

# Alzheimer's Disease Neuroimaging Initiative 4 (ADNI4): In-Clinic Cohort

Protocol Number: **ATRI-011-C**

National Clinical Trial (CT) Identified Number: **NCT05617014**

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Regulatory Sponsor: **University of Southern California**

Funded by: **National Institute on Aging**

Version Number: **v1.0**

**12 JUL 2022**

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## STATEMENT OF COMPLIANCE

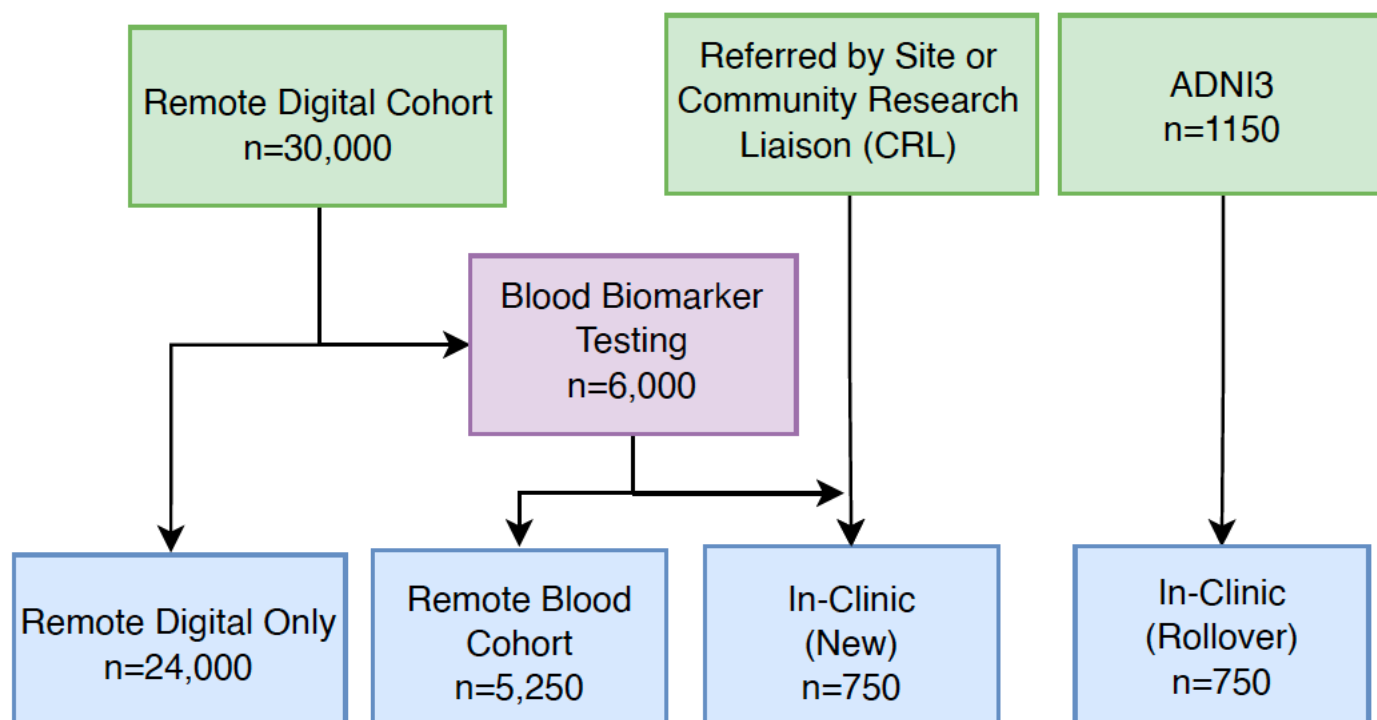
The study will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP) and applicable United States (US) Code of Federal Regulations (CFR). The investigator will assure that no deviation from, or changes to the protocol will take place without prior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

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

## 1.1 SYNOPSIS

|   |  |
|---|--|
| <b>Title:</b>   | Alzheimer's Disease Neuroimaging Initiative 4 (ADNI4): In-Clinic Cohort  |
| <b>Study Description:</b>                                       | Non-randomized, natural history, non-treatment study   |
| <b>Objectives:</b>  | <p>Primary Objectives:</p> <ul style="list-style-type: none"> <li>• Validation of biomarker measures</li> <li>• Inform clinical trial design</li> <li>• Increased inclusion of underrepresented populations (URPs) to improve generalizability of results and advance our understanding of health disparities across URPs.</li> <li>• Utility of web-based cognitive testing and blood-based biomarkers to remotely identify and monitor those with AD biomarker pathology</li> <li>• Longitudinal changes in cognition and associated biomarkers</li> <li>• Prediction of cognitive decline</li> <li>• Discovery of novel risk and protective genes and pathways, and other known disease proteins found in AD brains.</li> </ul> |
| <b>Study Population:</b>  | <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"> <li>• Up to 750 new participants will be enrolled into the in-clinic cohort. Up to 750 will be rollover participants from ADNI3.</li> </ul>  |
| <b>Phase:</b>   | N/A  |
| <b>Descriptions of Sites/Facilities Enrolling Participants:</b> | Approximately 65 sites across the United States and Canada   |
| <b>Description of Study Intervention:</b>                       | N/A  |
| <b>Study Duration:</b>  | 5 years  |
| <b>Participant Duration:</b>                                    | The participant journey from initial visit to final visit may last up to 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 NEWLY ENROLLED PARTICIPANTS (CN, MCI, DEM)

**CN participants** receive a phone check at Month 12 and Month 36. CN participants are seen in the clinic at Screening/Baseline and then biennially (every other year) at Month 24 and Month 48. Refer to the relevant study manual for a description of assessments conducted at phone checks.

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

**DEM** participants are seen in-clinic for 24 months from Baseline (total of 3 in-clinic visits at Baseline, Month 12, and Month 24) and then ongoing phone follow-up.

| ADNI4 Visit Activity                                       | Screening | Baseline | 12 Mon         | 24 Mon | 36 Mon           | 48 Mon         |
|--|-----------|----------|----------------|--------|------------------|----------------|
| Obtain consent   | X         |          |                |        |                  |                |
| Phone Check  |           |          | X <sup>1</sup> |        | X <sup>1,2</sup> | X <sup>2</sup> |
| GUID Creation  | X         |          |                |        |                  |                |
| Neuropath discussion/Provisional Registration <sup>3</sup> | X         | X        | X              | X      | X                | X              |
| Demographics, Family History, Medical History              | X         |          |                |        |                  |                |
| Inclusion and Exclusion Criteria                           | X         |          |                |        |                  |                |
| Physical Exam, Neurological Exam                           | X         |          | X              | X      | X                | X              |

|  |   |   |   |   |   |                |
|--|---|---|---|---|---|----------------|
| Vital Signs  | X | X | X | X | X | X              |
| Height   | X |   |   |   |   |                |
| Initial Labs (hematology, Chemistry panel, urinalysis, B12, TSH, HgbA1c, high sensitivity CRP) | X |   |   |   |   |                |
| Hollingshead Index Score   | X |   |   |   |   |                |
| Area Deprivation Index (ADI)   |   | X |   |   |   |                |
| Abbreviated Multidimensional Acculturation Scale (AMAS) <sup>4</sup>                           |   | X |   |   |   |                |
| American National Adult Reading Test (AMNART)  |   | X |   |   |   |                |
| Mini Mental State Examination (MMSE)   | X |   | X | X | X | X              |
| Logical Memory I and II  | X |   | X | X | X | X              |
| Montreal Cognitive Assessment (MoCA)   |   | X | X | X | X | X              |
| Category Fluency Test (CFT)  |   | X | X | X | X | X              |
| Trails A & B   |   | X | X | X | X | X              |
| Multi-Lingual Naming Test (MINT)   |   | X | X | X | X | X              |
| Auditory Verbal Learning Test  |   | X | X | X | X | X              |
| Geriatric Depression Scale (GDS)   | X |   | X | X | X | X              |
| Clock Drawing Test   |   | X | X | X | X | X              |
| Neuropsychiatric Inventory (NPI) / (NPI-Q for Phone Check)                                     |   | X | X | X | X | X              |
| ADAS-Cog 13 (w/Delayed Recall and Number Cancellation)   |   | X | X | X | X | X              |
| Clinical Dementia Rating (CDR)   | X |   | X | X | X | X              |
| Perceived Stress   |   | X | X | X | X | X              |
| Perceived Discrimination   |   | X | X | X | X | X              |
| Functional Assessment Questionnaire (FAQ)  |   | X | X | X | X | X              |
| 12-Item ECog (in-clinic) <sup>5</sup>  |   | X | X | X | X | X              |
| Plasma and Serum Biomarker Sample Collection <sup>6</sup>                                      |   | X | X | X | X | X              |
| PMBC Sample Collection <sup>6</sup>  |   | X |   |   |   |                |
| Lipid Panel <sup>6</sup>   |   | X |   |   |   |                |
| DNA Sample Collection <sup>6</sup>   |   | X |   |   |   |                |
| Ongoing Labs (HgbA1c, Cystatin C, Creatinine, BUN)   |   | X | X | X | X | X              |
| RNA and Buffy Coat Sample Collection <sup>6</sup>  |   | X | X | X | X | X              |
| Concomitant Medications  | X | X | X | X | X | X              |
| Adverse Events   | X | X | X | X | X | X              |
| Diagnostic Summary   | X | X | X | X | X | X              |
| Remote Assessments (Novoic Storyteller & 12-Item ECog) <sup>7</sup>                            |   | X | X | X | X | X              |
| Pregnancy Test <sup>8</sup>  |   | X |   | X |   | X              |
| 3T MRI Imaging <sup>9</sup>  | X |   | X | X | X | X              |
| Tau PET Imaging  |   | X |   | X |   | X <sup>2</sup> |
| Amyloid PET Imaging  |   | X |   | X |   | X <sup>2</sup> |
| LP Safety lab test: PT/PTT (coagulation profile) <sup>6,10</sup>                               |   | X |   | X |   | X              |
| CSF Collection by Lumbar Puncture (LP) <sup>6,11</sup>   |   | X |   | X |   | X              |

<sup>1</sup>**CN participants** receive a phone check at Month 12 and Month 36. CN participants are seen in the clinic at Screening/Baseline and then biennially (every other year) at Month 24 and Month 48. Refer to the relevant study manual for a description of assessments conducted at phone checks.

