genetic and biomarker at-risk older individuals thought to be in the preclinical stages of AD, as well as trials in the clinical stage of mild cognitive impairment (MCI) or prodromal AD, are underway or currently being planned. However, the timeframe, complexity and expense of the recruitment process and site activation for these secondary prevention trials are extremely challenging, and indeed site start-up and trial enrollment, in general, represent the greatest bottleneck for drug development for AD. Moreover, it is likely that future early-stage trials will move even earlier in the process of amyloid accumulation prior to the stage of "amyloid positivity". These prevention trials will increasingly rely on remote electronic contact and assessments due to the need to screen large number of individuals and follow participants over long periods of time. Thus, there is growing consensus that we must fundamentally overhaul the current clinical trial recruitment and assessment process for these early intervention trials. The overarching goal of this protocol is to accelerate current and future secondary prevention trial enrollment through an innovative, highly efficient approach to identify, evaluate, and enroll appropriate preclinical and prodromal trial candidates, supported by a new site network with enhanced capacities for more efficient and effective conduct of AD clinical trials.

2.2 OVERVIEW

TRC-PAD is an ambitious program, addressing wide-ranging issues in trial recruitment and site management. To succeed, it will build on existing efforts by expert collaborators in informatics, web-based consent, innovative cognitive assessments, biostatistics, and multiple existing registry programs.

The feeder registries (Brain Health Registry, Alzheimer's Prevention Registry, HealthyBrains.org, et al.) will filter participants based on age and cognitive status and invite older individuals not meeting criteria for dementia to enroll in the APT Webstudy, which in turn will conduct unsupervised, web-based capture of demographic, medical, lifestyle and genetic factors, as well as longitudinal web-based cognitive testing and symptom questionnaires, to assess their risk of elevated brain amyloid. The initial risk algorithm is derived from analysis of an existing study data. This algorithm is then iteratively updated through an appropriate regression-based statistical approach to biomarker testing results.

The individuals at highest risk within the APT Webstudy pool of asymptomatic (preclinical) and very mildly symptomatic (prodromal) individuals will be referred for in-person clinical and biomarker assessments at select AD clinical trial sites. Those who are identified with biomarker profiles indicative of AD pathology, including asymptomatic individuals with minimally elevated or "intermediate" levels of amyloid, will be eligible for the in-clinic trial-ready cohort (TRC), where they will be followed at semi-annual in person visits until they are ready for enrollment in preclinical/prodromal therapeutic trials, while continuing quarterly, remote, web-based cognitive assessments in the APT Webstudy. Biomarker-negative individuals will continue remote web-based follow-up in the APT Webstudy; if longitudinal trajectories and changes to other risk factors indicate increasing risk, those participants will be eligible for repeat in-person clinical and biomarker assessment. Participants with known

biomarker status may have direct referral to the in-clinic TRC cohort and will be encouraged to participate in the APT Webstudy.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

2.3.1.1 RISKS ASSOCIATED WITH POSITRON EMISSION TOMOGRAPHY (PET)

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 (pain and bruising or painful infiltration of a failed injection).

Any of the following radiotracers may be utilized for amyloid imaging in this study:

- florbetaben (Neuraceq),
- florbetapir (Amyvid)
- flutemetamol (Vizamyl)
- NAV-4694 (Flutafuranol)

Specific risk information for florbetaben, florbetapir and flutemetamol can be found in their corresponding Package Insert. Specific risk information for NAV-4694 can be found in the Investigator Brochure.

The radiation doses for each PET scan are not themselves expected to produce any harmful effects, although there is no known minimum level of radiation exposure considered to be totally free of the risk of causing genetic defects or cancer. The risk associated with the amount of radiation exposure participants receive in this study is considered low and comparable to everyday risks. If a female is not surgically sterile or post-menopausal by two years, a pregnancy test will be performed. Participants with positive pregnancy test will be ineligible for amyloid PET imaging.

2.3.1.2 RISKS ASSOCIATED WITH LUMBAR PUNCTURE (LP)

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

2.3.1.3 GENETIC RISKS

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

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

2.3.1.4 PSYCHOLOGICAL RISKS OF REFERRAL FROM THE APT WEBSTUDY

When a participant is identified as having increased risk for future development of AD based on their profile and performance in the APT Webstudy, they will be contacted by email or phone to present for an in-clinic evaluation to have their increased risk explained and to consent for screening to join the in-clinic TRC-PAD cohort. Participants deemed ineligible at the in-clinic evaluation may be referred for further clinical evaluation of a non-AD diagnosis and/or returned to the APT Webstudy for continued tracking. Risks associated with this process include negative outlook based on the invitation for further evaluation of memory performance as part of the APT Webstudy. In the case of individuals referred from other studies where their amyloid status may be known, they might be referred to in-clinic evaluation to join the TRC-PAD cohort if eligible. These individuals may therefore bypass the APT Webstudy completely.

2.3.1.5 PSYCHOLOGICAL RISKS FROM ELIGIBILITY RESULTS

Once eligibility testing is performed there will be an eligibility discussion session where results about study eligibility and increased risk for future development of AD will be shared with participants. It is possible that some participants may be upset by learning the results of their TRC eligibility assessment which indicates an increased risk of developing AD in the future. However, in recent studies, there was no deleterious effect of learning about increased risk for AD by learning amyloid status on depression or anxiety scales (Pontecorvo, Avid A18 study, Dementia Ger Cog Disord 2017; Mozersky et al, 2018 Sokrates study, JAMA Neurology). The Imaging Dementia – Evidence for Amyloid Scanning (IDEAS) study, led by Dr. Rabinovici, has scanned over 18,000 cognitively impaired patients with amyloid PET. The study is monitoring all known causes of death following amyloid PET disclosure, and thus far no suicides have been reported.

2.3.1.6 RISK ASSOCIATED WITH LOSS OF PRIVACY

In this study, a great deal of information about participant health status is collected. Study staff at the clinic sites will be collecting personal protected health information such as name, date of birth, address, phone number, and emails. All participants will be given a participant code number as part of the in-clinic TRC, and all data collected under this protocol will be associated with the code number. The data, associated with the code number, 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 that there will be a security failure, and that somehow the protected health information will be no longer protected. This is an extremely unlikely but possible occurrence and is a risk of this study.

2.3.2 KNOWN POTENTIAL BENEFITS

By enrolling in the in-clinic TRC cohort, individuals with increased risk for developing AD will have the opportunity to participate in AD prevention clinical trials. Volunteering for the study may be associated with a sense of altruism and helping the community to address a serious disease affecting many people.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Although there is some risk associated with PET imaging (e.g. radiation exposure) and lumbar puncture (pain), the benefits of enrolling in a prevention study for AD are far greater, as there are currently no treatments for the prevention of AD and the opportunity to have access to medications that slow the development of AD dementia outweighs these risks.

3 OBJECTIVES AND ENDPOINTS

Aim 1: To build an efficient and sustainable recruitment system in order to enroll and retain an initial TRC-PAD Cohort. This approach will markedly accelerate recruitment timelines, shorten time to site activation for trials, and reduce unexplained variance in pre-trial cognitive testing, as compared to current recruitment approaches.

