

Alzheimer's Disease Neuroimaging Initiative 4 (ADNI4): Remote Cohorts

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STATEMENT OF COMPLIANCE

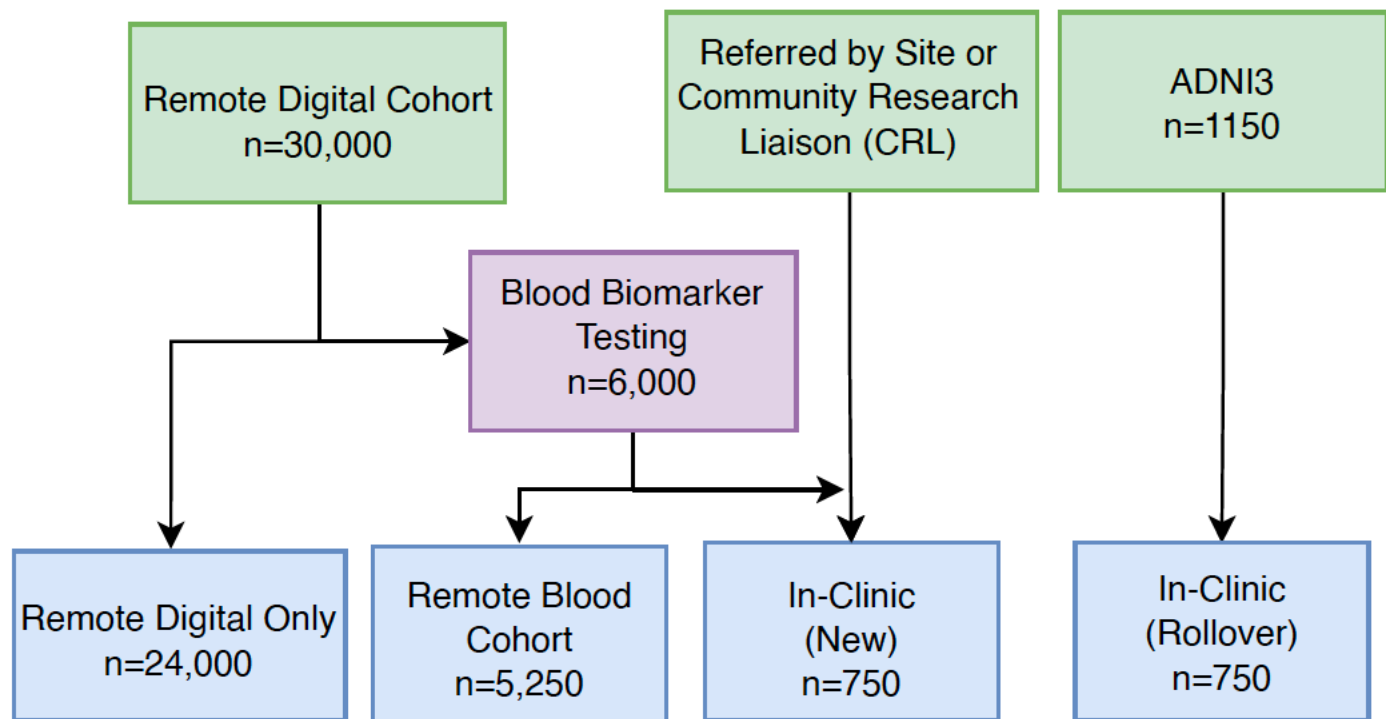
The study will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The investigator will assure that no deviation from, or changes to the protocol will take place without documented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

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

1.1 SYNOPSIS

Title:	Alzheimer's Disease Neuroimaging Initiative 4 (ADNI4): Remote Cohorts
Study Description:	Non-randomized, natural history, non-treatment study
Objectives:	<p>Primary Objectives:</p> <ul style="list-style-type: none"> • Validation of biomarker measures • Inform clinical trial design • Increased inclusion of underrepresented populations (URPs) to improve generalizability of results and advance our understanding of health disparities across URPs • Utilize web-based (remote) cognitive testing and blood-based biomarkers to remotely identify and monitor those with Alzheimer's Disease/Dementia biomarker pathology • Longitudinal changes in cognition and associated biomarkers • Prediction of cognitive decline • Discovery of other known disease proteins found in AD brains and genes
Study Population:	<p>Men and women aged 55-90 years across Cognitively Normal (CN), Mild Cognitive Impairment (MCI), and Dementia (DEM) populations.</p> <ul style="list-style-type: none"> • Remote Digital Cohort: Up to 30,000 participants will be enrolled into the remote digital cohort. • Remote Blood Cohort: Up to 6,000 participants will be enrolled into the remote blood cohort. • In-Clinic Cohort: Up to 750 new participants will be enrolled into the in-clinic cohort. Up to 750 will be rollover participants from ADNI3. Refer to ADNI4: In-Clinic Protocol.
Phase:	N/A
Descriptions of Sites/Facilities Enrolling Participants:	Centralized recruitment into the Remote Cohorts overseen by the Northern California Institute for Research and Education (NCIRE), University of California San Francisco (UCSF), University of Wisconsin and Fordham University. Remote cohorts will support referral and recruitment into the In-Clinic Cohort. Refer to In-Clinic Cohort protocol.
Description of Study Intervention:	N/A
Study Duration:	60 months
Participant Duration:	<ul style="list-style-type: none"> • Remote Digital Cohort: Participants who are not eligible to move to the remote-blood cohort will remain in the remote digital cohort for approximately 5 years. • Remote Blood Cohort: Participants who are not eligible to move to the in-clinic cohort will remain in the remote blood cohort for approximately 5 years.

1.2 SCHEMA



At every stage, Community Research Navigators (CRNs) are available to assist and provide information to all participants (via email, phone, online chat)

1.3 SCHEDULE OF EVENTS (SOE)

1.3.1 REMOTE DIGITAL COHORT

Task	Baseline	6 Mon ¹	12 Mon ¹	18 Mon ¹	24 Mon ¹	30 Mon ¹	36 Mon ¹	42 Mon ¹	48 Mon ¹	54 Mon ¹	60 Mon ¹
Collect Electronic Consent	X										
Self-Reported Demographic and Eligibility Questionnaire ^{2,3}	X										
12-Item ECog	X	X	X	X	X	X	X	X	X	X	X
Novoic Storyteller	X	X	X	X	X	X	X	X	X	X	X

¹Longitudinal participation in the remote digital cohort components after remote digital cohort baseline is optional for participants. Participants who indicate interest in longitudinal follow-up will be contacted via email every 6 months for up to 5 years after their baseline to repeat the cognitive assessments, 12-item ECog and Novoic Storyteller.

²Participants in the remote digital cohort will complete a questionnaire asking about demographics (age, gender, race and ethnicity, education, etc.) as well as questions on medical history that relate to eligibility for in-clinic cohort (metal in the body, claustrophobia, particular diseases that are exclusionary for ADNI4 in-clinic participation, etc.).

³Participants who provide a full address (optional) will have an Area Deprivation Index (ADI) measure included in their demographic profile

1.3.2 REMOTE BLOOD COHORT

Task	Baseline	6 Mon ¹	12 Mon ¹	18 Mon ¹	24 Mon ^{1,2}	30 Mon ¹	36 Mon ¹	42 Mon ¹	48 Mon ^{1,2}	54 Mon ¹	60 Mon ¹
Collect Electronic Consent	X										
Blood Draw ³ – Biomarker and Genetic Analysis	X				X				X		
12-Item ECog	X	X	X	X	X	X	X	X	X	X	X
Novoic Storyteller	X	X	X	X	X	X	X	X	X	X	X

¹ Participants who indicate interest in longitudinal follow-up will be contacted via email every 6 months for up to 5 years after their baseline to repeat the cognitive assessments, 12-item ECog and Novoic Storyteller.