<sup>2</sup>**DEM participants** are seen in-clinic for 24 months from Baseline (total of 3 in-clinic visits at Baseline, Month 12, and Month 24) and then ongoing phone follow-up.

<sup>3</sup>**Neuropath discussion** to confirm registration/interest should occur every 6 months or, at minimum, annually and at



every clinic visit. If a participant has refused to register, no further inquiry should take place.

<sup>4</sup>**AMAS** will only be given to participants who self-identify as Latinx/a/o.

<sup>5</sup>**12-item ECog** will be collected at every in-clinic visit for all participants. This in-clinic assessment will be uploaded/entered to the EDC. This assessment is collected by the site coordinator in-clinic in addition to the remote collection by the participant as noted in footnote #7.

<sup>6</sup>**Fasting requirement** for biospecimens including LP, plasma/serum, DNA, RNA, and Buffy Coat is a minimum of 6 hours.

<sup>7</sup>**Remote Assessments: Novoic Storyteller 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 register with Ebisu and create a username and password before completing the Novoic and 12-item ECog remotely. CN and MCI participants will be prompted via email and/or phone to complete these remote assessments every 6-months after their baseline timepoint.

<sup>8</sup>**Pregnancy test** must be collected for all female participants, who are not post-menopausal, before every PET scan. Pregnancy test may be conducted at the scanning site.

<sup>9</sup>**MRI** to be conducted at every in-clinic visit for all participants.

<sup>10</sup>**PT/PTT** test is an optional procedure at the discretion of PI or Site Clinician

<sup>11</sup>**LP** is an optional procedure for all participants.

### 1.3.2 CN, MCI, DEM ROLLOVERS WHO **DID NOT** HAVE A FULL CLINIC VISIT IN THEIR FINAL YEAR IN ADNI3

A full clinic visit in the final year of ADNI3 is defined as having completed at least the following activities:

- CDR
- ADAS-Cog
- MMSE
- Logical Memory I and II
- Concomitant Medications
- Adverse Events
- Diagnostic Summary
- PET Scans; either Tau or Amyloid

If these activities were not completed, their last ADNI3 visit should not be defined as a full clinic visit. Table 1.3.2.1 below describes the activities that are to occur at every in-clinic visit for every rollover participant without a full clinic visit in their final year in ADNI3.

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

**Table 1.3.2.1**

| ADNI4 Visit Activity                                       | Initial <sup>1</sup> | 12 Mon         | 24 Mon | 36 Mon            | 48 Mon          |
|--|----------------------|----------------|--------|-------------------|-----------------|
| Obtain consent   | X                    |                |        |                   |                 |
| GUID Creation  | X                    |                |        |                   |                 |
| Phone Check  |                      | X <sup>2</sup> |        | X <sup>2,11</sup> | X <sup>11</sup> |
| Neuropath discussion/Provisional registration <sup>3</sup> | X                    | X              | X      | X                 | X               |
| Demographics, Family History, Medical History              | X                    |                |        |                   |                 |
| Inclusion and Exclusion Criteria                           | X                    |                |        |                   |                 |
| Physical Exam, Neurological Exam                           | X                    | X              | X      | X                 | X               |
| Vital Signs  | X                    | X              | X      | X                 | X               |
| Hollingshead Index Score                                   | X                    |                |        |                   |                 |
| Height   | X                    |                |        |                   |                 |
| Area Deprivation Index (ADI)                               | X                    |                |        |                   |                 |
| American National Adult Reading Test (AMNART)              | X                    |                |        |                   |                 |
| Abbreviated Multidimensional Acculturation                 | X                    |                |        |                   |                 |

|  |                   |   |   |   |   |
|--|-------------------|---|---|---|---|
| Scale (AMAS) <sup>4</sup>  |                   |   |   |   |   |
| Initial Labs (hematology, Chemistry panel, urinalysis, B12, TSH, HgbA1c, high sensitivity CRP) | X                 |   |   |   |   |
| Mini Mental State Examination (MMSE)   | X                 | X | X | X | X |
| Remote Assessments (Novoic Storyteller and 12-item ECog) <sup>5</sup>                          | X                 | X | X | X | X |
| Logical Memory I and II  | X                 | X | X | X | X |
| Montreal Cognitive Assessment (MoCA)   | X                 | X | X | X | X |
| Category Fluency (Animals)   | X                 | X | X | X | X |
| Trails A & B   | X                 | X | X | X | X |
| Multi-Lingual Naming Test (MINT)   | X                 | X | X | X | X |
| Auditory Verbal Learning Test  | X                 | X | X | X | X |
| Geriatric Depression Scale   | X                 | X | X | X | X |
| Clock drawing  | X                 | X | X | X | X |
| Neuropsychiatric Inventory (NPI) / (NPI-Q for Phone Check)                                     | X                 | X | X | X | X |
| ADAS-Cog 13 (w/Delayed Recall and Number Cancellation)   | X                 | X | X | X | X |
| Clinical Dementia Rating Scale   | X                 | X | X | X | X |
| Perceived Stress   | X                 | X | X | X | X |
| Perceived Discrimination   | X                 | X | X | X | X |
| Functional Assessment Questionnaire (FAQ)  | X                 | X | X | X | X |
| 12-Item ECog (in-clinic) <sup>6</sup>  | X                 | X | X | X | X |
| Plasma and Serum Biomarker Sample Collection <sup>7</sup>                                      | X                 | X | X | X | X |
| DNA Sample Collection <sup>7</sup>   | X                 |   |   |   |   |
| Lipid Panel <sup>7</sup>   | X                 |   |   |   |   |
| Ongoing Labs (HgbA1c, Cystatin C, Creatinine, BUN)   |                   | X | X | X | X |
| PBMC Sample Collection <sup>7,8</sup>  | X                 |   |   |   |   |
| RNA and Buffy Coat Sample Collection <sup>7</sup>  | X                 | X | X | X | X |
| Concomitant Medications  | X                 | X | X | X | X |
| Adverse Events   | X                 | X | X | X | X |
| Diagnostic Summary   | X                 | X | X | X | X |
| Pregnancy Test <sup>9</sup>  | X                 |   | X |   | X |
| 3T MRI Imaging   | X                 | X | X | X | X |
| Tau PET Imaging  | X <sup>2,10</sup> |   | X |   | X |
| Amyloid PET Imaging  | X <sup>2,10</sup> |   | X |   | X |
| LP Safety lab test: PT/PTT (coagulation profile) <sup>7,12</sup>                               | X                 |   | X |   | X |
| CSF Collection by Lumbar Puncture (LP) <sup>7,13</sup>   | X                 |   | X |   | X |

<sup>1</sup>Rollovers do not need a screening visit.

<sup>2</sup>For rollover participants in the CN cohort, clinic visits are to occur every other year with phone checks on the alternate years. If they did not have either an Amyloid or Tau PET scan during their last year of ADNI3, then they will have PET scans at their first visit in ADNI4.

<sup>3</sup>Neuropath discussion to confirm registration/interest should occur every 6 months or, at minimum, annually and at every clinic visit. If a participant has refused to register, no further inquiry should take place.

<sup>4</sup>AMAS will only be given to participants who self-identify as Latinx/a/o.

<sup>5</sup>Novoic Storyteller and the 12-Item ECog will be collected remotely from CN and MCI participants every 6 months through Ebusu. Rollover participants (CN and MCI only) will be provided an information sheet with instructions for how to register for Ebusu, remotely, 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.

<sup>6</sup>12-item ECog will be collected at every in-clinic visit for all participants. This in-clinic assessment will be

uploaded/entered to the EDC. This assessment is collected by the site coordinator in-clinic in addition to the remote collection by the participant as noted in footnote #5.

<sup>7</sup>**Fasting requirement** for biospecimens including plasma/serum, DNA, RNA, Buffy Coat, and the optional LP is a minimum of 6 hours.

<sup>8</sup>**PMBC Sample** should only be collected once from any rollovers who have not yet had this sample collected in ADNI3.

<sup>9</sup>**Pregnancy test** must be collected for all female participants, who are not post-menopausal, before every PET scan. Pregnancy test may be conducted at the scanning site.