Aim 2: To optimize an innovative, adaptive risk algorithm to efficiently identify the most appropriate trial participants. Once optimized, this algorithm will be able to select amyloid positive individuals (and eventually tau and other neurodegenerative biomarkers) with >75% accuracy, greatly reducing future costly biomarker screen fails.

Aim 3: To develop and validate web-based cognitive and functional outcome measures for future clinical trials. Baseline and longitudinal cognitive performance (including lack of practice effect on repeated web-based cognitive tests), decline on performance based functional measures, and a combination of self- and study-partner report will predict and subsequently track with in-person measures of cognitive (PACC) and functional (CDR-SB) decline.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a prospective, longitudinal observational study primarily aimed at enrolling well-characterized, AD biomarker-positive individuals into preclinical and prodromal AD clinical trials.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The rationale for the study design is to develop and utilize the APT Webstudy and the TRC cohort to accelerate AD prevention trial enrollment through an innovative, highly efficient approach to identify, evaluate, and enroll appropriate preclinical and prodromal trial candidates as the current methods of recruitment for prevention studies is slow and has extremely high screen fail rates (~80%) and adds years to the duration of such studies.

4.3 END OF STUDY DEFINITION

Given the overarching goal of the study to facilitate and accelerate enrollment of participants into clinical trials, there is no specific end point. Study activities are anticipated to continue until funding is no longer available.

5 STUDY POPULATION FOR IN-CLINIC TRC

5.1 INCLUSION CRITERIA

In order to be eligible, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated availability and willingness to comply with all study procedures until referred to a clinical trial
3. Age 50-85 (inclusive)
4. Global CDR score of 0 or 0.5 and no diagnosis of dementia
5. Has a study partner that is willing to participate as a source of information and has at least weekly contact with the participant (contact can be in-person, via telephone or electronic communication). The study partner must have sufficient contact such that the investigator feels the study partner can provide meaningful information about the participant's daily function.
6. In good general health as evidenced by medical history
7. Adequate visual and auditory acuity to allow neuropsychological testing
8. Fluent in English or Spanish
9. For females who are not surgically sterile or post-menopausal by two years, receiving a PET scan for amyloid biomarker confirmation: negative pregnancy test prior to amyloid PET scan
10. Completed six grades of education or has a good work history
11. Evidence of elevated or intermediate (subthreshold) levels brain amyloid as assessed by central review of amyloid PET or CSF data. Prior amyloid testing results may be used with approval from the Coordinating Center.

Exceptions to these guidelines may be considered on a case-by-case basis at the discretion of the Project Director and Coordinating Center.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Treatment with an investigational anti-amyloid drug or other experimental intervention within 12 months. Use of aducanumab or other approved anti-amyloid treatments allowed if stable for at least 3 months.
2. Enrolled in another interventional clinical trial within the last 12 weeks
3. Any significant neurologic disease such as Alzheimer's disease dementia, Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic deficits or known structural brain abnormalities.

4. Major depression, bipolar disorder as described in DSM-V within the past 1 year or psychotic features, agitation or behavioral problems within 3 months, which could lead to difficulty complying with the protocol
5. History of schizophrenia (DSM V criteria)
6. History of alcohol or substance abuse or dependence within the past 2 years (DSM V criteria)
7. Clinically significant or unstable medical condition, including uncontrolled hypertension, uncontrolled diabetes, or significant cardiac, pulmonary, renal, hepatic, endocrine, or other systemic disease in the opinion of the Investigator, may either put the participant at risk because of participation in the study, or influence the results, or the participant's ability to participate in the study.
8. History within the last 3 years of a primary or recurrent malignant disease with the exception of non-melanoma skin cancers, resected cutaneous squamous cell carcinoma in situ, basal cell carcinoma, cervical carcinoma in situ, or in situ prostate cancer with normal prostate-specific antigen post-treatment
9. Clinically significant abnormalities in B12 or TFTs that might interfere with the study. A low B12 is exclusionary, unless follow-up labs (homocysteine (HC) and methylmalonic acid (MMA)) indicate that it is not physiologically significant.
10. Clinically significant abnormalities in screening laboratories.
11. For participants undergoing CSF collection: a current blood clotting or bleeding disorder, or significantly abnormal PT or PTT at screening or if on anti-coagulation (e.g. warfarin)
12. Participants whom the Site PI deems to be otherwise ineligible.
    - Site PIs should consult with the Coordinating Center on any issues that may disqualify the participant from participation in future clinical trials to determine whether enrollment into TRC would be appropriate.

Exceptions to these guidelines may be considered on a case-by-case basis at the discretion of the Project Director and Coordinating Center.

5.3 SCREEN FAILURES

Screen failures are defined as participants who do not meet inclusion criteria or do meet exclusionary criteria and therefore are not entered in the TRC cohort. A minimal set of screen failure reasons is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities.

Individuals who screen fail on the basis of amyloid results, may be rescreened in the future with approval by the Coordinating Center or, if cognitively impaired, may be referred by the clinic for evaluation of possible non-AD diagnosis.

Screen fail participants may continue in the APT Webstudy for ongoing remote, longitudinal monitoring of their cognitive performance to assess for any increased risk of developing AD.

5.4 CLINICAL TRIAL PARTICIPATION AND TRC STATUS

Individuals enrolled into TRC and then screened for clinical trials are placed on temporary inactive status at the time of consent for the clinical trial. Data regarding clinical trial screening and participation will be reported in the eCRF. Upon completion of trial activities, participants are reactivated in TRC, resuming 6 months visits as per the SOA.

The Site PI may request from the Medical Monitor that he/she be provided amyloid testing results to inform pre-screening for a specific trial protocol. In some cases, certain screening procedures may need to be repeated at the time of re-entry into TRC. Consult with the Coordinating Center for guidance on a case-by-case basis.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment will occur through a variety of mechanisms. ATRI will use a coordinated recruitment plan to ensure that enrollment occurs in a timely fashion. The overall goals of the plan are to raise awareness of AD trials among targeted populations to ensure rapid and adequate enrollment in prevention trials. The study recruitment and retention team will develop materials specific to the APT Webstudy and the TRC-PAD Cohort for use by the sites, provide ongoing recruitment assistance and support, and develop tracking procedures to monitor effectiveness of recruitment efforts. Efforts will be made to target at least 20% minority enrollment, through minority community outreach initiatives facilitated by the coordinating center.

The study's goal is to enroll at least 2,000 participants, however in support of the overarching goal to facilitate and accelerate enrollment of participants into clinical trials, enrollment into TRC is anticipated to continue over the entire study period and may exceed 2,000 participants.

6 PET TRACERS

Each participant receiving a PET scan for eligibility confirmation will be scanned with an Amyloid PET tracer – which tracer is used will be determined based on availability at the site for this study. Amyloid PET results will be generated centrally using quantitative metrics to assess level of amyloidosis, and eligibility information for continuing in the TRC cohort will be returned to site.