² Participants who indicate interest in ongoing blood draws will provide a sample to Quest every other year after Baseline for up to 5 years.

³ Participants will have fasted for at least 6 hours prior to providing a blood sample.

1.3.3 IN-CLINIC COHORT REMOTE LONGITUDINAL MONITORING

All CN and MCI participants in the in-clinic cohort, whether rollover or newly enrolled, in the in-clinic cohort will be asked to complete the 12-Item ECog and the Novoic cognitive assessments remotely, via Ebisu.

Task	Baseline	6 Mon	12 Mon	18 Mon	24 Mon	30 Mon	36 Mon	42 Mon	48 Mon
12-Item ECog ¹	X ²	X	X ²	X	X ²	X	X ²	X	X ²
Novoic Storyteller ¹	X	X	X	X	X	X	X	X	X

¹Remote Assessments: Novoic and the 12-Item ECog will be collected remotely every 6 months through Ebisu. Participants who join the in-clinic portion of the study from the remote cohorts will remain on the same 6-month interval frequency for collecting Novoic and 12-Item ECog. New CN and MCI participants who did not go through the remote cohorts will be provided an information sheet with instructions for how to log into Ebisu and create a username and password before completing the Novoic and 12-item ECog remotely. All participants will be prompted via email and/or phone to complete these remote assessments every 6-months after their baseline timepoint. Note that the 12-item ECog is also collected in-clinic at every visit by the site coordinator (see the In-Clinic protocol).

2 INTRODUCTION

2.1 STUDY RATIONALE

ADNI plays a central role in improving treatment trials. Since the study's launch, ADNI Investigators with regulators in both the US and abroad have facilitated the design of major completed and ongoing drug trials. One of the most pressing challenges in the Alzheimer's Disease (AD) field, with immense scientific and ethical ramifications, is the chronic lack of ethnocultural, socio-economic, and educational diversity in research and trial populations, including in ADNI. ADNI4 aims to address this by enhancing recruitment of underrepresented populations (URPs). Another major challenge is the lack of efficient, scalable methods to identify cognitive impairment or those at risk for future impairment, in the population. ADNI4 addresses this using novel remote cohorts to assist with identifying, screening, and longitudinal monitoring of a large participant pool using remote, online cognitive assessments, and blood-based biomarker testing.

2.1.1 RATIONALE FOR EXPANDED URP OUTREACH AND USE OF REMOTE COHORTS IN ADNI4

Results from research and clinical trials, including ADNI, have been limited in their interpretive power due to relative homogeneity in the study populations, which typically are dominated by college educated whites individuals. To improve the generalizability of our data, ADNI4 will engage and recruit new participants, with the goal of 50-60% being from URPs. ADNI4 will use evidence-based, community-engaged methods to reach wider participant groups, and will integrate novel, scalable methods to identify and monitor participants across the study using remote digital cognitive testing and blood biomarker testing.

A large participant pool will be reached through community-engaged strategies including targeted online marketing, in order to recruit 30,000 individuals to join a remote digital cohort. These participants will complete a questionnaire and cognitive assessments, all of which is done remotely via ADNI4's web-based platform called Ebusu. The participants will self-report their personal histories as well as answer questions about subjective memory complaints and will complete cognitive assessments. The resulting data will help to identify approximately 6,000 individuals who will be asked to have blood tests to collect AD biomarker data. The remaining approximate 24,000 participants will remain in the remote digital cohort and be invited to complete remote cognitive assessments every six months, as individuals may subsequently become eligible to join the remote blood or in-clinic cohorts later into the ADNI4 study.

The baseline blood samples from 6,000 participants will be tested for AD biomarkers found in plasma as well as genetic data including APOE genotype, genome-wide association studies (GWAS), and more. The results from these analyses, in conjunction with the online data previously collected, will be used to select 750 participants for the in-clinic cohort. The 5,250 participants who had blood tests but who do not join the in-clinic cohort will be invited to participate in the remote blood cohort with longitudinal data collection, where they can provide a blood sample every other year to monitor potential changes to plasma biomarkers over time. Additionally, these participants will be invited to complete remote cognitive assessments every six months to allow for comparisons between changes in subjective and objective cognitive test results and plasma biomarkers over time.

Finally, 1,500 participants will join the in-clinic cohort for the full clinical battery (750 new participants and 750 rollovers from ADNI3). This includes remote cognitive assessments used for longitudinal monitoring. See the In-Clinic Cohort protocol.

2.2 BACKGROUND

Since its launch in 2004, the overarching aim of the Alzheimer's Disease Neuroimaging Initiative (ADNI) has been to validate biomarkers and procedures for Alzheimer's disease (AD) clinical trials. ADNI4 continues the previously funded ADNI1, ADNI-GO, ADNI2, and ADNI3 studies that have combined public/private collaborations between academia and industry to determine the relationships between the clinical, cognitive, imaging, genetic and biochemical biomarker characteristics of the entire spectrum of AD.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

For participants in the remote blood cohort, primary risks to participants include risks associated with traveling to a laboratory in the community for blood sample collection, and risk of venipuncture. Long-range risks for participants in both remote digital and remote blood cohorts may include risk of loss of privacy. These risks will be mitigated by communicating potential risks in each cohort's consent form, utilizing secure databases and coded participant identifiers.

2.3.1.1 STUDY PROCEDURES

2.3.1.1.1 Self-administered demographic and eligibility questionnaires

Participants in the remote digital cohort will complete a demography questionnaire (age, gender, race and ethnicity, education, etc.) as well as questions on medical history that relate to eligibility for in-clinic cohort (metal in the body, claustrophobia, particular diseases that are exclusionary for ADNI4 in-clinic participation, etc.).

2.3.1.1.2 Remote (Online) Cognitive Testing

Completing remote cognitive testing may cause some participants to become upset, frustrated, bored, or tired.

2.3.1.1.3 Blood Sample Collection

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

2.3.1.2 STUDY PARTICIPATION

2.3.1.2.1 Loss of Privacy

Participants in the remote digital cohort and remote blood cohort will be asked to self-report personal protected health information (PHI) such as name, date of birth, address, phone number, and email address. Participants will be assigned a study identification code for the data collected in the remote digital and blood cohorts. The collected data will be maintained on secure HIPAA compliant, cloud-based servers that are managed by ADNI Admin Core personnel. Study personnel will have access to participants' self-reported personal PHI such as name, date of birth, address, phone number, and emails. All study personnel with access to PHI will be up-to-date and compliant on all human subjects required trainings and certifications. Additionally, audio recordings of participants' voices will be collected for analysis of cognitive digital biomarkers using the Novoic Ltd. Testing Platform's Storyteller cognitive assessment, and audio files will be stored on secure, HIPAA compliant servers.

All deidentified data will be shared through the ADNI LONI website, with the exception of audio files which will not be available for download, but anonymized transcripts will be available. In order to obtain ADNI data, investigators must sign a "Data Use Agreement" which prohibits any attempts to identify the study participants. The agreement also prohibits any subsequent transfer of ADNI data.

2.3.2 KNOWN POTENTIAL BENEFITS

There are no individual benefits for research participants in this study. The results of this study may help future research become more efficient at identifying suitable candidates for intervention studies using biomarkers and may indirectly benefit people with a similar condition in the future.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

There is minimal risk associated with the procedures described in section 2.3.1. There is no direct benefit to participants; however, the knowledge gained will be beneficial to society in improving the risk for cognitive decline in older individuals; participants may be informed about opportunities to participate in clinical trials which may be benefit to them; participants may have access to new diagnostics that may be of benefit to them; the knowledge gained from participants in this study will help advance the field.