<sup>10</sup>**For rollover participants in the MCI and DEM cohorts**, clinic visits occur annually with Amyloid and Tau PET scans every other year. All rollover participants in the MCI and DEM cohorts have a clinic visit for their first year of ADNI4. However, if they had either an Amyloid or Tau PET scan during their last year of ADNI3, then they will not have PET scans at their first visit in ADNI4.

<sup>11</sup>**Rollover participants enrolled into the DEM cohort** will be followed for a total of 24 months with 3 clinic visits: Initial, 12 months, 24 months. After that, they will be followed by phone.

<sup>12</sup>**PT/PTT** test is an optional procedure at the discretion of PI or Site Clinician.

<sup>13</sup>**LP** is an optional procedure for all participants.

### 1.3.3 CN, MCI, DEM ROLLOVERS WHO DID HAVE A FULL CLINIC VISIT IN THEIR FINAL YEAR IN ADNI3

A full clinic visit in the final year of ADNI3 is defined as having completed at least the following activities:

- CDR
- ADAS-Cog
- MMSE
- Logical Memory I and II
- Concomitant Medications
- Adverse Events
- Diagnostic Summary
- PET Scans; either Tau or Amyloid

If these activities were not completed, their last ADNI3 visit should not be defined as a full clinic visit. Table 1.3.3.1 below describes the activities that are to occur at every in-clinic visit for every rollover participant with a full clinic visit in their final year in ADNI3.

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

**Table 1.3.3.1**

| ADNI4 Visit Activity   | Initial <sup>1</sup> | 12 Mon         | 24 Mon | 36 Mon            | 48 Mon          |
|--|----------------------|----------------|--------|-------------------|-----------------|
| Obtain consent   | X                    |                |        |                   |                 |
| Phone Check  |                      | X <sup>2</sup> |        | X <sup>2,11</sup> | X <sup>11</sup> |
| GUID Creation  | X                    |                |        |                   |                 |
| Neuropath discussion/ Provisional registration <sup>3</sup>                                    | X                    | X              | X      | X                 | X               |
| Demographics, Family History, Medical History  | X                    |                |        |                   |                 |
| Inclusion and Exclusion Criteria   | X                    |                |        |                   |                 |
| Physical Exam, Neurological Exam   | X                    | X              | X      | X                 | X               |
| Vital Signs  | X                    | X              | X      | X                 | X               |
| Hollingshead Index Score   | X                    |                |        |                   |                 |
| Height   | X                    |                |        |                   |                 |
| American National Adult Reading Test (AMNART)  | X                    |                |        |                   |                 |
| Area Deprivation Index (ADI)   | X                    |                |        |                   |                 |
| Abbreviated Multidimensional Acculturation Scale (AMAS) <sup>4</sup>                           | X                    |                |        |                   |                 |
| Initial Labs (hematology, Chemistry panel, urinalysis, B12, TSH, HgbA1c, high sensitivity CRP) | X                    |                |        |                   |                 |

|   |   |   |   |   |   |
|---|---|---|---|---|---|
| Mini Mental State Examination (MMSE)                                  | X | X | X | X | X |
| Remote Assessments (Novoic Storyteller and 12-item ECog) <sup>5</sup> | X | X | X | X | X |
| Logical Memory I and II   | X | X | X | X | X |
| Montreal Cognitive Assessment (MoCA)                                  | X | X | X | X | X |
| Category Fluency (Animals)  | X | X | X | X | X |
| Trails A & B  | X | X | X | X | X |
| Multi-Lingual Naming Test (MINT)                                      | X | X | X | X | X |
| Auditory Verbal Learning Test   | X | X | X | X | X |
| Geriatric Depression Scale  | X | X | X | X | X |
| Clock drawing   | X | X | X | X | X |
| Neuropsychiatric Inventory (NPI) / (NPI-Q for Phone Check)            | X | X | X | X | X |
| ADAS-Cog 13 (w/Delayed Recall and Number Cancellation)                | X | X | X | X | X |
| Clinical Dementia Rating Scale  | X | X | X | X | X |
| Perceived Stress  | X | X | X | X | X |
| Perceived Discrimination  | X | X | X | X | X |
| Functional Assessment Questionnaire (FAQ)                             | X | X | X | X | X |
| 12-Item ECog (in-clinic) <sup>6</sup>                                 | X | X | X | X | X |
| Plasma and Serum Biomarker Sample Collection <sup>7</sup>             | X | X | X | X | X |
| DNA Sample Collection <sup>7</sup>                                    | X |   |   |   |   |
| Lipid Panel <sup>7</sup>  | X |   |   |   |   |
| Ongoing Labs (HgbA1c, Cystatin C, Creatinine, BUN)                    |   | X | X | X | X |
| PBMC Sample Collection <sup>7,8</sup>                                 | X |   |   |   |   |
| RNA and Buffy Coat Sample Collection <sup>7</sup>                     | X | X | X | X | X |
| Concomitant Medications   | X | X | X | X | X |
| Adverse Events  | X | X | X | X | X |
| Diagnostic Summary  | X | X | X | X | X |
| 3T MRI Imaging  | X | X | X | X | X |
| Pregnancy Test <sup>9</sup>   |   | X |   | X |   |
| Amyloid PET Scan <sup>10</sup>  |   | X |   | X |   |
| Tau PET Scan <sup>10</sup>  |   | X |   | X |   |
| CSF Collection by Lumbar Puncture (LP) <sup>7,12</sup>                |   | X |   | X |   |
| LP Safety lab test: PT/PTT (coagulation profile) <sup>7,13</sup>      |   | X |   | X |   |

<sup>1</sup>Rollovers do not need a Screening visit.

<sup>2</sup>For rollover participants in the CN cohort, clinic visits are to occur every other year with phone checks on the alternate years. If a rollover participant in the CN cohort had either an Amyloid or Tau PET scan during their last year of ADNI3, then they will have a phone check for the first year of ADNI4.

<sup>3</sup>Neuropath discussion to confirm registration/interest should occur every 6 months or, at minimum, annually and at every clinic visit. If a participant has refused to register, no further inquiry should take place.

<sup>4</sup>AMAS will only be given to participants who self-identify as Latinx/a/o.

<sup>5</sup>Novoic Storyteller and the 12-Item ECog will be collected remotely from CN and MCI participants every 6 months through Ebisu. Rollover participants (CN and MCI only) will be provided an information sheet with instructions for how to log into Ebisu (when participant is at home) 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.

<sup>6</sup>**12-item ECG** will be collected at every in-clinic visit for all participants. This in-clinic assessment will be uploaded/entered to the EDC. This assessment is collected by the site coordinator in-clinic in addition to the remote collection by the participant as noted in footnote #5.

<sup>7</sup>**Fasting requirement** for biospecimens including plasma/serum, DNA, RNA, Buffy Coat, and the optional LP is a minimum of 6 hours.

<sup>8</sup>**PMBC Sample** should only be collected once from any rollovers who have not yet had this sample collected in ADNI3.

<sup>9</sup>**Pregnancy test** must be collected for all female participants, who are not post-menopausal, before every PET scan. Pregnancy test may be conducted at the scanning site.

<sup>10</sup>**For rollover participants in the MCI and DEM cohorts**, clinic visits occur annually with Amyloid and Tau PET scans every other year. All rollover participants in the MCI and DEM cohorts have a clinic visit for their first year of ADNI4. However, if they had either an Amyloid or Tau PET scan during their last year of ADNI3, then they will not have PET scans at their first visit in ADNI4.

<sup>11</sup>**Rollover participants enrolled into the DEM cohort** will be followed for a total of 24 months with 3 clinic visits: Initial, 12 months, 24 months. After that, they will be followed by phone.

<sup>12</sup>**LP** is an optional procedure for all participants.

<sup>13</sup>**PT/PTT** test is an optional procedure at the discretion of PI or Site Clinician.

## 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 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 white 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 assessments and blood biomarker testing, see ADNI4: Remote protocol for more information on remote digital cohort and remote blood cohort.

1,500 participants will join the in-clinic cohort for the full clinical battery (750 new participants and 750 rollovers from ADNI3). This includes clinical/cognitive assessments, 3T MRI and collection of plasma and serum for biomarkers that will be conducted annually for MCI and AD, and biennially for CN. Blood samples will be collected for peripheral blood mononuclear cell (PBMC) banking for genetic analysis at the Baseline Visit for new participants, and at the Initial Visit for rollover participants (if not previously obtained). In addition, blood will be collected for longitudinal DNA and RNA genetic analyses at follow-up clinical visits. Amyloid PET imaging, tau PET imaging, and CSF collection for biomarkers will occur biennially for all participants.

This project will collect MRI (structural, diffusion weighted imaging, perfusion, and resting state sequences, as well as collecting six cerebral vascular disease measures); amyloid PET using one of the following tracers, florbetapir F18 (FBP), florbetaben F18 (FBB), or NAV4694 F18; tau PET using one of the following tracers, flortaucipir F18 PET (FTP), MK6240 F18, or PI2620 F18; CSF for A $\beta$ , tau, phosphorylated tau, and other proteins; plasma biomarkers including A $\beta$ 42/40 and ptau isoforms; and genetic and autopsy data to determine the relationship of these biomarkers to baseline clinical status and cognitive decline.