6.1 DOSING AND ADMINISTRATION OF AMYLOID PET TRACERS

Florbetaben (Neuraceq):

Florbetaben will be provided by Piramal Imaging Ltd. One mL (1 mL) of the solution for each injection/vial contains 300 MBq of florbetaben. The other ingredients are ascorbic acid, ethanol anhydrous, macrogol 400, sodium ascorbate, and water for injections. Image acquisition should begin 90 minutes after injection. The effective dose resulting from a 300 MBq (8.1 mCi) administration of Neuraceq in adult participants is 5.8 mSv. The use of a CT scan to calculate attenuation correction for reconstruction of Neuraceq images (as done in PET/CT imaging) will add radiation exposure. Diagnostic head CT scans using helical scanners administer an average of 2.2 ± 1.3 mSv effective dose (CRCPD Publication E-07-2, 2007). The actual radiation dose is operator and scanner dependent. Thus, the total combined radiation exposure from Neuraceq administration and subsequent scan on a PET/CT scanner is estimated to be 8 mSv.

Florbetapir (Amyvid):

Scanning entails 10mCi injection of tracer administered through an intravenous line and a 50-minute uptake until 20-minute image acquisition begins. Image acquisition occurs over a 20-minute period. The effective dose resulting from a 370 MBq (10 mCi) dose of Amyvid is 7.0 mSv in an adult, (19 x 370 = 7030 µSv = 7.030 mSv). The use of a CT scan to calculate attenuation correction for reconstruction of Amyvid images (as done in PET/CT imaging) will add radiation exposure. Diagnostic head CT scans using helical scanners administer an average of 2.2 ± 1.3 mSv effective dose (CRCPD Publication E-07-2, 2007). The actual radiation dose is operator and scanner dependent. The

total radiation exposure from Amyvid administration and subsequent scan on a PET/CT scanner is estimated to be 9 mSv.

Flutemetamol (Vizamyl):

The recommended dose for Vizamyl is 185 megabecquerels (MBq) [5 millicuries (mCi)] in a maximum dose volume of 10 mL, administered as a single intravenous bolus within 40 seconds. The maximum mass dose is 20 micrograms. Follow the injection with an intravenous flush of 5 to 15 mL of 0.9% sterile sodium chloride injection.

NAV-4694 (Flutafuranol):

The recommended dose is 8.1 mCi (300 MBq) (± 10%) of [^{18}F]NAV-4694 will be injected intravenously followed by an infusion line flush of 15-20 mL of normal saline. The Investigator's Brochure has additional details regarding this amyloid radiotracer.

7 PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE IN-CLINIC TRC STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for any reason. Examples include:

- Participant develops dementia: Any participant who develops dementia will be discontinued from the study at the next follow up visit.
- Adverse experience: The participant has experienced an adverse event that requires early termination. This may include abnormal laboratory values.
- Death
- Protocol violation: The participant fails to meet protocol entry criteria or did not adhere to protocol requirements.
- Non-compliance: The participant is non-compliant with completion of study-related evaluations.
- In the investigator's judgment, it is in the participant's best interest to discontinue participation in the study.
- Consent is withdrawn. The participant wishes to withdraw from the study, or the legally authorized representative wish the participant to be withdrawn.
- Lost to follow up. Participant could not be recalled back to conduct follow up visits.
- Loss of informed study partner. The participant no longer has an informed study partner.

7.1.1 CLINICAL TRIAL PARTICIPATION

Participants who screen into clinical trials will be placed in temporary inactive status in TRC-PAD at the time of consent into the clinical trial, the participant would return to active status following completion of participation in the trial (see Section 5.4).

7.2 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for two scheduled visits and is unable to be contacted by the study site staff.

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

- The site will attempt to contact the participant and reschedule the missed visit within 30 days or at the discretion of the PI. The site will also counsel the participant on the importance of maintaining the assigned visit schedule 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, 2 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, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 CLINICAL AND COGNITIVE ASSESSMENTS

8.1.1 PRESCREEN PHASE

During the prescreen phase, participants will be enrolled in the APT Webstudy and once triggered for increased risk of developing AD, will be referred to in-person clinical evaluation. Participants for whom evidence of brain amyloid has already been confirmed, may be referred for in-person clinical evaluation to participate in TRC and bypass the APT Webstudy.

Prior amyloid testing, when applicable, should be confirmed prior to screening.

8.1.2 SCREENING

The purpose of the Screening Visit is to further determine eligibility for the TRC cohort and to complete the informed consent. The screening procedures will be conducted as outlined in the Schedule of Activities (section 1.3).

Procedures may be performed on separate days as long as all procedures are conducted within the visit window. Screening Stages 1 and 2 must be completed within a 60-day window. Screening stage 3 should be completed within 84 days of the start of screening activities. It is acceptable to delay some assessments if the study cannot be properly conducted due the COVID-19 pandemic. In these cases, reach out to the Coordinating Center for additional guidance.

Screening Stage 1 data will be centrally reviewed prior to site being authorized to proceed with Stage 2 (amyloid testing via PET or CSF) and again prior to the site being authorized to proceed with Stage 3 (eligibility discussion). Sites may not proceed with Stages 2 or 3 of screening until authorized.

If a female is not surgically sterile or post-menopausal by two years, a pregnancy test will be performed locally at the site prior to conducting the PET scan. Participants with positive pregnancy test will be ineligible for amyloid PET imaging.

Screening visit procedures may be repeated if clinically necessary (e.g. to follow-up on an abnormality identified on clinical labs) or if data from the initial procedure is not analyzable (e.g. PET scan QC failure).

8.1.2.1 BIOMARKER CONFIRMATION USING SHARED IMAGES AND/OR RESULTS

Participants who have previously undergone amyloid testing via PET or CSF under another research study may provide consent to have their PET scan, CSF sample, PET scan results and/or CSF results shared with the Coordinating Center for the purposes of biomarker confirmation at Screening Stage 2.

In such instances, approval from the sponsor of the other research study may be required prior to sharing of data or images. The Coordinating Center will work with the site and, if needed, the study sponsor on securely transferring the relevant data, ensuring that no identifiable information is shared with the Coordinating Center. The following are examples of how data may be shared with TRC:

- PET scan or CSF sample – scan/sample will be submitted to the Coordinating Center using standard submission procedures for central analysis
- PET or CSF analysis results (e.g. quantitative data) – data will be transmitted from the study sponsor or site to the Coordinating Center for review and evaluation against TRC entry requirements
- A report indicating that the participant was deemed eligible for a particular study based on amyloid testing results – report will be transmitted from the study sponsor or site to the Coordinating Center for review and evaluation against TRC entry requirements

To the extent possible, data will be incorporated into the TRC data sets and will be shared along with other TRC data as described in Section 10, however this may not be possible if the study sponsor requires restrictions on data sharing with the site or with other investigators.

In the event that a participant consents to having prior results shared, but the study sponsor does not provide their approval for sharing, the site investigator will consult with the Coordinating Center to obtain approval prior to enrollment.