3 OBJECTIVES AND ENDPOINTS

ADNI4 will continue to discover, optimize, standardize, and validate clinical trial measures and biomarkers used in Alzheimer's Disease research. ADNI4 will address low rates of engagement and inclusion of underrepresented populations (URPs) in AD clinical cohorts. With the explosion of AD plasma biomarkers, ADNI4 will also expand its biorepository including remote blood collection and analyses for more participants. To achieve these aims, ADNI4 will use remote digital assessments to enroll up to 30,000 participants (remote digital cohort). Using information from these digital assessments, up to 6,000 participants will be selected for referral for blood tests (remote blood cohort). Based on the results of both the blood biomarkers and digital assessments, participants will be referred to the clinics. The ADNI4 in-clinic cohort will include 750 new participants (primarily referred using digital and blood test information) as well as up to 750 rollover participants from ADNI3 (total in-clinic cohort: up to 1500).

Aim 1: Validation of biomarker measures

Validate biomarker measures obtained at baseline and longitudinally by correlating results with "gold standard" clinical measurements and pathology. See In-Clinic Cohort protocol.

Aim 2: Inform clinical trial design

Determine the optimum outcome measures with attention to cognitive decline and tau/amyloid PET, predictors of cognitive decline, and inclusion/exclusion criteria for clinical trials of cognitively normal (CN) participants (for secondary preclinical AD trials), MCI patients (for prodromal AD trials) and participants with early dementia due to AD (DEM). See In-Clinic Cohort protocol.

Aim 3: Increased inclusion of underrepresented populations (URPs) to improve generalizability of results and advance our understanding of health disparities across URPs.

ADNI4 will recruit at least 50-60% URPs using community-engaged research strategies with culturally tailored outreach, including digital marketing. This will produce more generalizable data concerning the relationships of biomarkers and pathology to cognitive decline and dementia across ethnocultural groups.

Aim 4: Utilize web-based (remote) cognitive testing and blood-based biomarkers to remotely identify and monitor those with AD/Dementia biomarker pathology

Recent developments in plasma biomarkers for the AD pathophysiologic cascade have the potential to lower the cost of AD research, improve the feasibility of clinical trials, and vastly expand access to previously excluded groups. However, many of these novel analyses require further validation, and ADNI4 will contribute to this research by collecting blood samples from participants using local phlebotomy service centers. Blood will be analyzed for multiple AD biomarkers (amyloid, tau, APOE) and resulting data will be compared with other biomarker data (clinical/cognitive, MRI, PET, etc.) to help validate the utility of these biomarkers for future trials.

Aim 5: Longitudinal changes in cognition and associated biomarkers

Determine and define those measures of cognition and function, including composite measures, and biomarker measures, which capture longitudinal change with the highest statistical power to detect treatment effects in clinical trials. Longitudinal change of cerebral amyloid and tau measured with FBP, FBB, NAV4694, and FTP, MK6240, and PI2620, respectively, will be correlated/compared with other measures including use of novel plasma biomarkers. See In-Clinic Cohort protocol.

Aim 6: Prediction of cognitive decline

Determine which clinical, cognitive, and biomarker measures best predict cognitive decline in CN, MCI, and DEM participants. In addition, determine which biomarker changes correlate with cognitive decline, with a focus on plasma biomarkers, as well as amyloid and tau PET. See In-Clinic Cohort protocol.

Aim 7: Discovery of disease proteins found in DEM brains and genes

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

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a non-randomized, natural history, non-treatment study. In total, ADNI4 aims to enroll over 30,000 participants across the study cohorts: remote digital cohort, remote blood cohort, and in-clinic cohort. The remote digital cohort will enroll 30,000 participants to complete a personal history questionnaire and cognitive tests via an online study platform (Ebisu). From that group, 6,000 participants will be asked to provide blood samples for biomarker analyses (remote blood cohort). Finally, an in-clinic cohort will include 1,500 participants across 65 sites in the United States and Canada. Approximately 750 will be rollover participants from ADNI3, and 750 participants will be newly enrolled (primarily selected from those who completed both the remote digital and blood components of the study). The in-clinic cohort will be assessed using clinical/cognitive testing, imaging, biomarkers and genetics across 3 diagnostic groups: CN, MCI, and DEM. R

Visit frequency and assessments are outlined in more detail in Description of Study Visits and Schedule of Events.

4.1.1 SAMPLE SIZE BY COHORT

4.1.1.1 REMOTE DIGITAL COHORT

Using the community-engaged research strategies, we will enroll 30,000 participants into the remote digital cohort. ADNI4 aims to have 24,000 individuals from the remote digital cohort followed longitudinally. Participants will self-report via an online questionnaire (demographics, brief medical history related to exclusionary criteria for in-clinic participation) and complete cognitive assessments; the results of which will be used to determine eligibility and invitation for the remote blood cohort.

4.1.1.2 REMOTE BLOOD COHORT

6,000 participants (referred from the remote digital cohort) will be invited to join the remote blood cohort. This cohort will include at least 50-60% URPs, and individuals with and without cognitive complaints. ADNI4 aims to have 5,250 individuals from the remote blood cohort followed longitudinally. Blood samples from these 6,000 participants will be analyzed for AD biomarkers (plasma and genetic markers) and resulting data will be used in conjunction with demographic and cognitive assessment data (gathered through participation in remote digital cohort) to identify eligible participants and invite them to join the in-clinic cohort.

4.1.1.3 IN-CLINIC COHORT

Refer to In-Clinic Cohort protocol.

4.2 END OF STUDY DEFINITION

A participant is considered to have completed the study if they have completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Events (SoE), Section 1.3.

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

5 STUDY POPULATION

The study will enroll participants aged 55-90 years across the remote digital cohort and remote blood cohort, as specified in the entry criteria below. Exceptions to these guidelines may be considered on a case-by-case basis at the discretion of the project director and ADNI Clinical Core (see section 9.1.1).

5.1 INCLUSION CRITERIA

5.1.1 INCLUSION CRITERIA FOR THE REMOTE DIGITAL COHORT

All participants in the remote digital cohort must meet the following criteria:

1. Age is between 55-90 inclusive.
2. Willing and able to provide consent for remote digital data collection.
3. Must be literate and speak English or Spanish fluently.
4. Must be located within 150 miles of an ADNI4 clinical site.
5. Must have access to a computer or tablet or smartphone that is connected to the internet, whether at home, at a friend or family member's house, or at a local community center.
6. Study partners are optional for the remote digital cohort.

5.1.2 INCLUSION CRITERIA FOR THE REMOTE BLOOD COHORT

All participants in the remote blood cohort must meet the above criteria for the remote digital cohort and the following criteria:

1. Must be located in the continental USA (Quest Diagnostics Patient Service Centers are only located in USA).
2. Study partners are optional for the remote blood cohort. However, since the goal of the blood cohort is to identify participants to invite to the in-clinic cohort, participants with study partners will be given preference, and participants without study partners may be excluded on this basis.
3. Must have completed the remote digital cohort components (questionnaire and cognitive assessments).
4. The Administrative Core, described in section 9.1.1, will collaborate with leadership from all Cores to review the data from the remote digital cohort and select participants to join the remote blood cohort.

5.2 LIFESTYLE CONSIDERATIONS

5.2.1 LIFESTYLE CONSIDERATIONS FOR REMOTE DIGITAL COHORT

All participants in the remote digital cohort are required to:

- Have access to a computer or tablet or smartphone that is connected to the internet, whether at home, at a friend or family member's house, or at a local community center.