## 2.2 BACKGROUND

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

## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 KNOWN POTENTIAL RISKS

Alzheimer's disease (AD) is currently an irreversible neurodegenerative condition that over time causes progressive deterioration in a person's cognitive, emotional, and behavioral functioning. In addition, AD is widely known as a highly disabling illness and a diagnosis can carry stigma affecting both the participant and family. Accordingly, participants who enroll in the study may be vulnerable to psychological reactions and issues if they progress to varying and more advanced stages of AD. Such psychological reactions and issues may range from very mild symptoms of depression and anxiety to more serious psychopathology, including agitation, major depression, and suicidal ideation and actions.

## 2.3.1.1 STUDY PROCEDURES

### 2.3.1.1.1 Clinical, Cognitive, Neuropsychological Testing

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

### 2.3.1.1.2 Imaging

#### **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).

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

- Florbetaben (Neuraceq)
- Florbetapir (Amyvid)
- NAV-4694 (Flutafuranol)
- Flortaucipir (AV-1451, T807)
- MK-6240
- PI-2620

Information about safety and risk can be found in respective Investigator Brochures and/or Package Inserts.

The radiation doses for each PET scan are not themselves expected to produce any harmful effects, although there is no known minimum level of radiation exposure considered to be totally free of the risk of causing genetic defects or cancer. The risk associated with the amount of radiation exposure participants receive in this study is considered low and comparable to everyday 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 PET imaging.

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

Radiation exposure from all 6 radiotracers in ADNI can be found in relevant study manuals.

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

All participants in this study will receive one amyloid PET scan (either FBP, FBB, or NAV4694), and one tau PET scan (either FTP, MK6240, or PI2620) every other year.

#### **Magnetic Resonance Imaging (MRI)**

There are no proven biological risks associated with MRI scanning. All participants will be screened for medical contraindications for MRI, which include metallic foreign bodies in the brain or eye, or cardiac pacemakers. However, there is a slight risk that a participant may accidentally bring metal into the MR scanner room, which could be pulled into the MRI magnet and injure the participant.

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

### 2.3.1.1.3 Biospecimens

#### **Blood Draw**

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

## **Lumbar Puncture**

Lumbar puncture (LP) 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 some elderly people who undergo LP. Less commonly, 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 LP include infection, damage to nerves in the back, and bleeding into the CSF space. In an effort to mitigate these risks, an experienced clinician must perform the LP.

### **2.3.1.2 STUDY PARTICIPATION**

#### **2.3.1.2.1 Returning Results**

All medically relevant results, which might impact the future diagnosis or treatment of the participant will be provided to the participant and the site PI. With the exception of results from amyloid PET, it is the general policy of this study not to reveal research results to participants; however, if information is obtained that the site PI (or medically qualified designee) determines to be medically relevant, such information may be shared. For example, results from cognitive testing may be shared as part of a dementia diagnosis. Similarly, MRI scan findings of clinical significance, as determined by either the central read or local read, may be shared with the participant. Additionally, the site PI may also return clinical labs from the clinical visit.

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

The Neuropathology Core, described in section 9.1.1, will provide a neuropathology report to the site PI to return to families of those who register for brain donation and wish to review these findings.

#### **Returning Amyloid Status:**

Participants will be given the option of learning the results from their amyloid PET imaging. If a participant so chooses, those results will be disclosed as described in relevant study manual. Participants who receive a positive or elevated result may believe that the person is going to develop Alzheimer's disease dementia, which, in turn, could cause psychological distress and an experience of stigma. In contrast, participants who received a negative result may experience a mistaken belief that they will never develop AD, or they may develop concern born of the uncertainty that they have some but not enough amyloid.

#### **2.3.1.2.2 Genetic**

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 to attempt to identify any study participants.

#### **2.3.1.2.3 Loss of Privacy**

In this study, a great deal of information about participant health status will be collected. Study staff personnel will collect personal protected health information such as name, date of birth, address, phone number, and emails. Each study staff will maintain the personal protected health information in a secure and locked location. All participants will be assigned a PTID and all data collected under this protocol will be associated with that PTID. The data, associated with the PTID, will be shared widely, but it will not be possible to identify an individual participant from the data. However, there is a very unlikely possibility of a security failure, in which case the protected health information will be no longer protected. This is an extremely unlikely, but possible, occurrence and is a risk of this study (and almost all other medical research studies).

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



Participants will be asked to share personal protected health information 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 ADNI Admin Core secure servers. Additionally, audio recordings of participants' voices will be collected for analysis of cognitive digital biomarkers using the Novoic Ltd. Testing Platform, 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.

Speech recordings, transcripts, and other measures extracted from the speech recordings and transcripts will be stored in secure databases and shared with other, carefully selected parties, including Novoic Ltd. These can be used for research and to develop better measures of brain health, including training machine learning algorithms. Sharing of speech recordings will be subject to a separate data use agreement to better safeguard participant privacy.

#### 2.3.1.2.4 GUIDs

ADNI4 will be incorporating Global Unique Identifiers (GUIDs) for all ADNI participants. Each GUID unambiguously identifies a research study participant across different research studies without exposing protected health information (PHI). When investigators pool data together from multiple studies, GUIDs provide the means to detect participants who participate in more than one study.

ADNI sites will download a GUID generator to convert participant PHI (e.g., birth name, birth date, place of birth) into irreversible hash codes. These hash codes will be sent to the GUID authority operated by NIA, which will assign GUIDs and store them along with ADNI participant information in the clinical database. Sites will use the currently adopted GUID generator, known as the NINDS Centralized GUID solution, developed by The National Institute of Neurological Disorders & Stroke (NINDS), in conjunction with the National Institute of Aging (NIA), and the Parkinson's Disease Biomarkers Program (PDBP) using the Biomedical Research Informatics Computer System (BRICS) platform.

## 3 OBJECTIVES AND ENDPOINTS

ADNI4 will continue to discover, optimize, standardize, and validate clinical trial measures and biomarkers used in AD research. ADNI4 will address low rates of engagement and inclusion of underrepresented populations (URPs) in AD clinical cohorts. The ADNI4 in-clinic cohort will include up to 750 new participants as well as up to 750 rollover participants from ADNI3.

### *Aim 1: Validation of biomarker measures*

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

### *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 participants (for secondary preclinical AD trials), MCI patients (for prodromal AD trials) and participants with early dementia due to AD.

### *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 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 blood-based biomarkers to remotely identify and monitor those with AD 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.

#### *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.

#### *Aim 7: Discovery of novel risk and protective genes and pathways, and other known disease proteins found in AD brains.*

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.

## 4 STUDY DESIGN

### 4.1 OVERALL DESIGN

This is a non-randomized, natural history, non-treatment study. Clinical and cognitive testing, imaging, biomarkers and genetics will be assessed across 3 diagnostic groups: CN, MCI, and DEM.

For in-clinic assessments, MCI and DEM will be seen annually, CN participants every other year. Remote assessments (per SoE) will be conducted 2x/year for CN and MCI; remote assessments will not be conducted for DEM participants.

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

#### 4.1.1 SAMPLE SIZE

Up to 1,500 participants will be enrolled to the in-clinic cohort of ADNI4 at approximately 65 sites in the United States and Canada. Up to 750 will be rollover participants from ADNI3, and up to 750 will be newly enrolled. Clinical/cognitive, imaging, biomarker, and genetic characteristics will be assessed across the three cohorts: CN, MCI, and DEM.

##### 4.1.1.1 ROLLOVER IN-CLINIC PARTICIPANTS

ADNI4 is targeting to retain at least 75% of the ADNI3 Cognitively Normal (CN) cohort, 50% of the symptomatic Mild Cognitive Impairment (MCI) cohort, and 15% of those with dementia (DEM).

##### 4.1.1.2 NEW IN-CLINIC PARTICIPANTS

ADNI4 is aiming to include up to 750 new participants for the in-clinic cohort with at least 50-60% URPs, and target diagnostic categories of at least 40% CN, 40% MCI, 20% DEM, and overall, an 80% amyloid positive rate.

### 4.2 END OF STUDY DEFINITION

A participant in the in-clinic cohort is considered to have completed the ADNI4 study if they have completed all phases of the study including the last visit or the last scheduled procedure shown in the SoE, Section 1.3.

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

## 5 STUDY POPULATION

The study will enroll people aged 55-90 years across the remote digital cohort, remote blood cohort and the in-clinic 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.

Inclusion/Exclusion criteria for the in-clinic cohort are detailed in the tables below. The criteria aims to increase generalizability of ADNI findings by increasing flexibility (e.g., around study partner requirements and need to complete lumbar punctures and all imaging procedures), relaxing some medical restrictions (particularly around vascular comorbidity) and allowing newly FDA approved and clinically available disease-modifying treatments.