8.1.2.2 WELLNESS TELEPHONE CHECK

Telephone calls will be made to participants within 72 hours after amyloid PET tracer administration or lumbar puncture, and after an in-person eligibility discussion to ascertain if adverse events occurred post procedure. The phone check following an in-person eligibility discussion will also include the administration of the Impact of Events Scale.

Additional telephone visits may be conducted during the study period at the discretion of the Site PI.

8.1.2.3 ELIGIBILITY DISCUSSION

Participants deemed eligible for TRC enrollment following completion of all screening procedures, including amyloid testing, will meet with a licensed clinician (M.D., M.B.B.S., N.P., D.O., PA-C, A.P.R.N.) in person to discuss their eligibility for the study. A telephone call rather than in-person discussion of eligibility results may be done at the discretion of the Site PI in the following scenarios:

- For eligible participants who had previously been disclosed results of prior amyloid testing.
- For ineligible participants.

Participants who are ineligible for TRC may remain in the APT Webstudy.

For participants having an in-person discussion of eligibility results, the Concerns about Alzheimer's Disease Questionnaire and Future Time perspective Scale will be administered following the discussion and a 72-hour wellness telephone check will be conducted that includes administration of the Impact of Events Scale.

8.1.3 ACTIVE STUDY PHASE (ONGOING 6-MONTH ASSESSMENTS)

The remaining study procedures will be conducted as outlined in Schedule of Activities (section 1.3). Timing of each follow-up visit is calculated from the start of screening. Procedures for each visit may be completed over multiple days but must occur within the window of +/-21 days from the visit's target date.

Screening visit procedures may be repeated at follow-up visits, with approval from the Coordinating Center, if needed to assess potential changes in eligibility for clinical trials, e.g. after participation in a clinical trial or prolonged enrollment in TRC without successful enrollment in a trial.

8.1.4 PHYSICAL AND NEUROLOGICAL EXAMINATION

A physical and neurological examination will be performed at each visit as listed in SOA (section 1.3) by a medically qualified, licensed clinician. The physical examination will consist of a review of the major body systems (i.e. skin, HEENT (head/ears/eyes/ nose/throat), cardiovascular, pulmonary, abdomen, musculoskeletal, and extremities). Neurological examination will include an assessment of cranial nerves, strength, coordination, reflexes, sensation, tremor, gait and mental status.

8.1.5 VITAL SIGNS

Vital signs will be collected at each visit as indicated in SOA (section 1.3) and include weight, systolic and diastolic blood pressure, pulse, temperature and respiration rate. Height will be taken at the screening visit only.

8.1.6 MEDICAL HISTORY

The participant's lifetime medical history will be collected as listed in SOA (section 1.3). Medical history includes previous and current diseases, psychiatric history, and substance use history.

8.1.7 COGNITIVE, FUNCTIONAL, AND WELL-BEING ASSESSMENTS

Study participants will undergo the following cognitive and functional assessments:

- **PACC (PACC)**: The PACC is a composite measure that comprises the Total Recall score from the Free and Cued Selective Reminding Test (FCSRT), the Delayed Paragraph Recall score on the Logical Memory Iia test from the Wechsler Memory Scale, the Digit-Symbol Substitution test from the Wechsler Adult Intelligence Scale-Revised, and the MMSE total score (Mormino et al. 2017). Psychometrists administering the PACC are required to complete an PACC training and certification process. The administration of the PACC will be recorded (audio only) for quality review purposes and for additional analyses according to locally applicable laws and regulations.
- **COGNITIVE FUNCTION INDEX Index (CFI)**: The CFI is a modified version of the Mail-in Cognitive Function Screening Instrument, a participant- and study partner-reported outcome (patient-reported outcome) measure. This assessment includes 15 questions that assess the participant's perceived ability to perform high level functional tasks in daily-life and their sense of overall cognitive functional (Walsh et al. 2006; Amariglio et al. 2015)

- **CLINICAL DEMENTIA RATING SCALE SUM OF BOXES (CDR-SB)**: The CDR-SB[37, 38] is a clinical scale that rates the severity of dementia as absent, questionable, mild, moderate, or severe (global CDR scores of 0, 0.5, 1, 2, or 3, respectively). The score is based on interviews with the participant and study partner, using a structured interview that assesses six domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The Sum of Boxes score affords a more refined measure of change. Reliability and validity of both global and SB scores have been established.
- **CONCERNS ABOUT ALZHEIMER'S DISEASE:** Concerns about Alzheimer's Disease is a short self-report instrument about one's concern about developing Alzheimer's disease dementia. It is adapted from Roberts and Connell 2000.
- **IMPACT OF EVENTS SCALE**: The IES (Horowitz et al. 1979) is a 15-item self-report measure that assesses two 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 participants 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 testing related distress.
- **FUTURE TIME PERSPECTIVE SCALE**: The Future Time Perspective scale (Roberts 2000; Lang and Carstensen 2002) measures a person's perception of his or her remaining time which in turn has been shown to explain the priority of specific goals.
- **ASSESSMENT OF PSYCHOLOGICAL WELL-BEING (STAI, GDS)**: The Assessment of Psychological Well Being is composed of questions from a validated shortened version (Marteau and Bekker 1992) of the "state anxiety" portion of the State-Trait Anxiety Inventory (STAI; Spielberger et al. 1983) and from the Geriatric Depression Scale (GDS; Sheikh and Yesavage 1986). It is a self-report assessment designed to identify symptoms of anxiety and depression in the elderly. The anxiety portion of the assessment consists of 6 questions that the subject indicates on a scale from 1 (not at all) to 4 (very much) on how much of a given anxiety symptom they are currently experiencing to assess anxiety level. The depression portion of the assessment has 15 questions that the subject is asked to answer yes or no based on how they felt over the past week in an effort to assess depression symptoms. The more benign items are asked first. Answers to 5 of the items are negatively oriented for depression (for example, Do you feel full of energy?) and 10 positively oriented (for example, Do you often feel helpless?).

8.2 LUMBAR PUNCTURE

CSF samples will be collected in the morning after an 8-hour fast. Consult with ATRI for guidance if adherence to this scheduling requirement is problematic, e.g. due to participant travel. If the participant arrives for the procedure without having fasted as instructed, sites may still proceed with the procedure and record fasting status on the relevant eCRF.

Prior to lumbar puncture (LP), a coagulation panel and platelet count will be obtained to rule out a clotting disorder. Labs will be analyzed locally or centrally within 3 months prior to the LP. Participants taking an anti-platelet agent (e.g. aspirin) may be discontinued from that agent for a period of time before and after the LP at the discretion of the PI (or qualified designee). Participants who are taking anticoagulants (e.g. warfarin (Coumadin) and/or dabigatran (Pradaxa)) may not undergo an LP.

An MRI or CT prior to LP and LP under fluoroscopy are permitted, if needed, with approval by the Medical Monitor on a case-by-case basis. The participant should be appropriately consented prior to the additional procedure according to local site requirements.