5.2.2 LIFESTYLE CONSIDERATIONS FOR REMOTE BLOOD COHORT

All participants in the remote blood cohort are required to:

- Fast for at least 6 hours prior to all blood draws.
- Have access to a computer or tablet or smartphone that is connected to the internet, whether at home, at a friend or family member's house, or at a local community center.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

In ADNI4, participants will be recruited to join the remote digital cohort that will provide a large, diverse participant pool from which a subset of participants can be referred to join the remote blood and in-clinic cohorts. The use of a remotely screened and longitudinally monitored participant pool (remote digital and blood cohorts) allows ADNI4 to identify participants who meet basic eligibility criteria for ADNI4 in-clinic participation and reducing the likelihood of clinical site screen failures. ADNI4 will build on the experience of online programs such as the Brain Health Registry and the Alzheimer Prevention Trials (APT) Web study to connect with a large number of potential participants. Further, the use of community-engaged research (CER) strategies as well as tailored marketing to reach diverse populations will allow greater engagement and recruitment of URPs. ADNI4 aims for new in-clinic enrollments to include 50-60% URPs.

This ambitious diversity goal will be achieved through the efforts of the new Engagement Core, described in detail in section 9.1.1.3.

Some of the ADNI clinical sites have the capability of enrolling monolingual Spanish speaking participants. For those sites, the ADNI study provides Spanish translation for both traditional and newly-developed instruments (e.g., questionnaires) for clinical trials. The translation process is designed to develop a single translation for use across the multiplicity of Spanish cultures represented in the U.S. population. Each instrument goes through an initial translation by a native Spanish speaker and is then back-translated by a panel of native speakers representing 3 to 5 different cultural origins. Discrepancies are reviewed by the panel and resolved by consensus. ADNI will not create new translations of previously validated Spanish-language measures.

5.3.1 INCLUSION OF WOMEN AND MINORITIES

This study will make every effort to maximize diversity of participants enrolling into the study, as there remains a lack of diversity in biomarker intensive clinical trials in aging and AD/dementia. All participants meeting the inclusion and exclusion criteria standards will be enrolled into the remote digital cohort, regardless of gender or race, but every effort will be made to actively recruit women and persons from Underrepresented Populations including Black or African American, Hispanic or Latino/a/x, Asian, Native Hawaiian/Other Pacific Islander, American Indian/Alaska Native adults and persons with less than 12 years of education. We are working to include at least 50-60% of newly enrolled participants will be URPs.

5.3.1.1 INCLUSION OF WOMEN

Based on the ADNI3 study, we anticipate that over 50% of the participants will be women. Female participants are expected to be over-represented in this age group (55-90), due to earlier mortality in men, and increased risk of AD, perhaps partially due to interaction between female sex and APOE e4 allele risk. Women of child-bearing potential are not eligible for this study.

5.3.1.2 INCLUSION OF MINORITIES

ADNI4 will strive to enroll at least 50-60% of newly enrolled participants from underrepresented populations (URPs) including Black or African American, Hispanic or Latino/a/x, Asian, Native Hawaiian/Other Pacific Islander, American Indian/Alaska Native adults and persons with less than 12 years of education. We are targeting that at least 50-60% of newly enrolled participants will be URPs. Historically, ADNI has failed to enroll representative populations, just as industry and academic trials have failed in this regard; only about 10% of participants have been from URPs. In ADNI3, broadly-based outreach efforts by the Diversity Taskforce increased diversity in the cohorts; 21% of new enrollees were from URPs.

ADNI4 will deploy a scalable, intensive, and culturally-informed CER approach, including tailored advertising and digital marketing, for recruiting 30,000+ individuals to participate in the remote digital cohort, with the ultimate goal of 50-60% of new in-clinic participants coming from underrepresented backgrounds. ADNI4 study teams will work together to facilitate the full and immersive participation of URPs in all study components. Our multi-faceted plan includes:

(1) Culturally informed, comprehensive CER-based digital marketing and engagement campaigns that will include multiple languages and diverse images;

(2) ADNI4 Engagement Core Team that will include:

2a) Community Research Liaisons (CRLs) to promote URP recruitment through community-based engagement with local clinicians and community-based organizations (CBOs). They will do screenings and triage eligible participants at the participating Diversity Recruitment Hub Sites (see In-Clinic Cohort protocol);

2b) Community Research Navigators (CRNs) to promote study engagement and retention by providing navigational assistance to all participants and study partners. CRNs will provide general 'help-desk' support and will communicate with participants via email, phone, or online chat to help troubleshoot any technological issues related to the remote cohort components (e.g., trouble logging in, issues with the online questionnaire and/or online cognitive testing, etc.), as well as assist participants with scheduling appointments for blood draws, and can assist with connecting participants with clinical site staff (such as following up on referrals from the remote digital to the remote blood cohort, and from the remote blood to the in-clinic cohort). CRNs will be available to help answer questions and assist all ADNI4 participants and study partners across their entire experience of the ADNI4 study.

(3) Community Partnerships (e.g., national and local CBOs) that will be facilitated through our Community-Science Partnership Board (CSPB). The CSPB will provide guidance and iterative feedback on: 3a) the recruitment/engagement of URP and low SES participants (e.g. research participation motivators/barriers, culturally-informed participant communications and comprehensive marketing effort, incentives, study implementation, troubleshooting). They will be involved in planning the strategies for recruitment and engagement, marketing efforts, and they will review all materials before implementation; 3b) training materials to ensure cultural competence of all investigators and staff; and 3c) the dissemination of study findings for both academic and community audiences.;

(4) Culturally-informed Sampling and Incentives to address barriers to URP recruitment/engagement (e.g., trust, burden) include: 4a) less restrictive inclusion/exclusion criteria and 4b) a new ADNI-wide system of consistent incentives (e.g., financial remuneration, disclosure of amyloid PET results); and

(5) Workforce Training to 5a) enhance cultural competency of all ADNI investigators and staff, and 5b) provide targeted mentored training to URP trainees and early career investigators utilizing ADNI data so they can conduct innovative dementia research.

6 DISCONTINUATIONS AND WITHDRAWALS

An investigator may withdraw a participant from the study at any time for safety or administrative reasons.

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

6.1 LOST TO FOLLOW-UP

6.1.1 REMOTE DIGITAL COHORT LOST TO FOLLOW-UP

The following actions must be taken if a participant in the remote digital cohort fails to complete ongoing study procedures:

- For participants in the remote digital cohort, upon starting a timepoint, participants have one month to finish all tasks (questionnaires and cognitive assessments) associated with that timepoint. Participants who do not complete all tasks within that standard timeframe will be contacted by study personnel. Study staff, including CRNs, will attempt contact three times to the participant by email (via CRNs and/or automated emails from the ADNI4 Ebisu system) and/or phone. Such participants will be considered temporarily inactive; however, may be recontacted by ADNI study staff in the future.

6.1.2 REMOTE BLOOD COHORT LOST TO FOLLOW-UP

The following actions must be taken if a participant in the remote blood cohort fails to complete ongoing study procedures:

- For participants in the remote blood cohort, study personnel will attempt to contact the participant if they fail to complete the steps for providing a blood sample (scheduling an appointment at a Quest patient service center). Study staff, including CRNs, will make every effort to regain contact with the participant (where possible, 3 telephone calls and/or emails from Ebisu system or CRNs). Should the participant continue to be unreachable, he or she will be considered temporarily inactive; however, may be recontacted by study staff in the future.