### 5.1 INCLUSION CRITERIA

#### 5.1.1 INCLUSION CRITERIA FOR THE IN-CLINIC COHORT

##### 5.1.1.1 NEWLY ENROLLED PARTICIPANTS

|    | CN  | MCI  | DEM   |
|----|---|--|---|
| 1. | Participant may or may not have a significant subjective memory concern as reported by participant, study partner, or clinician.  | Participant must have a subjective memory concern as reported by participant, study partner, or clinician.   | Same as MCI   |
| 2. | Normal memory function documented by scoring above demographically-adjusted cutoffs on the Logical Memory II subscale (Delayed Paragraph Recall, Paragraph A only) from the Wechsler Memory Scale – Revised (the maximum score is 25):<br>a. $\geq 9$ for 16 or more years of education<br>b. $\geq 5$ for 8-15 years of education<br>c. $\geq 3$ for 0-7 years of education<br>d. Note: cut-offs may be modified over time as the field evolves in this area | Abnormal memory function documented by scoring within the demographically-adjusted ranges on the Logical Memory II subscale (Delayed Paragraph Recall, Paragraph A only) from the Wechsler Memory Scale – Revised (the maximum score is 25):<br>a. $\leq 11$ for 16 or more years of education<br>b. $\leq 9$ for 8-15 years of education<br>c. $\leq 6$ for 0-7 years of education.<br>d. Note: cut-offs may be modified over time as the field evolves in this area. | Same as MCI   |
| 3. | Mini-Mental State Exam score between 24 and 30 (inclusive) (Exceptions may be made for participants with less than 8 years of education at the discretion of the Project Director and/or Clinical Core)   | Same as CN   | Mini-Mental State Exam score between 20 and 28 (inclusive) (Exceptions may be made for participants with less than 8 years of education at the discretion of the Project Director and/or Clinical Core) |

|    |   |   |   |
|----|---|---|---|
| 4. | Clinical Dementia Rating = 0.<br>Memory Box score must be 0.  | Clinical Dementia Rating = 0.5.<br>Memory Box score must be at least 0.5  | Clinical Dementia Rating = 0.5 or 1.0.  |
| 5. | Cognitively normal, based on an absence of significant impairment in cognitive functions or activities of daily living.   | General cognition and functional performance sufficiently preserved such that a diagnosis of dementia cannot be made by the site physician at the time of the screening visit.  | Meets the National Institute on Aging/Alzheimer's Association Diagnostic Guidelines for Dementia (2011) |
| 6. | Stability of Permitted Medications for 4 weeks. In particular, participants may: <ul style="list-style-type: none"> <li>a. Take stable doses of antidepressants lacking significant anticholinergic side effects (if they are not currently depressed and do not have a history of major depression within the past 1 years)</li> <li>b. Estrogen replacement therapy is permissible</li> <li>c. Gingko biloba is permissible, but discouraged</li> <li>d. Washout from psychoactive medication (e.g., excluded antidepressants, neuroleptics, chronic anxiolytics or sedative hypnotics, etc.) for at least 4 weeks prior to screening.</li> </ul> | Stability of Permitted Medications for 4 weeks. In particular, participants may: <ul style="list-style-type: none"> <li>a. Take stable doses of antidepressants lacking significant anticholinergic side effects (if they are not currently depressed and do not have a history of major depression within the past 1 year)</li> <li>b. Estrogen replacement therapy is permissible</li> <li>c. Gingko biloba is permissible, but discouraged</li> <li>d. Washout from psychoactive medication (e.g., excluded antidepressants, neuroleptics, chronic anxiolytics or sedative hypnotics, etc.) for at least 4 weeks prior to screening</li> <li>e. Cholinesterase inhibitors and memantine are allowable if stable for 12 weeks prior to screen</li> <li>f. Aducanumab and any other approved treatments for the neurobiology of AD if stable for 24 weeks prior to screen</li> </ul> | Same as MCI   |

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

1. Geriatric Depression Scale score less than 10.
2. Age between 55-90 years (inclusive).
3. Study partner who has frequent contact with the participant (i.e., minimum average of 2 hours per week) and may be able to accompany the participant to clinic visits or provide information remotely

(e.g. over the phone).

4. Visual and auditory acuity adequate for neuropsychological testing.
5. Good general health with no diseases expected to interfere with the study.
6. Participant is not pregnant, lactating, or of childbearing potential (i.e., women must be two years post-menopausal or surgically sterile).
7. Willing and able to participate in a longitudinal imaging study.
8. Must be literate and speak English or Spanish fluently.
9. Agrees to collection of blood for GWAS, APOE testing, DNA and RNA testing
10. Agrees to collection of blood for biomarker testing.
11. The Administrative Core, described in section 9.1.1, will collaborate with leadership from all Cores to review the blood biomarker data from the remote blood cohort and select participants to join the in-clinic cohort. See ADNI4: Remote protocol.
12. Agrees to participate in the ADNI study which includes cognitive evaluation, MRI and PET scans.
13. Flexibility can be made to all criteria for those with at least 8 years in a low socio-economic status (SES) neighborhood.

### 5.1.1.2 ROLLOVER PARTICIPANTS

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

1. Must have been enrolled and followed in one of the following previous ADNI studies: ADNIGO, ADNI2, ADNI3 for at least one year.
2. Willing and able to continue to participant in an ongoing longitudinal study. A reduced battery of tests is allowable.
3. Study partner may be available who has frequent contact with the participant (i.e., minimum average of 2 hours per week), and may be able to accompany the participant to clinic visits or provide information remotely (e.g. over the phone).

### 5.1.1.3 CONVERSIONS AFTER BASELINE

During each clinical visit, all participants are assessed to determine if they are CN, MCI, or DEM. Conversion from one category to another is left to the discretion of the site PI based on clinical judgement.

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## 5.1.2 EXCLUSION CRITERIA FOR THE IN-CLINIC COHORT

All newly enrolled participants must not meet the following criteria:

|    | <b>CN</b>  | <b>MCI</b>  | <b>DEM</b>  |
|----|--|---|-------------|
| 1. | Any significant neurologic disease, such as Parkinson’s disease, vascular cognitive impairment/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 defaults or known structural brain abnormalities | Any significant neurologic disease other than suspected Alzheimer’s disease, such as Parkinson’s disease (Parkinsonian symptoms complicating MCI/AD are acceptable), vascular cognitive impairment dementia (multiple lacunes less than or equal to 1.5 cm and/or extensive white matter changes are acceptable), Huntington’s disease, normal pressure hydrocephalus, brain tumor (clinically insignificant meningioma | Same as MCI |

|  |  |   |  |
|--|--|---|--|
|  |  | acceptable), progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic deficits or known structural brain abnormalities. |  |
|--|--|---|--|

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

1. Screening/Baseline MRI brain scan with evidence of infection, or other clinically significant focal lesions. Participants with cortical strokes, not large enough to distort anatomy, multiple lacunar infarctions or extensive white matter disease are allowed.
2. Screening/Baseline MRI brain scan with evidence of large structural abnormalities that would corrupt image analytical pipelines – e.g. large hemispheric infarcts, large areas of encephalomalacia, large arachnoid cysts
3. Unable to complete MRIs for any reason (e.g. pacemaker or other implanted metal devices, severe claustrophobia, anxiety which prevents MRI scans, too large to fit, etc.).
4. Current major depression, bipolar disorder as described in DMS-IV within the past 1 year. Psychotic features, agitation or behavioral problems within the last 3 months which could lead to difficulty complying with the protocol.
5. Currently treated with medication for obsessive-compulsive disorder or attention deficit disorder.
6. History of schizophrenia (DSM-5 criteria).
7. History of alcohol or substance disorder within the past 2 years (DSM-5 criteria).
8. Any significant systemic illness or unstable medical condition which could lead to difficulty complying with the protocol.
9. Clinically significant abnormalities in B12, or thyroid function tests 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. Residence in skilled nursing facility
11. Current use of specific psychoactive medications (e.g. certain antidepressants, neuroleptics, chronic anxiolytics or sedative hypnotics, etc.), at the discretion of the clinician.
12. Current use of any other exclusionary medications.
13. Investigational agents are prohibited for five half-lives or one month, whichever time period is longer, prior to entry and for the duration of the trial.
14. Participation in clinical studies involving neuropsychological measures being collected more than once time per year.
15. Female that is pregnant, lactating, or of childbearing potential.
16. Flexibility can be made to all criteria for those with at least 8 years in a low socio-economic status (SES) neighborhood.

## 5.2 LIFESTYLE CONSIDERATIONS

### 5.2.1 LIFESTYLE CONSIDERATIONS

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

- Fast for blood draws and the optional Lumbar Puncture.
- Proactively discuss initiation of new medications or occurrence of procedures (e.g., surgical procedures, vaccinations) in advance with the site to ensure appropriate management of study participation.
- For those in the CN and MCI cohort, it is 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, at a local community center, or at another convenient location, to complete cognitive assessments online, see section 7.2.1.

## 5.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the study but are not entered in the study. A minimal set of screen failure information 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. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) because of transient issue(s) may be rescreened one-time following resolution of previously identified transient issue(s). Rescreened participants will be assigned a new PTID. The original PTID will be recorded in the eCRF. Reconsent will be required prior to rescreen.

A minimum of 3 months will be required between the original screen and rescreen. Exceptions may be granted with Coordinating Center approval.

More than one re-screen may be permitted with Coordinating Center approval.

Individual screening assessment(s) may be repeated with Coordinating Center approval and if clinically necessary (e.g., to follow up on an abnormality identified on clinical labs) or if data from the initial procedure cannot be utilized for analysis purposes (e.g., PET scan QC failure, major quality or administration error). A minimum of 30 days is required between the initial administration of cognitive/clinical assessments and subsequent administration.

## 5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

ADNI4 is targeting to retain at least 75% of the ADNI3 CN cohort, 50% of the MCI cohort, and 15% of those with dementia for the In-Clinic cohort.

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, including 50-60% from 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.

In ADNI4, participants will be recruited to join the remote digital cohort, which 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, see the ADNI4: Remote Protocol for more information about remote cohorts. The use of a remotely screened and longitudinally monitored participant pool, remote digital and remote blood cohorts, allow ADNI4 to identify participants who meet basic eligibility criteria for ADNI4 in-clinic participation and reducing likelihood of clinical site screening failures

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 be creating new translations of previously validated Spanish-language measures.