A total volume of 20 mL of CSF should be collected for each LP. To clear blood associated with needle insertion, the first 1-2 mL (or more if needed) of CSF should be discarded. 1-2 mL CSF (or volume per local laboratory requirements) will be sent to the local laboratory for protein, glucose, and cell counts. Remaining CSF will be frozen on dry ice or in a -80 freezer and shipped overnight frozen to the ATRI Laboratory and Biorepository for processing and analysis. Analyses will include AD biomarkers (e.g. Aβ and tau, exploratory biomarkers). Amyloid CSF results will be generated centrally using quantitative metrics to assess level of amyloidosis, and eligibility information for continuing in the TRC cohort will be returned to site.

Each study participant or a person designated to speak for them will be contacted by phone 72 hours after the LP to confirm participant well-being and to query about any adverse events.

CSF samples will be shipped to the Alzheimer's Therapeutic Research Institute (ATRI) Laboratory and Biorepository at the University of Southern California (USC). Sample analysis will be performed by the ATRI Laboratory and Biorepository and laboratories they contract with.

8.3 GENOMIC AND PLASMA AD BIOMARKER SAMPLES

Blood for genomic and plasma AD biomarker analyses will be collected after an 8-hour fast. Consult with ATRI for guidance if adherence to this scheduling requirement is problematic, e.g. due to participant travel. If the participant arrives for the procedure without having fasted as instructed, sites may still proceed with the procedure and record fasting status on the relevant eCRF.

There is growing evidence that genomic characteristics may impact a participant's response to therapy. Variable response to therapy may be due to genomic determinants that impact drug absorption, distribution, metabolism, and excretion, the mechanism of action of the drug, the disease etiology and/or the molecular subtype of the disease being treated. Therefore, blood samples will be collected for several types of genomic analysis. Apolipoprotein E (APOE) genotyping is a mandatory part of this study. Neither participants nor investigators will receive the genotyping results unless there is a country-specific law or regulation that requires notification of the results. The samples will be coded with the participant number and stored indefinitely for future analyses. The samples and any data generated from them can only be linked back to the participant by investigator site personnel.

Whole blood samples will be shipped to the Alzheimer's Therapeutic Research Institute (ATRI) Laboratory and Biorepository at the University of Southern California (USC) for extraction of genomic and plasma samples. At sites where the capabilities exist, additional blood will be collected and processed locally for plasma, then shipped to the ATRI Laboratory and Biorepository. Genomic and biomarker analysis will be performed by the ATRI Laboratory and Biorepository and laboratories they contract with.

Plasma concentrations of Aβ species and tau will be determined from processed blood samples using either validated or research grade immunoassay and/or mass spectrometry methods. Analysis of Aβ species and tau is intended to understand these plasma-based biomarkers as compared to other clinical, cognitive, and imaging measures. Other sources of Aβ species, including plasma exosome-based amyloids thought to be associated with amyloid accumulation may also be analyzed. Our goal is to determine the optimal pre-processing pathway and analytical approach to measurement of plasma Aβ ratios to reduce negative amyloid PET scans and LP studies. Banked plasma specimens may also be used for other emerging biomarkers that may become available, including measures of Neurofilament Light chain (NfL), and specific tau fragments.

8.3.1 SAMPLES FOR BIOMARKER STORAGE AND FUTURE RESEARCH

Collection of biomarker samples for long-term storage and future research is also part of this study. Plasma, whole blood, and CSF samples will be shipped to the Alzheimer's Therapeutic Research Institute (ATRI) Laboratory and Biorepository at the University of Southern California (USC) for long-term storage and future research. Sample collection, handling, and shipment will occur according to the procedures described in the relevant ATRI Biomarker Procedures Manual. Analysis may be conducted on possible novel biomarkers to evaluate their association with clinical outcomes. Analysis of these data could provide an important biomarker that would guide future decisions by clinicians and researchers. The stored samples will be coded with the participant number and stored indefinitely for future research. The samples and any data generated from them can only be linked back to the participant by investigator site personnel. Because of the exploratory nature of these analyses and because the results should not change medical management, neither participants nor investigators will receive the test results.

8.4 SAFETY AND OTHER ASSESSMENTS

8.4.1 CONCOMITANT MEDICATION REVIEW

Concomitant medications will be reviewed at every visit as indicated in SOA (section 1.3).

8.4.2 CLINICAL LABORATORY ASSESSMENTS

Clinical labs will be performed centrally as indicated in SOA (section 1.3) and will consist of Hematology, Chemistry Panel, TSH, Vitamin B12, and urinalysis. Lab reports will be reviewed, signed and dated by the site Principal Investigator (or a medically-qualified individual delegated by the PI). If a value is outside of the laboratory's normal range, the clinician will indicate if it is clinically significant or not. Those results that are deemed clinically significant may need to be repeated and follow up with the participant's primary care physician for further evaluation should occur.

If a participant is having lumbar puncture, a coagulation panel and platelet count will be obtained either locally or centrally prior to the LP (within 3 months), in order to rule out a clotting disorder.

If a female is not surgically sterile or post-menopausal by two years, a pregnancy test will be performed locally at the site prior to conducting the PET scan. Participants with positive pregnancy test will be ineligible for amyloid PET imaging.

8.5 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.5.1 DEFINITION OF ADVERSE EVENTS

An adverse event (AE) is defined as any untoward medical occurrence. Adverse events deemed related to the study compounds (e.g. PET tracers) or procedures by the site investigator and serious adverse events occurring within 2 days of PET tracer administration, regardless of causality, will be tracked during the study.

The following events are considered adverse events:

(1) worsening or change in nature, severity, or frequency of conditions or symptoms present at the start of the study

(2) participant deterioration due to primary illness
(3) intercurrent illness
(4) drug interaction

Abnormal laboratory and imaging findings will only be reported as an AE if the PI or medical designee considers it to be clinically significant or if it leads to the participant being withdrawn from the study.

The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs or symptoms. Symptoms and conditions present at the beginning of the study will be characterized, so that AEs can be defined as any new symptom, or any increase in frequency or severity of an existing symptom. Adverse events should be described with medical terminology so that the event can be matched against a medical coding dictionary, such as Medical Dictionary for Regulatory Activities (MedDRA).

Investigators should report their assessment of the potential relatedness of each AE to the protocol compounds and procedures. Following questioning and evaluation, only AEs, determined to be related to the protocol compounds or procedures by a medically qualified Site PI or medical designee or serious adverse events occurring within 2 days of PET tracer administration, regardless of causality, must be documented in the participant's records, in accordance with the investigator's normal clinical practice, and on the AE eCRF.

8.5.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

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

1. Death
2. A life-threatening adverse event
3. In-patient hospitalization or prolongation of existing hospitalization (see below for more information regarding hospitalization)
4. A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5. 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 and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Hospitalizations that fulfill one of the following conditions will not have to be reported as SAE:

- Admission for treatment of a pre-existing condition that is not associated with the development of a new AE or with a worsening of the pre-existing condition (i.e., work-up for persistent lab abnormality that occurred prior to the study)
- Social admission (i.e., participant has no place to sleep)
- Administrative admission (i.e., yearly physical exam)
- Protocol-specified admission (i.e., for a procedure required by the study protocol)

- Optional admission not associated with a precipitating clinical AE (i.e., pre-planned treatments, elective cosmetic surgery)

For more detail, refer to the Code of Federal Regulation Title 21 Part 312:

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32

8.5.3 CLASSIFICATION OF AN ADVERSE EVENT (AE)

Reporting standards for reporting AEs will be provided in the relevant procedures manual and must be followed regardless of applicable regulatory requirements that may be less stringent.