7.1 REMOTE DIGITAL COHORT VISITS

Remote “visits” via Ebusu will primarily be facilitated/prompted through email and/or phone communication to participants. Participants may also be supported by Clinical Research Navigators (CRNs) to help with questions or troubleshooting issues that participants may experience; CRNs will communicate with participants via phone, chat, or email. Participants may also be contacted and recruited to join the remote digital cohort by Clinical Research Liaisons (CRLs). CRLs will refer individuals to join the study via Ebusu, or will put individuals in contact with a CRN if they need help navigating or troubleshooting the digital tools recruitment website to register and participate in the remote digital cohort.

Follow-up “visits” for the remote digital cohort to return to Ebusu for longitudinal cognitive testing will be prompted via automated email from Ebusu and/or email or phone communication (by CRNs) to participants every six months after their initial baseline visit is completed, for the duration of the study or until a participant withdraws consent.

If participants identify a study partner/informant, that individual will be contacted via email and/or phone call to complete a baseline questionnaire about the participant. The study partner will be asked to return to Ebusu every 6 months to update their responses (prompted via email and/or phone communication). CRNs will be able to assist study partners with any questions, issues, or troubleshooting.

7.1.1 PRESCREENING / REGISTRATION VIA EBISU FOR REMOTE DIGITAL COHORT

Prior to providing consent, participants will be asked to provide their name and contact information (email and/or phone), month and year of birth, zip code, and create a username and password to register with Ebusu (online platform being used by ADNI) and to confirm basic eligibility.

7.1.2 BASELINE VISIT

Participants who register and consent via ADNI’s Ebusu platform (n=30,000) will be asked to complete a baseline questionnaire and cognitive assessments. Participants are encouraged to complete all components which include basic demographic questions, questions related to personal history including medical exclusionary criteria to indicate ineligibility for the ADNI4 in-clinic cohort, as well as the ECog 12-item and Novoic Ltd. Storyteller cognitive assessments.

At the baseline visit, participants in the remote digital cohort will:

1. Provide electronic consent.
2. Answer questions related to demographics and personal history, including medical exclusionary criteria to indicate ineligibility for the ADNI4 in-clinic cohort.
3. Identify Study Partner / Informant (optional). Participants can opt to identify a Study Partner/Informant and provide that persons’ email address and/or phone number.
4. Complete the ECog 12-item cognitive assessment.
5. Complete the Novoic Storyteller cognitive assessment.

For participants that identify a study partner/informant, the study partner is invited (via email or phone contact from a CRN) to register with Ebusu and provide electronic consent. From there, the study partner can complete questionnaires about the participant (informant version of the ECog 12-item).

We estimate 6,000 individuals who participate in the remote digital cohort will be referred to join the remote blood cohort based (see Section 7.2) on the data gathered in the remote digital cohort (demographics, responses to questionnaire including medical history, and results on cognitive assessments).

7.1.3 LONGITUDINAL VISITS

Participants who are not referred to the remote blood cohort (see section 7.2) will be followed longitudinally and will be asked every six months after their baseline visit to log into Ebusu to:

1. Complete the ECog 12-item assessment.
2. Complete the Novoic Storyteller assessment.

For participants that opted to identify a study partner/informant, study partners will be invited to return and update the informant version of the ECog 12-item every 6 months as well.

7.2 REMOTE BLOOD COHORT VISITS

The remote blood cohort (n=6,000) will provide a baseline blood sample by visiting a Quest Patient Service Center (Quest PSC). The biomarker and genetic data extracted from the blood samples will help with selecting 750 participants to join the in-clinic cohort. Participants who do not join the in-clinic cohort (n=5,250) will be invited to provide a blood sample every other year, as well as complete the ECog 12-item assessment and the Novoic Storyteller assessment via Ebusu twice annually. If a participant identified a study partner as part of their involvement in the remote digital cohort, that study partner will be contacted and invited to complete questionnaires about the participant (the ECog 12-item assessment) twice a year.

Remote “visits” via Ebusu will primarily be facilitated/prompted through email and/or phone communication to participants. Participants may also be supported by Clinical Research Navigators (CRNs) to help with questions or troubleshooting issues that participants may experience; CRNs will communicate with participants via phone, chat, or email. Participants may also be contacted and recruited to join the remote digital cohort by Clinical Research Liaisons (CRLs). CRLs will refer individuals to join the study via Ebusu, or will put individuals in contact with a CRN if they need help navigating the digital tools.

Follow-up “visits” for the remote blood cohort to return to Ebusu for longitudinal cognitive testing will be prompted via automated email from Ebusu and/or email or phone communication (by CRNs) to participants every six months after their initial visit is completed, for the duration of the study or until a participant withdraws consent.

If participants identify a study partner/informant, that individual will be contacted via email and/or phone call to complete a baseline questionnaire about the participant. The study partner will be asked to return to Ebusu every 6 months to update their responses (prompted via email and/or phone communication). CRNs will be able to assist study partners with any questions, issues, or troubleshooting.

7.2.1 BASELINE VISIT

At the baseline visit, those participants who are invited to join the remote blood cohort will:

1. Provide Electronic Consent.
2. Schedule a blood draw at a local Quest PSC.
3. Complete blood draw at a Quest PSC.
4. Complete the ECog 12-item and the Novoic Storyteller cognitive assessments via Ebusu if they did not complete these assessments within the past year.

7.2.2 LONGITUDINAL VISITS

Participants who return longitudinally will be asked every six months after their baseline visit to log into Ebusu to:

1. A follow-up blood draw every other year after the baseline visit.
2. Complete the ECog 12-item and the Novoic Storyteller cognitive assessments via Ebusu twice annually after the baseline visit (baseline visit date for these components is derived from their previous participation in the remote digital cohort).

7.3 REMOTE COGNITIVE ASSESSMENTS

The following assessments will be collected from all participants in the remote digital cohort, the remote blood cohort, and the in-clinic cohort every 6 months, remotely, on Ebusu.

7.3.1 MEASUREMENT OF EVERYDAY COGNITION 12-ITEM (12-ITEM ECOG)

Everyday Cognition (ECog) is a brief questionnaire assessing the participant’s capability to perform normal everyday tasks, in comparison to activity levels at their own understanding of their prior baseline, using a 5-point scale. Previous research on this instrument indicates that ECog correlates well with established measures of functional status and global cognition but only weakly

with age and education. ADNI4 will use the 12-item ECog⁴⁷ with language updates meant to improve generalizability across diverse groups⁴⁸. The assessment will be conducted in all remote and in-clinic cohorts at Baseline/Initial “visit” and subsequently every six months (via Ebisu). Study Partners will be asked to complete the corresponding informant version at the same time intervals (baseline and then every 6 months) also via Ebisu, but informant responses are not required.

7.3.2 NOVOIC – STORYTELLER

Novoic Ltd’s Storyteller assessment is an artificial intelligence-enhanced audio-verbal cognitive test with automated administration. The participant hears two stories and is asked to recall them in as much detail as possible. The participant completes a category fluency (animal naming) distraction task and finally is asked to repeat the first story they were told (similar to Wechsler Logical Memory II). The participant’s verbal responses are recorded and automatically analyzed for both recall performance and audio-linguistic biomarker features. The test is effective in discriminating between unimpaired and cognitively impaired individuals. Audio recordings are stored by Novoic Ltd. on HIPAA compliant servers located in the USA for the duration of the study. Audio recordings will be securely transferred for permanent storage on USA-based HIPAA compliant servers at the Laboratory of Neuro Imaging (LONI) (more details in section 9.9). Audio files will not be shared broadly via LONI, rather the written transcript (deidentified and containing no PHI) and subsequent derived data will be shared in a way that protects participant privacy at all times.

7.3.3 AREA DEPRIVATION INDEX (ADI)*

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

*ADNI study staff will include the ADI measurement for remote digital cohort participants who provide their full address, which is optional.