The ADNI Clinical Core and ADNI Engagement Core will monitor enrollment and retention at each site. The Engagement Core will leverage the success in the ADNI3 study to duplicate and build on the successful community outreach measures engaging local and national media along with more targeted involvement of local community leaders and organizations. Along with these measures a more traditional approach of developing educational materials for health care professionals serving URPs will also be undertaken. These materials address research efforts and opportunities for patient participation and can be targeted to professional organizations represented by and/or serving communities with high URP representation.

### 5.4.1 INCLUSION OF WOMEN AND MINORITIES

This study will make every effort to maximize diversity of participants enrolling in the study, as there remains a lack of diversity in biomarker intensive clinical trials in aging and AD. All participants meeting the inclusion and exclusion criteria standards will be enrolled, regardless of gender or race, but every effort will be made to actively recruit women and persons from Underrepresented Populations (URPs) including Black or African American, 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% (e.g., Black, Latinx, persons with less than 12 years of education) of newly enrolled participants will be URPs.

### 5.4.1.1 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.

### 5.4.1.2 INCLUSION OF MINORITIES

ADNI4 will strive to enroll at least 50-60% of newly enrolled participants from Under Represented 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 working to include 50-60% of newly enrolled participants from 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 community-engaged research (CER) approach for recruiting ~30,000+ individuals, 50-60% of whom are URPs, to participate in the remote digital cohort, with the ultimate goal of 50-60% of new in-clinic participants coming from underrepresented backgrounds, see ADNI4: Remote protocol. 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 Engagement Campaign that will include multiple language and diverse images;

(2) ADNI4 Engagement 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;

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 can 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), 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, see ADNI4: Remote protocol). 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) Diversity Recruitment Hub Sites (approximately 20 clinical sites), will be selected based on local demographics and previous URP recruitment/engagement track record. They will receive additional financial and instrumental support (e.g. staff, CBO funds) for URP recruitment and engagement;

(4) 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;

(5) Culturally-informed Sampling and Incentives to address barriers to URP recruitment/engagement (e.g., trust, burden) include: 5a) less restrictive inclusion/exclusion criteria and 5b) a new ADNI-wide system of consistent incentives (e.g., financial remuneration, disclosure of amyloid PET results); and

(6) Workforce Training to 6a) enhance cultural competency of all ADNI investigators and staff, and 6b) provide targeted mentored training to URP trainees and early career investigators so they can conduct innovative dementia research.



## 6 DISCONTINUATIONS AND WITHDRAWALS

### 6.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. Participants may stay enrolled as “brain donation registration only” even if they do not want to participate actively.

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

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

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

In the event where a participant decides to stop ADNI participation to enroll in a treatment trial, they may be allowed the opportunity to return to full or partial participation in the ADNI4 study. Participants who return to ADNI4 after participation in a treatment trial will be asked to provide information about their participation in that trial. Contact the ATRI Coordinating Center for guidance on re-entry.

### 6.2 LOST TO FOLLOW-UP

A participant will be considered lost to follow up if he or she is unable to be contacted by the study 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 visit within the standard window within one month, and 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, 3 telephone calls and, if necessary, a certified letter to the participant’s last known mailing address or local equivalent methods). These contact attempts should be documented in the participant’s medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

In the event where a participant is considered lost to follow up but wishes to return in the future, they may be allowed the opportunity to return to full or partial participation in the ADNI4 study. Participants who return to ADNI4 after participation in a treatment trial will be asked to provide information about their participation in that trial. Contact the ATRI Coordinating Center for guidance on re- entry.

## 7 STUDY ASSESSMENTS AND PROCEDURES

### 7.1 VISITS

#### 7.1.1 DESCRIPTION OF STUDY VISITS

Study visit procedures in ADNI4 will be very similar to ADNI3 to maximize the value of the very long-term longitudinal data. Notable changes include an emphasis on recruitment of URPs, novel web-based unsupervised computerized cognitive assessments, extensive testing for AD blood biomarkers, inclusion of several new PET tracers, the discontinuation of FDG-PET imaging and the Financial Capacity Instrument. The estimated time for an ADNI4 participant to complete all cognitive/clinical assessments is approximately two hours.

- Demographic information and vital signs – approximately 15 minutes
- Physical and neurological exams – approximately 15 minutes
- Medical history – approximately 10 minutes
- Cognitive, mood, behavioral and functional status data, including the newly added acculturation and SES scales (described below) – approximately 2 hours
- Lumbar Punctures – approximately 1 hour
- MRI and PET (amyloid and tau) brain scans – approximately 1 hour for the MRI; approximately 2 hours each for amyloid and tau PET scans
- Disclosure of amyloid PET, basic clinical labs/vitals, and any clinically relevant results, if requested by the participant – approximately 15 minutes
- Biospecimen collection, including blood, urine and cerebrospinal fluid, for APOE genotyping, genetic and biomarker research and sample storage – approximately 10 minutes

Frequency of visits will be dependent on cohort. Visits have a scheduling window of 2 weeks before and after the target date. Once the visit begins, all imaging, biofluid collection, and clinical/cognitive assessments must take place within the next 2 weeks. However, to accommodate the scheduling of participants and ADNI study staff, exceptions will be provided to extend the window. The most important priority is to collect as much clinical, cognitive and biomarker data as possible, even if this takes longer than 2 weeks.

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

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

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

1. Blood draw
2. Tau PET scan
3. Amyloid PET scan
4. MRI
5. Lumbar puncture

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

The in-clinic cohort will be asked to participate in remote longitudinal cognitive testing to provide more frequent monitoring of these participants but with reduced burden. Participants enrolled in the in-clinic cohort will be asked to complete the 12-Item ECog assessment and the Novoic assessment via Ebisu twice annually, remotely. We anticipate that many of the participants who are newly enrolled in ADNI4 will have come to participate in the in-clinic cohort via referral from the remote digital and remote blood cohorts, and will continue visiting Ebisu every 6 months for remote cognitive testing on the same schedule from participation in

those previous cohorts, see ADNI4: Remote Protocol for more information about visit schedules in the remote cohorts. Participants who rollover from ADNI3 or are directly recruited at ADNI4 clinical sites as new enrollees will be provided information about how to access the Ebisu platform for remotely completing the 12-Item ECog and Novoic assessments via Ebisu twice annually for the duration of the study.

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## 7.1.2 VISIT SCHEDULING

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

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

All participants should be contacted every six months or, at a minimum, annually through the end of the study to obtain brain donation registration, establish and confirm logistical support for autopsy, and maintain updated participant contact information.

### 7.1.2.1 NEWLY ENROLLED IN-CLINIC PARTICIPANTS

New participants will go through Pre-screening and Screening periods. The Screening and Baseline visits must be completed in-person by the participant. The study partner must participate either in-person or remotely.

### 7.1.2.2 ROLLOVER IN-CLINIC PARTICIPANTS

Rollover participants who are being followed from ADNI3 should be enrolled into ADNI4 for a complete In-Clinic Visit without need for screening.

### 7.1.2.3 RETRIEVED DROPOUTS

Participants who miss visits will be encouraged to come in for subsequent visits until withdrawal of consent. In cases where consent has been withdrawn in previous ADNI studies, participants can be invited to consent and participate in ADNI4.

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## 7.1.3 SCREENING

Individual screening assessment(s) may be repeated with Medical Monitor approval and if clinically necessary (e.g. to follow-up on an abnormality identified on clinical labs) or if data from the initial procedure cannot be utilized for analysis purposes (e.g. PET scan QC failure, major quality or administration error). A minimum of 30 days is required, between the initial administration of cognitive/clinical assessments and subsequent administration.

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

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

1. Consent
2. Screening assessments listed in the SoE up to but not including the MRI, which requires both Site PI/Site Clinician and monitor approval
3. Proceed to MRI
4. Local read of MRI
5. Site PI/Site Clinician and monitor verifications of all eligibility requirements

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## 7.1.4 BASELINE/INITIAL

The Baseline visit may only be initiated following completion of all Screening assessments and must take place within 30 days of Screening. There is an additional 2 weeks to complete other Baseline procedures. The procedures conducted are based on current diagnosis at the Initial visit.

Baseline procedures include cognitive, functional, and behavioral assessments, review of concurrent medications and adverse events, amyloid PET, tau PET, and biofluid collection (blood and CSF from lumbar punctures). The complete list of all Baseline procedures is provided in the SoE.

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

#### 7.1.4.1 ROLLOVER PARTICIPANTS

For rollover participants in the CN cohort, clinic visits are to occur every other year with phone checks on the alternate years. If a rollover participant in the CN cohort had either an Amyloid or Tau PET scan during their last year of ADNI3, then they will have a phone check for the first year of ADNI4. If a CN rollover participant did not have an Amyloid or Tau PET scan during their last year of ADNI3, then their baseline visit will be in the clinic and includes Amyloid and Tau PET scans for their first year of ADNI4.

For rollover participants in the MCI and DEM cohorts, clinic visits occur annually with Amyloid and Tau PET scans every other year. All rollover participants in the MCI and DEM cohorts have a clinic visit for their first year of ADNI4. However, if they had either an Amyloid or Tau PET scan during their last year of ADNI3, then they will not have PET scans at their first visit in ADNI4. If they did not have an Amyloid or Tau PET scan during their last year of ADNI3, then their baseline visit includes Amyloid and Tau PET scans for their first year of ADNI4.