8.5.3.1 SEVERITY OF EVENT

All AEs will be assessed by the study clinician using a protocol defined grading system. The following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – 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".

8.5.3.2 RELATIONSHIP TO STUDY COMPOUNDS OR PROCEDURES

The investigator or designated, licensed clinician is responsible for determining whether or not an event is related to study compounds (e.g. PET radiotracer), specific study procedures or "other study procedure(s)". "Other study procedure(s)" refers to any other procedure outside of those specified that may have a causal relationship to the AE.

- **Definitely Related** – The event is clearly related to a study compound or procedure. There is clear evidence to suggest a causal relationship. The influence of other factors can be ruled out.
- **Probably Related** – The event is likely related to a study compound or procedure. There is evidence to suggest a causal relationship, such as reasonable temporal sequence. The influence of other factors is unlikely. Suggest a causal relationship. The influence of other factors can be ruled out.
- **Possibly Related** – suggest a causal relationship. The influence of other factors can be ruled out.
- **Unlikely Related** – A poor temporal relationship exists between the event onset and study compound or procedure. The event could easily be explained by the participant's clinical state, intercurrent illness, or concomitant therapies.
- **Not Related** - There is no evidence of a causal relationship and a causal relationship cannot be reasonably attributed to the study compound or procedures. The event is clearly due to extraneous causes.

8.5.3.3 EXPECTEDNESS

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB, package insert, or device labeling or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the protocol, as amended.

8.5.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

Adverse events will be reported from the time of signing the TRC informed consent until signing an ICF for a clinical trial, and will resume following completion of the trial and reactivation in TRC.

Following up on AEs: The investigator is obliged to follow participants with AEs until the events have resolved, the conditions are considered medically stable, or the participants are no longer available for follow up. Participants who discontinue due to adverse experiences will be treated and followed according to established medical practice. All pertinent information will be entered into the eCRF.

8.5.5 ADVERSE EVENT REPORTING

Adverse events deemed related to the study compounds (e.g. PET tracers) or procedures by the Site PI will be tracked during the study. The principal investigators and ATRI staff will monitor the study procedures for this study for overall safety and scientific relevance on an ongoing basis. The local site PI (in conjunction with, as needed, the Medical Monitor and the data safety monitoring board (DSMB)) will evaluate each serious adverse event for safety and causality and will determine whether the adverse event affects the risk/benefit ratio of the study and whether modifications to the protocol or consent form are required.

8.5.6 SERIOUS ADVERSE EVENT REPORTING

Serious adverse events deemed related to the study compounds (e.g. PET tracers) or procedures by the Site PI or occurring within 2 days of PET tracer administration, regardless of causality, will be tracked during the study. Any serious adverse event meeting either requirement which occurs during the course of the investigation (i.e. any time after informed consent) or within 30 days of last study visit must be reported to the Medical Monitor at ATRI within 24 hours of learning of the event. ATRI Medical Safety team will generate an SAE report, which will be distributed to all participating sites and to the central IRB.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by ATRI's Medical Safety group and should be provided as soon as possible.

8.5.7 REPORTING EVENTS TO PARTICIPANTS

Study participants at an aggregate level will be informed by the Investigator or designated site clinician as deemed clinically necessary by ATRI.

8.5.8 EVENTS OF SPECIAL INTEREST

N/A

8.5.9 REPORTING OF PREGNANCY

Pregnancy is not an adverse event, but some studies will require unique considerations if pregnancy was to occur during the study. A participant who is enrolled in the TRC cohort who becomes pregnant can continue in the cohort but eligibility for enrollment in to a preclinical/prodromal AD trial will occur once pregnancy (and any interval of breast feeding) are complete.

8.6 UNANTICIPATED PROBLEMS

8.6.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

ATRI Coordinating Center staff will monitor the unanticipated problems for overall safety and scientific relevance on an ongoing basis and provide information to the Data Safety Monitoring Board.

8.6.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Coordinating Center via the AE eCRF. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the Coordinating Center within 24 hours of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB and to the Coordinating Center within 24 hours of the investigator becoming aware of the problem.
- All UPs should be reported by the site to appropriate institutional officials (as required by an institution's written reporting procedures), upon receipt of the report of the problem from the investigator.

8.6.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Participants will be informed by the Investigator or designated site clinician as deemed clinically necessary by the Coordinating Center.

8.7 GLOBAL UNIQUE IDENTIFIER

A Global Unique identifier (GUID) will be generated for each participant if permissible based on local and regional laws/requirements. A GUID provides a method to link collections of research data and specimens, balancing the competing goals of distinguishing individuals, collecting accurate information for matching, and protecting confidentiality. Certain personal identifying information (PII) is collected by the site and submitted to an algorithm to create the GUID, which will then be recorded in the CRF. The PII fields employed in this approach are invariant over the lifetime of the subject. This approach has proven to adequately discriminate individuals in both simulation and field studies (Johnson et al., 2010). Software will be provided to sites to generate the GUID using a standard algorithm so that the PII itself will not be submitted or stored centrally.

9 STATISTICAL CONSIDERATIONS

All statistical analyses will be based on a pre-specified statistical analysis plan (SAP). This plan will be informed by preliminary data analysis done mid-way during the study to identify the presence of potential sources of bias, including but not limited to the distribution and nature of the data, confounding effects, and amount and type of missing data. Each metric of interest will be initially assessed descriptively. For categorical data, we will use rates as the outcome measures, excluding the missing and unknown cases. For continuous data, parametric (one-sample t-test), non-parametric (Wilcoxon signed rank test) or resampling approaches (bootstrap or jackknife techniques) will be used, as appropriate. Comparisons between metrics from recent, current-technology trials and the TRC-PAD metrics will be made using 95% confidence intervals. A p-value of 0.05 will be used to conclude significant differences between the two study groups. For comparisons of metrics across different sub-groups of interest, t-tests, chi-square tests or resampling techniques will be used, as appropriate for the type (continuous, categorical) and distribution (normal, non-normal) of the data. Regression models (generalized linear models or generalized linear mixed models), as appropriate, will be used to examine associations of covariates of interest with the TRC-PAD metrics.

All statistical analyses will be conducted at the end of the grant cycle with all available data at the point of data cut-off date. Due to the exploratory nature of these aims, no adjustments will be made for multiple comparisons. However, data will be reported as point estimates and confidence intervals to provide the magnitude and variability around each of the estimates. All analyses will utilize R (*www.r-project.org*).

Statistical Aim 1: This approach will markedly accelerate recruitment timelines, shorten time to site activation for trials, and reduce unexplained variance in cognitive testing.