7.4 BIOSPECIMENS

7.4.1 BLOOD DRAW

7.4.1.1 REMOTE BLOOD COHORT

Participants in the remote blood cohort will be provided instructions via email and/or phone on how to schedule a blood draw at a local Quest PSC. Detailed instructions for the collection, processing, and shipping of blood samples are provided to Quest PSC phlebotomists via the Quest Test Code system (via ADNI4 Scope of Work in contract with Quest Diagnostics). Samples will be collected to accommodate the broadest range of biomarkers/analytes. Fasting overnight (minimum 6 hours) is required for plasma collection. Only water is permitted (no food but water is encouraged) until the blood draw is completed. Blood samples collected at Quest PSCs will be shipped to the ADNI4 laboratories at the University of Pennsylvania and Indiana University/NCRAD, see for biomarker and genetic analyses.

8.1 POPULATIONS FOR ANALYSES

The Biostatistics Core will carry out interim and final analyses of ADNI4 data, separately and in combination with previous phases, for the primary aims and hypotheses. Strategies for analysis goals are summarized briefly below.

We will use two main analytic datasets. First, the ADNI4 cohort (those recruited for ADNI4 combined with rollover participants from ADNI3) will provide information on cognitive and biomarker characteristics and change in all current measures. The newly recruited participants are critical to include a more diverse cohort. Second, we will also analyze merged data from all phases of ADNI, to facilitate analysis of progression and long-term trajectories. This will require harmonization of data collected from different protocols, assays, and tracers. All ADNI4 participants will be included in analyses except for those focused on hypotheses about specific subgroups, e.g. predictors of progression for participants who are MCI at baseline. Secondary analyses will assess the potential impact of missing data, outliers, and other questions regarding sensitivity and robustness of findings.

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

8.2 STATISTICAL ANALYSIS GOALS

Goal 1: To support the design of the ADNI4 cohorts, particularly the remote blood and in-clinic cohorts. Participant referrals will be informed by results from the remote digital cohort components (questionnaire, cognitive testing) and the plasma-based AD biomarkers to ensure sample diversity for those selected for in-clinic participation, to allow testing of hypotheses and to increase generalizability to a larger population.

Goal 2: Characterize baseline distribution of biomarkers and associations. Baseline characteristics will be summarized graphically and numerically, separately for baseline diagnostic categories (CN, MCI, DEM). Associations among biomarkers and with cognitive, clinical, and functional levels at baseline will be summarized numerically and graphically. Performance of baseline biomarkers as predictors of cognitive and functional change, disease progression, and post-mortem findings will be assessed by regression models (linear, logistic, survival, etc.).

Goal 3: Assess the potential of biomarkers for use in screening, inclusion/exclusion, stratification, and covariate adjustment for clinical trials. We will report and compare predictive abilities and impact on sample size, power, and duration of study in hypothetical clinical trials. To assess the explanatory power of a candidate biomarker, we will build models incorporating additional variables (demographics, genotype, baseline clinical or cognitive status, additional biomarkers). Sex as a biological variable will be considered both as a predictor and a potential effect modifier.

Goal 4: Characterize longitudinal trajectories of biomarkers and their associations. Longitudinal change in biomarkers will be characterized using linear mixed models for continuous measures, possibly transformed to deal with floor or ceiling effects, nonlinearity, practice effects, nonnormality, or heteroscedasticity. Extensions of these models allow for the simultaneous modeling of change in multiple outcomes for estimating correlation between change in multiple biomarkers or change in a biomarker with cognitive and functional change.

Goal 5: Assess the potential associations of comorbidities and sociocultural factors with biomarker, cognitive, and functional levels and longitudinal change. We hypothesize that ethnocultural differences will be associated with differences in baseline levels and longitudinal trajectories of biomarker, cognitive, and functional measures. This will be tested by building models as in Goals 1-4 and incorporating ethnocultural variables as primary predictors, while adjusting for age and sex. Initially the analysis will consider race/ethnicity separately from sociocultural variables, then models including both will be considered to examine intersectionality. Race/ethnicity will be included as categorical variables, while sociocultural variables (e.g., years of education, acculturation, SES) will as much as possible be included as quantitative or ordinal variables to maximize power.

Goal 6: Formally compare performance across biomarkers for all previous goals. Biomarker performance will be operationalized as a correlation (for predictor) or required sample size for a clinical trial (screening tool/outcome). Our comparison strategy first identifies dimension-free participant-level contributions to the correlation or to the formula for sample size. We compare biomarkers with Friedman's rank test to account for patient-level blocking, followed by pairwise comparisons adjusted for multiple comparisons.

9 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS.

9.1 KEY ROLES AND STUDY GOVERNANCE

The ADNI4 Study is funded by a grant to the Northern California Institute for Research and Education (NCIRE) and will utilize the Ebusu platform (overseen by the Admin Core) to gather data on participant activities collected in a remote setting, and the Alzheimer's Therapeutic Research Institute (ATRI) as the Data and Coordinating Center for in-clinic activities.

9.1.1 ADNI CORES

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

9.1.1.1 ADMINISTRATIVE CORE

The overall goal of the Administrative (Admin) Core is to ensure the success and impact of the entire ADNI study. The Admin Core developed and oversees the Ebusu platform used for data collection on the ADNI4 remote digital and remote blood cohorts as well as the remote longitudinal monitoring of in-clinic participants. The Admin Core will collaborate with leadership from all Cores to review the data from the remote digital cohort and select participants to join the remote blood cohort, and subsequently review the blood biomarker data from the remote blood cohort to invite participants to join the in-clinic cohort. The Admin Core will work closely with the Engagement Core and Clinical Core on tailored marketing and other culturally-engaged recruitment strategies to attract a wide diversity of participants to join the ADNI4 study, especially through joining the remote digital cohort.

9.1.1.2 CLINICAL CORE

The ADNI4 Clinical Core (including the Coordinating Center at the USC Alzheimer's Therapeutic Research Institute (ATRI)) will continue to oversee all in-clinic participant activities (refer to the ADNI4 In-Clinic Protocol), including clinical site start-up and monitoring, regulatory oversight and data management. All ADNI4 in-person data collection will utilize the ATRI Electronic Data System, with nightly uploads to LONI for sharing. Further, the Clinical Core will continue its investigations of the relationship among biomarker and cognitive/clinical data in the progression along the AD continuum, supporting therapeutic trial design.

9.1.1.3 ENGAGEMENT CORE

The Engagement Core will lead ADNI4's effort to increase the representation and engagement of participants from URPs into ADNI4 and other Alzheimer's disease and related dementias (ADRD) clinical trials more broadly. The Engagement Core will work closely with the Admin and Clinical Cores to deploy an evidence-based, community-engaged research approach to URP recruitment and retention, with the goal of assuring that 50-60% of new enrollees into ADNI are from a URP background. Critical to this effort, the Engagement Core will hire 20 Community Research Liaisons (CRLs) and 23 Community Research Navigators (CRNs). The CRLs will promote URP recruitment by liaising with Community-Based Organizations and community members; and conducting eligibility screenings and facilitating the referral process. The CRNs will promote continuous engagement, aimed at high retention of all ADNI4 participants. They will serve as guides, including a "help desk" function, to support up to 30,000 in the remote digital cohort, up to 6000 in the remote blood cohort, up to 750 rollover ADNI3 participants, up to 750 new in-clinic participants (or will refer to local site

staff) and all study partners through every step of the remote activities for the ADNI4 study. Moreover, the Engagement Core will work closely with all other Cores to assure participants immersive participation and consideration in all components of the ADNI study (e.g., Genetics, Neuropathology, Biostatistics). Additionally, the Engagement Core will deliver an array of training opportunities aimed at cultivating a diverse, culturally-competent ADRD workforce; and investigate the biological, psychological, and sociocultural factors that contribute to ADRD health disparities utilizing culturally-informed methods.