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### 7.1.5 ONGOING LONGITUDINAL VISITS

CN and MCI participants, both newly enrolled and rollover, will be provided with an information sheet with instructions for completing the remote cognitive tests, the 12-Item ECog and the Novoic assessments, every 6 months via the Ebusu online system. For participants who join the in-clinic cohort via referral from the remote digital and/or remote blood cohorts, those participants will use their existing Ebusu access information (same user name/password) and testing schedule (every six months after baseline remote digital visit). For participants who rollover from ADNI3 to ADNI4 and new participants directly enrolled at the sites (therefore participants who did not previously join the remote digital and/or remote blood cohorts), they will be provided an information sheet with instructions for how to log into Ebusu and create a user account to complete the remote assessments, the 12-Item ECog assessment and the Novoic assessment, every 6 months.

The ongoing In-Clinic Visits will be timed every 12 months from Baseline Visit Day 1. Ongoing in-clinic visits include cognitive, functional, and behavioral assessments, review of concurrent medications and adverse events, blood collection, and MRI.

Amyloid and Tau PET scans and LPs are conducted every two years.

#### 7.1.5.1 ROLLOVER PARTICIPANTS

Ongoing In-Clinic Visits for MCI participants will be scheduled every 12 months (annually) from the Initial ADNI4 Visit.

A total of 3 Ongoing In-Clinic visits for DEM will be scheduled every 12 months (annually) from the Initial ADNI4 visit, if they did not complete a full In-Clinic visit during their final year in ADNI3.

A total of 2 Ongoing In-Clinic visits for DEM will be scheduled every 12 months (annually) from the Initial ADNI4 visit, if they did complete a full In-Clinic visit during their final year in ADNI3.

A full clinic visit in the final year of ADNI3 is defined as having completed at least the following activities:

- CDR
- ADAS-Cog
- MMSE
- Logical Memory I and II
- Concomitant Medications
- Adverse Events
- Diagnostic Summary
- PET Scans; either Tau or Amyloid

If these activities were not completed, their last ADNI3 visit should not be defined as a full clinic visit.

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## 7.1.6 OTHER TYPES OF STUDY VISITS – APPLICABLE TO BOTH NEWLY ENROLLED AND ROLLOVER PARTICIPANTS

### 7.1.6.1 TELEPHONE VISITS IN REPLACEMENT OF IN-CLINIC VISITS

Participants that are no longer able or willing to be seen in the clinic may opt to have a Telephone Visit instead of an ongoing in-clinic visit. This option is available for ADNI3 rollover participants upon entry into ADNI4, as well as new ADNI4 participants that have completed their Baseline Visit. This requires signature of a new informed consent form acknowledging the replacement procedures and schedules.

### 7.1.6.2 TELEPHONE CHECKS

For applicable participants the brief Telephone Check occurs for up to 5 years. The brief Telephone Check will be a shorter version of the Telephone Visit. Study partner will still join, and similar questions will be asked for the participant and the study partner. Refer to the relevant study manual for a list of activities that are conducted during telephone checks. See SoE for details on applicable participants.

For all participants, the purpose of the 6-month Neuropathology Telephone Check is to discuss current wishes with regard to brain donation, update participant contact information to ensure continued contact until time of death, ensure appropriate autopsy arrangements are in place, and reiterate who should be contacted at the time of death. If a participant decides that he or she is not interested in brain donation program, they will not be called. See SoE for details.

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## 7.1.7 EARLY TERMINATION

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

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

## 7.2 ASSESSMENTS

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

Participants will be given the option of learning the results from their amyloid PET imaging. If a participant so chooses, those results will be disclosed either in-clinic whenever feasible, or over the phone by a qualified clinician.

A qualified clinician is encouraged to disclose results from cognitive testing when the participant opts in to learn about their results from cognitive research tests. Participants will be given the option of learning the results from their cognitive testing and clinical labs. If a participant so chooses, those results will be disclosed in clinic whenever feasible, or over the phone by a qualified clinician. See relevant study manual for more details on returning results to participants.

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## 7.2.1 REMOTE COGNITIVE ASSESSMENTS

The following assessments will be collected from all participants every 6 months, remotely, on Ebisu.

### 7.2.1.1 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 ECog with language updates meant to improve generalizability across diverse groups<sup>49</sup>. 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.

### 7.2.1.12 NOVOIC – STORYTELLER

Novoic Ltd's Storyteller assessment is an artificial intelligence-enhanced audio-verbal cognitive test with automated administration. The participant first completes a brief sentence repetition task. Next the participant hears two stories and is asked to recall them in as much detail as possible. The participant completes a category fluency (e.g., 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. Automated quality control is also run, to ensure data quality for these remotely conducted, self-administered tests. Outputs from Novoic's testing platform, including performance measures and quality control measures, will be stored in a database, which ADNI can securely access via authenticated API endpoints.

Audio recordings, transcripts, and speech-derived measures are stored by Novoic Ltd. on HIPAA compliant servers located in the USA. Audio recordings, transcripts, and speech-derived measures will be securely transferred for permanent storage on USA-based HIPAA compliant servers at the Laboratory of Neuro Imaging (LONI).

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## 7.2.2 COGNITIVE ASSESSMENTS PERFORMED IN-CLINIC

In addition to the assessments below, collected in-clinic, the in-clinic cohort will collect the 12-Item ECog and the Novoic cognitive assessments every 6 months, remotely, using Ebisu.

### 7.2.2.1 ABBREVIATED MULTIDIMENSIONAL ACCULTURATION SCALE (AMAS)

The AMAS is a self-report, bidirectional measure that assesses acculturation levels to both majority culture (US) and culture of origin (Latinx). It includes six subscales (three for each culture) related to language competence, cultural competency, and cultural identity, producing two summary scores: 1) Total US Acculturation Score and 2) Total Latinx Acculturation Score (scores range from 1 to 4; higher scores indicate higher acculturation levels). The AMAS has excellent psychometric characteristics and has been validated with urban populations similar to the URPs to be included in this sample. For this study, the AMAS Total US Acculturation and Total Latinx Acculturation Scores will be used<sup>44</sup>. This measure will only be given to participants who self-identify as Latinx/a/o.

### 7.2.2.2 AMERICAN NATIONAL ADULT READING TEST (AMNART)

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

### 7.2.2.3 ALZHEIMER'S DISEASE ASSESSMENT SCALE-COGNITIVE (ADAS-COG13)

The ADAS-Cog is an in-person examiner-administered, structured scale that evaluates memory (word recall, word recognition), reasoning (following commands), language (naming, comprehension), orientation, ideational praxis (placing letter in envelope) and constructional praxis (copying geometric designs). Ratings of spoken language, language comprehension, word finding difficulty, and ability to remember test instructions are also obtained<sup>19</sup>.

### 7.2.2.4 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<sup>45,46</sup>.

#### 7.2.2.5 CATEGORY FLUENCY (ANIMALS) TESTS

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

#### 7.2.2.6 CLOCK DRAWING TEST

This task tests visuo-perceptual constructional function. The Clock Drawing Test is effective for discriminating between participants with AD and normal elderly individuals<sup>23</sup>.

#### 7.2.2.7 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 ECog with language updates from Farias et al. 2021 meant to improve generalizability across diverse groups.<sup>49</sup>

#### 7.2.2.8 HOLLINGSHEAD INDEX SCORE

The Hollingshead Two Factor Index of Social Position was developed by August B. Hollingshead in 1965 at Yale University to estimate social positions that individuals occupy in society<sup>50</sup>. The scale comprises a combination of educational attainment and occupational role. It outlines 7 strata of occupations from professionals/ executives to lesser professions, administrators and skilled labor employees and calculates a Hollingshead score based on education and occupation. This allows for a single score to rate social position than using education alone. Since the development of the Hollingshead, occupations have changed in society. The ACTC, under the leadership of Dorene Rentz, PsyD and Rema Raman, PhD, modernized the Hollingshead Educational Strata with the 2017 Occupational Employment Statistics table of profiles. ADNI4 will utilize this modernized Hollingshead scale.

#### 7.2.2.9 LOGICAL MEMORY TEST I AND II (IMMEDIATE AND DELAYED PARAGRAPH RECALL)

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

#### 7.2.2.10 MINI-MENTAL STATE EXAMINATIONS (MMSE)

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

#### 7.2.2.11 MONTREAL COGNITIVE ASSESSMENT (MOCA)

The Montreal Cognitive Assessment test (MoCA) is, similar to the MMSE, a brief, 30- point cognitive assessment designed to detect participants at the MCI stage of cognitive dysfunction<sup>26</sup>. This instrument has been shown to have adequate sensitivity and specificity in clinical settings to detect suspected MCI. The performance of the MoCA will be followed to determine its ability to differentiate among the three diagnostic groups in ADNI4.