Analysis Plan: The use of adaptive approaches to participant selection, data capture and data monitoring will continually optimize the approach. At the end of the five years, formal tests of hypotheses will be conducted to assess the success of the web-based mechanisms by quantitative and qualitative analysis, in particular comparing timelines, cost, screen failure rates and the measured change and variance in cognitive scores to those in preclinical and prodromal studies for which similar data can be obtained. Two-sided, one-sample tests of means (recruitment timelines and time to site activation) or variances (variance in cognitive testing) or corresponding resampling techniques will be used to detect differences between the TRC-PAD sample and comparator data.

Power Analysis: Power analyses for these hypotheses were done using a two-sided, one-sample t-test for means and a one-sample test of variance using the software PASS. A reduction of 10% in mean recruitment timeline, mean time to site activation and unexplained variance in cognitive testing is considered scientifically meaningful. While the sample size selected was based on the need for a Cohort sufficiently large to support an efficacy trial, we have examined the power of this sample to test our hypotheses. 1. A sample size of 2000 participants achieves 90% power to detect a change as little as 3 days (3%) in recruitment timelines and time to site activation for trials,

assuming current estimates of 120+/-40 days respectively. 2 Estimates of baseline variability from completed AD trials range between 4.5 and 10 points in ADASCog11 score within a site. A sample size of 2000 participants achieves 90% power to detect a difference of at least 0.4 points (5% change) in unexplained standard deviation of cognitive scores, assuming a type I error rate of 5%. Thus, there is adequate power to detect very small differences and looking at multiple sub-groups of interest would not compromise power.

Statistical Aim 2: Once optimized, this algorithm will be able to select amyloid positive individuals (and eventually tau and other neurodegenerative biomarkers) with >75% accuracy, greatly reducing future costly biomarker screen fails.

Analysis Plan: Initial amyloid PET results will be compared to historical data from preclinical and prodromal studies for which similar data can be obtained and, for prodromal participants, published data from gantenerumab and avagacestat studies. Standard statistical methods (t-tests for continuous measures and chi-square tests for categorical measures) will be used to compare the participants identified as biomarker positive and biomarker negative. Associations between an indicator of biomarker positivity and each of the potential risk factors will be assessed in a two-staged manner using a generalized linear model with a logit-link function or a generalized linear mixed model for binary data (to account for the measurements over time for an individual participant). Univariate associations deemed to be statistically significant ($p < 0.15$) will be included in a multivariable logistic regression model. Potential confounding and effect-modifying variables will be included in the model as covariates, if necessary. The risk factors and the appropriate functional form of these factors that will be utilized in the model will be clearly stated in the SAP and will be based on the results of the preliminary analysis. An individual participant's predicted risk of biomarker positivity will be calculated using the final multivariable risk prediction model and serve as a risk-algorithm. The performance of this model will be assessed using four measures: the concordance index (c-index) to evaluate the discrimination ability, the calibration slope and calibration in the large to evaluate the model calibration, and decision-curve analysis to assess clinical usefulness. The model will be internally validated using 10-fold cross-validation and bootstrap sampling.

Power Analysis: Power analysis was done using a comparison of the area under a ROC curve (AUC) with a null hypothesis value of 0.75. Assuming a total sample size of 2000 participants and a 60% amyloid expected positivity rate, we have 90% power to detect an AUC of at least 0.80 using a two-sided z-test and a level of significance of 5%.

Statistical Aim 3: Baseline and longitudinal cognitive performance, (including lack of practice effect on repeated web-based cognitive tests), decline on performance based functional measures, and a combination of self- and study-partner report will predict and subsequently track with in-person measures of cognitive (PACC) and functional (CDR-SB) decline.

Analysis Plan: To assess the associations between web-based cognitive tests and in-person measures, linear mixed models will be used to accommodate the dependencies of scores over the follow-up time period. Such models accommodate different times of measurement, time varying and time invariant covariates as well as missed measurements and data from participants who are lost to follow-up. Permutation tests may be implemented to verify that valid p-values will be obtained even if model assumptions are not correct.

Power Analysis: Assuming a correlation coefficient of 0.6 as the true correlation between these measures, we have 90% power to observe a correlation as low as 0.67 with a sample size of 1000 participants and a type I error rate of 5%. Hence, the sample size will have adequate power to detect clinically meaningful associations between the web-based and in-person measures of decline.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Informed consent will be obtained in accordance with 45 CFR 46, 21CFR 50, 21 CFR Part 56 and in adherence to ICH GCP. Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and/or legally authorized representative (LAR) and written documentation of informed consent is required prior to starting study procedures.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that will be initiated prior to the individual's agreeing to participate in the study and will continue throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate if they wish. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. For participants with cognitive impairment, a legally authorized representative is allowed to provide consent on their behalf. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The informed consent will not only cover consent for the study itself, but broad sharing of all study data (including clinical, cognitive, imaging, biomarker and genetic data), as well as storage of biological samples for future research (genetic and biomarker samples). Consent forms will specify that genetic and biomarker samples are for research purposes only; the tests on the genetic and biomarker samples are not diagnostic in nature and participants will not receive results.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (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.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

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

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. 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 reviewing IRB, Institutional policies, or sponsor requirements.

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

CERTIFICATE OF CONFIDENTIALITY

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

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study, including audio recordings, will be analyzed and stored at the ATRI. After the study is completed, the archived study data will be transmitted to and stored at the ATRI, for use by other researchers including those outside of the study. Transition of all study data to the ATRI will be included in the informed consent.

With the participant's consent, biological samples will be stored at the ATRI Biospecimen Repository with the same goal as the sharing of data by the ATRI. These samples could be used to research the causes of AD and related neurodegenerative diseases, and its complications. The ATRI Biospecimen Repository 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 biospecimen 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 ATRI and the ATRI Biospecimen Repository.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator Project Director	**Principal Investigator**	**Principal Investigator**	**Medical Monitor**
Paul Aisen, MD	Reisa Sperling, MD	Jeffrey Cummings, MD	Michael Rafii, MD
ATRI USC	Brigham and Women's Hospital	University of Nevada Las Vegas	ATRI USC
9860 Mesa Rim Road San Diego, CA 92121 USA	60 Fenwood Road Boston, MA 02115 USA	4505 S Maryland Parkway Las Vegas, NV 89154-4022 USA	9860 Mesa Rim Road San Diego, CA 92121 USA
[redacted]	[redacted]	[redacted]	[redacted]

10.1.6 SAFETY OVERSIGHT

The Data Safety Monitoring Board (DSMB) is an independent group providing recommendations to the ATRI Director, study leadership and the NIA. No investigator involved in the study is a member of the DSMB.

The initial task of the DSMB will be to review the protocol to identify any necessary modifications. If modifications are necessary, revisions will be reviewed by the DSMB prior to its recommendation on initiation of the project. The DSMB, based on its review of the protocol, will work with the Coordinating Center personnel to identify the study-specific data parameters and format of the information to be regularly reported. All adverse events and serious adverse events will be reported to the DSMB. The DSMB and NIA representative will meet in person or by conference call on an annual basis. The DSMB may at any time request additional information from ATRI.