9.1.1.4 MRI CORE

The overall mission is to optimize and standardize MRI for AD clinical trials providing curated images and numeric summary values from a variety of multisite MRI modalities. Numeric summary values will be created by ADNI Core PIs for each sequence in each exam at every time point. ADNI4 anticipates that the emphasis on recruiting underrepresented groups will result in a higher prevalence of cerebral vascular disease (CVD) in comparison to prior ADNI cycles. The MRI Core will make a significant contribution in support of this new direction by greatly increasing emphasis on MRI measures of CVD. We plan a total of six CVD-related measures in ADNI4.

9.1.1.5 PET CORE

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

9.1.1.6 BIOMARKER CORE

The overall mission of the Biomarker Core is 24/7 management of the ADNI fluid repository and providing highly standardized analyses of AD biomarker analytes in CSF and plasma. The Biomarker Core will oversee the plasma analyses of the 6,000 samples from the remote blood cohort participants. The Biomarker Core will ensure timely data turnaround on those samples so as to provide AD biomarker results to the ADNI4 study to guide participant selection for invitation to join the ADNI4 in-clinic cohort. The Biomarker Core will continue to provide biofluid aliquot samples to investigators following review and approval of their study by the RARC as described in the documents on the ADNI/LONI website.

9.1.1.7 GENETICS CORE

The mission of the Genetics Core is to identify and validate genetic markers for use in drug discovery and clinical trials. APOE genotype contributes to clinical trial stratification and enrichment as it influences onset age, A β deposition/clearance, and susceptibility to adverse effects of anti-amyloid treatment. The Core will continue its focus on advances in genetics and related omics to discover, validate, and implement novel genetic markers that can improve the precision and power of AD clinical trials. The Genetics Core will oversee the genetic analyses of the 6,000 samples from the remote blood cohort participants. The Core will provide APOE genotype, polygenic risk scores, increase statistical power for all analyses, and include new phenotypes to enable novel questions. New bioinformatics strategies will be used to analyze the growing longitudinal multi-omics and multimodal endophenotype data. Enhanced recruitment of diverse populations will foster discovery of novel variants beyond those observed in participants of European ancestry.

9.1.1.8 NEUROPATHOLOGY CORE

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

9.1.1.9 BIOSTATISTICS CORE

The goal of the Biostatistics Core is to ensure that sound designs and statistical analyses are used to address the overall goal of ADNI4, which is to validate biomarkers for clinical trials. As ADNI's experts in biostatistical methods and the data across cores, we collaborate with all Cores/Project on design and analyses for each research theme and specific aim: harmonizing data across ADNI phases and technologies, characterizing change, identifying predictors, improving clinical trial design, and discovery.

9.1.1.10 INFORMATICS CORE

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

9.2 REGULATORY CONSIDERATIONS

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

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

9.3 INFORMED CONSENT

9.3.1 REMOTE DIGITAL COHORT INFORMED CONSENT

Potential participants will be directed to ADNI4's Ebusu landing page through online marketing campaigns or locally branded websites (specific to ADNI clinical sites). The landing page describes the study and invites them to participate. If interested, the individual can provide basic contact information (name, month and year of birth, zip code, email and/or phone) and create an account (username, password) with Ebusu. Once logged in, participants will see a longer description of the study and will be able to read the online Information Sheet (electronic informed consent form) where they will be asked to provide their consent by clicking either "I agree" or "I decline." Participants who decline to participate in the study will be automatically redirected to a 'Thank You for considering contributing to Alzheimer's Disease Research' webpage.

9.3.1 REMOTE BLOOD COHORT INFORMED CONSENT

Participants in the remote digital cohort who have completed all online components may be selected to join the remote blood cohort and provide a blood sample. These participants will receive an invitation, either through email or phone, describing this part of the ADNI4 study and inviting them to participate. If the participant is interested, they can use a link in the email to log into their Ebusu online account using their username and password. Once logged in, participants will see a longer description of the study and will be able to read the online Information Sheet (electronic consent form 2) where they will be asked to provide their consent by clicking either "I agree" or "I decline." If the participant is already logged into their Ebusu online account, they will be directed to the consent form after they indicate they are interested in the study. Participants who decline to participate in the remote blood cohort will be automatically redirected to a 'Thank You for considering contributing to Alzheimer's Disease Research' webpage and will be contacted every six months to complete online cognitive assessments (ECog 12-item and Novoic Storyteller) for the duration of the study or until a participant opts-out.

9.4 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by the Institutional Review Board (IRB) in the United States, and by local Independent Ethics Committees (IEC) / Research Ethics Boards (REB) in Canada, and functioning in accordance with International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 GCP, Section 3, and any local regulations. Any protocol amendment or revisions to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (e.g., change in clinical research associates [CRAs], change of telephone number[s]). Documentation of IRB compliance with ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor or designee.

Documented study approval from the IRB/IEC must be sent to the investigator (or if regionally required, the head of the medical institution) with a copy to the ATRI Coordinating Center before study start.

9.5 QUALITY ASSURANCE AND QUALITY CONTROL

Data collected from the ADNI4 participants via the Ebusu platform will be overseen and managed by the ADNI4 Administrative Core. The Admin Core will perform internal quality assurance including documentation review and completion, internal quality management of study data collection, and personnel training and documentation. The Admin Core will implement quality control (QC) procedures that cover the data entry system and include data QC checks to be run on the database. Admin Core personnel are responsible for maintaining the Ebusu platform and database in compliance with the protocol.

9.6 DATA HANDLING AND RECORD KEEPING

9.6.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES – EBISU

All data collected remotely for ADNI4 participants will be the responsibility of the ADNI4 Admin Core. The Admin Core will oversee all remote data collection via Ebusu, including data standardization, data management, data transfer, and quality control.

9.6.1.1 DATA COLLECTION AND STORAGE

Study data will be collected remotely in the following ways:

- via Ebusu (electronic record of data as well as audio recordings of speech)

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

9.6.1.1.1 Remotely Collected Data: Ebusu

In order to provide the data generated from this project to ADNI investigators, Pharmaceutical Industry scientists, and the public through LONI in an anonymized manner (free of any identifying information such as name, address, or phone number), this remotely collected data will be linked to the imaging database at LONI. The LONI database will be frequently updated, and all data acquired by the ADNI4 Ebusu platform will be provided to LONI at weekly intervals. No personal identifying data will be in this database. All the personal identifying data will be kept in a secure location (via secured servers for remotely collected data).

All study data collected by Ebusu are stored and maintained on servers hosted on Microsoft Azure and Amazon Web Services under Enterprise Agreements with University of California Office of the President (UCOP). Study data is not stored at NCIRE or UCSF facilities. All communication with the servers is encrypted. Access is controlled on a per-user basis and access logs are kept and monitored on an ongoing basis to ensure data security and integrity, keeping data protected from improper use and disclosure.

There is a slight risk that there could be a breach in the security of the system resulting in the access of information. However, safeguards are in place to minimize this risk.

All subjects will be assigned a code, and this will be used for all data storage and communication between study staff and sites. PHI will be recorded and kept under the “need to know” principle (i.e., only when necessary). The data key linking the participant personal information and participant study code numbers will only be available to a limited number of authorized study staff. The ADNI ATRI Coordinating Center does not have access to these keys. Electronic data are password protected and maintained on secure networks.

All data for remote components of ADNI4 will be transmitted securely via the Internet to ADNI4 Admin Core. Access to the Ebusu system is role-based and will be limited to key personnel in the Admin Core (NCIRE and UCSF) and Engagement Cores (University of Wisconsin and Fordham University). Access is granted to study team members based on role. Each user of the system has an individual account with a password that meets UCSF requirements (currently 12 characters, three character classes used, no

repeated characters, must change every 90 days). Users are logged out of the system after a period of inactivity. All communication to and from the data system is encrypted. Data security and redundant data backups are monitored by the Admin Core staff.

9.6.2 RESEARCH BIOSPECIMENS AND GENETIC MATERIAL STORAGE: IU/NCRAD

Blood samples from the remote cohorts will be maintained in the same ways as described in this section.

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

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

Specific procedures for requesting and accessing specimens will be created by the Resource Allocation Review Committee (RARC) of ADNI, as well as the Biospecimen Review Committee (BRC) at Indiana University, in accordance with recommendations proposed in the NBAC Human Biological Materials Report. These specimen guidelines have also been developed in accordance with the American Society for Human Genetics' position paper on the NBAC report and the Ad Hoc Committee on Stored Tissue of the College of American Pathologists.

9.6.3 COHORT BIOMARKER DATA AND MATERIAL STORAGE: UPENN

Blood samples from the remote cohorts will be maintained in the same ways as described in this section.

At the University of Pennsylvania (UPENN), the ADNI Biomarker Core has established and maintains a database for the inventory of stored samples in conjunction uses a bar code reading system. Bar code labels affixed to each sample vial contain a Global Specimen Number which is a unique number that when used with the LDMS sample tracking system provides the following information: sample ID# (to preserve confidentiality), date of collection and processing, total initial volume collected, sample type (plasma, serum, CSF), volume, aliquot number, freezer, shelf, rack, box, location in the box. A bar code label will be used on the sample tracking form. The database system, LDMS, is powered by Oracle and database version 11b resides on the University of Pennsylvania Healthcare System (UPHS) network under high-level protection with the UPHS Enterprise class perimeter firewall that includes a default deny policy. Access to LDMS has 4 layers of security: controlled building access, controlled laboratory access, PC password and LDMS password. VPN access is disabled so data is available only locally. The data is backed-up daily with 256-bit encryption and a copy is stored in a secure location.

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

9.7 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by all participating study staff, and their designees. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the information relating to participants. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the ADNI4 Admin Core.

Any data, specimens, forms, reports, and other records that leave the Admin Core data servers will be identified by a PTID to maintain confidentiality. Information will not be released without written permission of the participant, except as necessary for monitoring by the IRB/IEC, applicable health authority (FDA/HC), NIA, and OHRP.

At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the IRB/IEC, institutional policies, ADNI4 Admin Core, or Data and Coordinating Center and/or the regulatory sponsor requirements.

9.7.1 CERTIFICATE OF CONFIDENTIALITY

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

9.8 FUTURE USE OF STORED SPECIMENS AND DATA

After the study is completed, the archived data will continue to be stored at the Admin Core (for data collected via Ebusu), and may be made available for use by other researchers including those outside of the study. Transmission and storage of data via Ebusu/the Admin Core will be described in the informed consent. In addition, all data shared via LONI will continue to be available (see 9.9.2).

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

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

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

9.9 PUBLICATION AND DATA SHARING POLICY

9.9.1 PUBLICATION OF RESULTS

The results of this study will be published in accordance with the National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. A committee will be formed to coordinate dissemination of data from this study. The committee will consist of site PIs, study biostatisticians, and others at the discretion of the ATRI Director.

This study will comply with the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov.

9.9.2 SHARING OF STUDY DATA, BIOSPECIMENS, AND GENETIC MATERIAL

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

NIH believes that data sharing is important for further translation of research results into knowledge, products, and procedures to improve human health. The NIH endorses the sharing of research data to serve these and other important scientific goals. To protect participant's rights and confidentiality, only anonymized data will be shared.

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

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

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

Genetics, genomics, and related data will be shared with other researchers pursuant to the NIA Alzheimer’s Disease Genetics sharing policy. National Institute on Aging Genetics of Alzheimer’s Disease Data Storage Site (NIAGADS), along with other NIA-approved sites, will make genetic, genomic, and related data and associated phenotypic data available to qualified investigators in the scientific community for secondary analysis in accordance with standards established by the NIA. These data repositories are under strict security provisions, including multiple firewalls, separate servers, and data encryption protocols. Investigators and their sponsoring institutions seeking access to data from the NIA-approved data repository must submit a data access request (that specifies both the data to which access is sought and the planned research use) and agree to the terms of access set forth in the Data Use Certification. Investigators are approved by a Data Access Committee for access to specific datasets for a specific use(s).

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

9.10 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 trial. The study leadership in conjunction with the NIA has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRLs	Community Research Liaisons
CRNs	Community Research Navigators
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event

EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HC	Health Canada
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

11 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale
1.0	XXJul2022	Initial	

1. Donohue, M.C., et al., The relative efficiency of time-to-threshold and rate of change in longitudinal data. *Contemp Clin Trials*, 2011. **32**(5): p. 685-93.
2. Donohue, M.C., A.C. Gamst, and P.S. Aisen, Requiring an amyloid-beta1-42 biomarker for prodromal Alzheimer's disease or mild cognitive impairment does not lead to more efficient clinical trials. *Alzheimers Dement*, 2011. **7**(2): p. 245-6; author reply 247-9.
3. Donohue, M.C. and P.S. Aisen, Mixed model of repeated measures versus slope models in Alzheimer's disease clinical trials. *J Nutr Health Aging*, 2012. **16**(4): p. 360-4.
4. Donohue, M.C., et al., Estimating long-term multivariate progression from short-term data. *Alzheimers Dement*, 2014. **10**(5 Suppl): p. S400-10.
5. Aisen, P.S., et al., Report of the task force on designing clinical trials in early (predementia) AD. *Neurology*, 2011. **76**(3): p. 280-6.
6. Vellas, B., et al., Alzheimer's disease therapeutic trials: EU/US Task Force report on recruitment, retention, and methodology. *J Nutr Health Aging*, 2012. **16**(4): p. 339-45.
7. Bernick, C., et al., Age and rate of cognitive decline in Alzheimer disease: implications for clinical trials. *Arch Neurol*, 2012. **69**(7): p. 901-5.
8. Grill, J.D., et al., Effect of study partner on the conduct of Alzheimer disease clinical trials. *Neurology*, 2013. **80**(3): p. 282-8.
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10. Grill, J.D., et al., Comparing recruitment, retention, and safety reporting among geographic regions in multinational Alzheimer's disease clinical trials. *Alzheimers Res Ther*, 2015. **7**(1): p. 39.
11. Sperling, R.A., C.R. Jack, Jr., and P.S. Aisen, Testing the right target and right drug at the right stage. *Sci Transl Med*, 2011. **3**(111): p. 111cm33.
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14. Andrieu, S., et al., Prevention of sporadic Alzheimer's disease: lessons learned from clinical trials and future directions. *Lancet Neurol*, 2015. **14**(9): p. 926-44.
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16. Sano, M., et al., Adding delayed recall to the Alzheimer Disease Assessment Scale is useful in studies of mild cognitive impairment but not Alzheimer disease. *Alzheimer Dis Assoc Disord*, 2011. **25**(2): p. 122-7.
17. Sperling, R.A., et al., Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*, 2011. **7**(3): p. 280-92.
18. Sperling, R.A., et al., The A4 study: stopping AD before symptoms begin? *Sci Transl Med*, 2014. **6**(228): p. 228fs13.
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