Based on the review of safety data, the DSMB will make recommendations regarding the conduct of the study. These may include amending safety monitoring procedures, modifying the protocol or consent, terminating the study or continuing the study as designed. Details of the process will be clearly described in the DSMB charter, finalized prior to study start.

10.1.7 CLINICAL MONITORING

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

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented beginning with the data entry system. Data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical study is conducted, data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

In accordance with ICH GCP, representatives of the Coordinating Center and/or regulatory agency may select this study for audit. The Investigator and study staff are responsible for maintaining the site master file containing all study-related regulatory documentation as outlined by Regulatory Affairs that will be suitable for inspection at any time by ATRI, its designees, and/or regulatory agencies. Inspection of site facilities (e.g., pharmacy, laboratories) to evaluate the study conduct and compliance with the protocol may also occur.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

ATRI is responsible for overseeing research clinical data collection and standardization, data management, data transfer, and quality control.

STUDY DATA COLLECTION AND STORAGE

Study data will be collected in the following ways:

- the Principal Investigator or designee will record data collected (either written or electronic record of data)
- the participant or study partner will complete assessments on paper

Written or electronic data of record must be entered on the electronic Case Report Form (eCRF) provided for that purpose, except where instructed 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 recorded directly on the eCRF is considered source data. The site will be suitably trained on the use of the eCRF and other computerized systems

used for data collection and appropriate site personnel will be authorized to provide electronic signatures. The Principal Investigator is responsible to verify the integrity of the data and acknowledge as such by signature.

All data will be collected in secure web sites or computer systems and the Principal Investigator will review the records for completeness. If corrections are necessary to the eCRFs or data collected via other systems, the Principal Investigator or designee will correct the data and provide documentation for the reason for change.

Sites will complete eCRFs and administer and submit data from computerized assessments according to ATRI's instructions. ATRI will review all data to determine their acceptability. If necessary, data correction requests will be generated for resolution by the study site.

STUDY FILES AND PARTICIPANT SOURCE DOCUMENTS

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

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

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

In the event that a participant revokes authorization to collect or use PHI, the 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.

RESEARCH BIOSPECIMENS AND GENETIC MATERIAL STORAGE

All research biospecimens, including DNA and other residual samples and derivatives from processing and analysis, will be coded and stored securely by the central research laboratories. Sample tubes will be identified only by a code number and descriptive data (such as the participant's age and gender). No other personal identifying information will be attached to the samples.

Samples collected from participants who do not consent to banking of those samples for future analysis will be destroyed after all protocol-related analyses are completed.

PET IMAGING DATA STORAGE

PET scans will be labeled according to each site's imaging machine capabilities using Participant ID and scanner specific series descriptions as detailed in the Technical Manual. All imaging data will be coded using participant identifiers as detailed in the Technical Manual and checked centrally to confirm the absence of participant identifying information.

10.1.9.2 STUDY RECORDS RETENTION

The investigator, institution or designated representative is responsible for retaining all study documents (including but not limited to essential documents and study records). Refer to your contract and institution for guidelines on duration of time study records should be retained. Coordinating Center approval is required prior to destruction of study records or offsite storage.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical study protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the 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.

The investigator may not implement any protocol deviation without prior notification to the Coordinating Center and prior review and documented approval of the IRB, except where necessary to eliminate an immediate hazard to study participants, or when change(s) involve only logistical or administrative aspects of the study (ICH 4.5.4).

10.1.11 PUBLICATION AND DATA SHARING POLICY

The results of this study will be published. To coordinate dissemination of data from this study, a publication committee will be formed. The committee will consist of the study PIs, the study biostatisticians, and others at the discretion of the ATRI Director.

SHARING OF STUDY DATA

Data from this research will be shared with other researchers pursuant to the 02/26/2003 "NIH Final Statement on Sharing Research Data" and pursuant to the 8/24/2014 "NIH Genomic Data Sharing Policy". The NIH policies can be found at:

http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html and
http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-124.html.

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

SHARING OF BIOSPECIMENS AND GENETIC MATERIAL

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

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

10.1.12 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.

10.1.13 DATA AND COORDINATING CENTER

The USC Alzheimer's Therapeutic Research Center (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 data management, clinical operations, clinical monitoring and regulatory oversight for this study.

All user and study data are stored and maintained on servers hosted on Amazon Web Services 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 1.0 and higher (Hypertext Transfer Protocol within a connection encrypted by Transport Layer Security) using secure 128 bit and stronger ciphers. 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.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

AD	Alzheimer's Disease
AE	Adverse Event
APOE/APOE4	Apolipoprotein E (APOE) epsilon 4 (APOE4)
APT	TRC-PAD Program: Alzheimer Prevention Trials Webstudy
ATRI	Alzheimer's Therapeutic Research Institute
CDR/CDR-SOB	Clinical Dementia Rating (CDR) Sum of Boxes (CDR-SOB)
CFI	Cognitive Function Index
CFR	Code of Federal Regulations
CNS	Central Nervous System
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CSF	Cerebrospinal Fluid
DNA	Deoxyribonucleic Acid
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GUID	Global Unique Identifier
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISO	International Organization for Standardization
LAR	Legally Authorized Representative
MedDRA	Medical Dictionary for Regulatory Activities
MR/MRI	Magnetic Resonance / Magnetic Resonance Imaging
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PET	Positron Emission Tomography
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
SAE	Serious Adverse Event

SUSAR	Suspected Unanticipated Serious Adverse Reaction
T	Tesla
TRC	TRC-PAD Program: In-Clinic Trial-Ready Cohort Study
TRC-PAD	Trial-Ready Cohort for Preclinical/Prodromal AD Trials Program
TSH	Thyroid Stimulating Hormone

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Overview of Changes	Brief Rationale
1.0	26NOV2018	Original	
2.0	14MAR2019	Revised screening and baseline procedures, including visit schedule, eligibility requirements, and options for use of prior testing for eligibility; clarified participant status while involved in a clinical trial; adjusted the definition of reportable AEs and SAEs; revised lab collection procedures and added location of central research specimen storage facility; added allowance for LAR to consent; updated information about coordinating center and data security; updated the name of the Medical Monitor	Study procedures being refined prior to study start.
3.0	15SEP2020	Allowing NAV-4694 tracer; Adding GUID; Removing C-SSRS; Removing ECG; Increase Sites to 50; Flexibility on out-of-window visits and phone visits due to COVID	Allowing a new tracer for amyloid PET scans for sites. Adding GUID for future linkage of participants in treatment trials, C-SSRS not required for this assessment, removing ECG and COVID disruptions increase need for out-of-window flexibility
4.0	14SEP2021	Typos and Formatting throughout document; Exclusion Criteria #1 was modified to include aducanumab; Change to screening visit window: Screening Stages 1 and 2 must be completed within a 60-day window and Screening stage 3 should be completed within 84 days of the start of screening activities	This will allow for central authorization to review blood plasma analysis
4.1	11NOV2022	Change to Navidea Dose from 8.1 mCi (300 MBq) (± 20%) to 8.1 mCi (300 MBq) (± 10%)	Providing a target dose of a single specified value

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