#### 7.2.2.12 MULTI-LINGUAL NAMING TEST (MINT)

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

#### 7.2.2.13 PERCEIVED STRESS (PSS)

An important consideration in measuring cognition is current stress. Research suggests that current perceived stress can affect neurocognitive functioning (Lupien et al., 2009). Thus, measuring current stress in the present study is an important element of study procedures. The PSS measures current stress levels and stressful experiences in the last month. It asks about experiences such as feeling in control of one's life, feeling the ability to be productive, feeling overwhelmed, and being upset by unexpected events (Cohen, Kamarck, & Mermelstein, 1983). These items are rated on a Likert scale of 1-5, with 1 representing "Almost Always" and 5

representing “Almost Never.” In scoring, the scale is reverse coded where appropriate, such that a low score is indicative of a lower level of perceived stress<sup>42,51</sup>.

#### 7.2.2.14 PERCEIVED DISCRIMINATION

The PED-Q (Contrada et al., 2001)<sup>43</sup> is a 17-item questionnaire assessing the frequency & intensity of instances when the participant felt discriminated against based upon his or her race/ethnicity. The questionnaire includes four subscales: social exclusion, stigmatization, workplace discrimination, and threat/harassment. The PED-Q has demonstrated high reliability (Cronbach’s  $\alpha = 0.87$ ) and is considered a valid measure of perceived discrimination (Brondolo et al., 2005).

#### 7.2.2.15 REY AUDITORY VERBAL LEARNING TEST (AVLT)

The AVLT is a list-learning task, which assesses multiple cognitive parameters associated with learning and memory<sup>28</sup>.

#### 7.2.2.16 TRAIL MAKING TEST: A AND B

These two tests progress from a numerical connect-the-dots puzzle to a more challenging alternation between alpha- and numerical order. Although both Parts A and B depend on visuomotor and perceptual-scanning skills, Part B also requires considerable cognitive flexibility in shifting from number to letter sets under time pressure<sup>29</sup>.

#### 7.2.2.17 CLINICAL DEMENTIA RATING SCALE (CDR)

The CDR describes five degrees of impairment in performance on each of 6 categories of cognitive functioning including memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care<sup>33,34</sup>.

Where a full CDR interview is not possible, the abbreviated CDR can be utilized.

#### 7.2.2.18 ACTIVITIES OF DAILY LIVING / FUNCTIONAL ASSESSMENT QUESTIONNAIRE (FAQ)

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

#### 7.2.2.19 NEUROPSYCHIATRIC INVENTORY (NPI)

The NPI is a well-validated, reliable, multi-item instrument to assess psychopathology in AD based on an interview with a caregiver or qualified study partner (defined in this study as having direct contact 2 hours/week)<sup>38,39</sup>. It evaluates both the frequency and severity of: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition irritability, lability, apathy, and aberrant motor behavior.

#### 7.2.2.20 NEUROPSYCHIATRIC INVENTORY Q (NPI-Q)

The NPI-Q was designed as a version of the NPI that could be administered more quickly and over the telephone<sup>40</sup>.

#### 7.2.2.21 GERIATRIC DEPRESSION SCALE (GDS) SHORT FORM

The GDS Short Form is a self-report scale designed to screen for symptoms of depression in the elderly<sup>41</sup>.

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### 7.2.3 PHYSICAL AND NEUROLOGICAL EXAMINATION

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

## 7.3 IMAGING

### 7.3.1 PET SCANNING: AMYLOID – FLORBETAPIR (FBP), FLORBETABEN (FBB), OR NAV4694; AND TAU – FLORTAUCIPIR (FTP), MK6240 OR PI-2620

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



### 7.3.1.1 SITE QUALIFICATION

Each site must be qualified for PET. If the PET scanner being used has already been certified by the ADNI PET Core and has not experienced any major software or hardware upgrades, re-qualification will not be required. Qualification of the PET scanner applies to all scan imaging protocols; a scanner requires qualification only once for all tracer studies. Qualification will employ the same methods utilized for site qualification in ADNI3, which entails scanning a Hoffman brain phantom. This phantom will be supplied to ADNI sites that do not have their own. Details of the phantom imaging protocol will be provided in a technical manual.

### 7.3.1.2 DATA ACQUISITION FOR PET SCANS

All ADNI participants will complete one amyloid PET scan and one tau PET scan every two years. Scans must be completed within 2 weeks before or 2 weeks after the in-clinic assessments at Initial/Baseline visit and at two-year intervals.

Individuals who are retained in ADNI4 from ADNI3 will continue to have amyloid PET scans with the ligand that was used in ADNI3 (either FBB or FBP) and will continue to have tau PET scans with the ligand that was used in ADNI3 (FTP). Participants that are newly recruited to ADNI4 will be assigned to tracers based on the clinical site proximity to PET tracer manufacturing sites. In ADNI4 because there are 3 possible amyloid tracers and 3 possible tau tracers, there are 9 possible combinations of tracers that new individuals will receive. Each participant will be assigned to one amyloid tracer and one tau tracer that is expected to remain stable for the duration of the study. In the United States, florbetapir, florbetaben and flortaucipir are all FDA approved tracers for PET imaging. NAV4694, MK6240, and PI2620 are not currently FDA approved and will be used under IND held by ATRI investigators. In Canada, only florbetaben is approved by Health Canada (HC) for PET imaging. Use of remaining tracers (florbetapir, flortaucipir, NAV4694, MK6240, and PI2620) will be submitted to HC by ATRI investigators for approval for use in the ADNI4 study.

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

| Tracer       | Injected Dose | Imaging Time (post-injection) |
|--------------|---------------|-------------------------------|
| Florbetapir  | 10 mCi        | 50-70 min                     |
| Florbetaben  | 8.1 mCi       | 90-110 min                    |
| NAV4694      | 8.1 mCi       | 50-70 min                     |
| Flortaucipir | 10 mCi        | 75-105 min                    |
| MK6240       | 5 mCi         | 90-110 min                    |
| PI2620       | 5 mCi         | 45-75 min                     |

### 7.3.1.3 AMYLOID PET EARLY FRAMES DATA ACQUISITION (OPTIONAL)

During ADNI3, participants were enrolled in a longitudinal study to collect PET data with Florbetapir or Florbetaben immediately following injection for 20 min, along with the standard imaging time shown in the table. Most of these “early frames” studies have been completed in ADNI3, but a small number of participants will be recruited. In ADNI4, all individuals who had a baseline early frames study will be invited to return for a second early frames study about 2 years after baseline. Participants that choose to participate and consent to the additional imaging, will be positioned in the scanner identically as they are positioned for the regular amyloid PET scan and data will be collected for 20 minutes beginning immediately with the injection of the amyloid tracer. Following this 20 min of data collection, participants will be outside the scanner until 50 min (FBP) or 90 min (FBB) after the tracer was injected at which time the standard imaging acquisition will commence. This early frames study will not involve any additional PET radiotracer administration, although participants studied in a PET/CT system will have an additional CT scan. Refer to the ADNI PET technical manual for procedural details.

Data will be collected on approximately 100 participants distributed across the diagnoses of CN/MCI/DEM.

### 7.3.1.4 DATA MANAGEMENT AND QUALITY CONTROL

Images are uploaded by site users to the Laboratory of Neuroimaging (LONI) at the University of Southern California. Data are de-identified as part of the upload and placed into quarantine until they pass quality assurance evaluation conducted by the PET Core. The aim of this work is not only to make sure that all PET scans are acquired and reconstructed using the appropriate protocols and

that image quality is good, but also to standardize the images from the different sites (and hence the different PET scanner vendors and models) as much as possible in order to reduce inter-site differences.

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

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## 7.3.2 MRI

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

### 7.3.2.1 SITE QUALIFICATION

Each site must be qualified for MRI. The ADNI4 MRI protocol differs from that used in ADNI3 in that several of the sequences will be modernized. Therefore, all scanners will have to be qualified with the ADNI4 protocol MRI protocol.

The procedure for MRI site qualification will consist of a test imaging session on a human volunteer and/or phantom. If the scanner to be used in ADNI4 is currently qualified for ADNI3, then ADNI4 qualification only involves scanning a phantom (no human scan required). However, if the scanner in ADNI4 is not qualified for ADNI3 (i.e., a new scanner for the site's ADNI participants), then a human volunteer scan is needed for ADNI4 qualification. The site will be sent an electronic file containing the ADNI4 protocol that has been ported to the site's scanner make/model/operating system. The site will load the file onto the scanner to be qualified, and then image either a volunteer participant (typically a site staff member) or phantom with the protocol and send the images to LONI. The MRI Core will check each parameter in each of the pulse sequences in the protocol. If the scan has not been performed according to protocol, the site will be asked to perform another qualification scan. This will be repeated as many times as necessary until the site has demonstrated exact execution of the MR protocol in a volunteer participant (or phantom), at which point the scanner will be qualified for ADNI4. Human volunteers do not need to be elderly controls; in fact, scanning for site qualification may be more easily performed with normal younger volunteers. If repeat human volunteer attempts are needed, repeat scans need not be on the same volunteer participant. Once a site has demonstrated perfect execution of the protocol, the protocol will be stored permanently on the scanner at that site that will be used in the study.

### 7.3.2.2 DATA ACQUISITION

All participants will be scanned on a 3T MRI System with a protocol consisting of several sequences that conform to FDA safety standards. All sequences will be vendor product (FDA approved). The MRI protocol includes: a scout, structural T1-weighted MRI, FLAIR, T2 GRE, T2, diffusion tensor imaging, ASL perfusion MRI, and task free resting state functional MRI. The total scan time will be approximately one hour but may be slightly longer depending on technical factors. If the subject becomes uncomfortable, they can ask to be removed from the scanner at any time.

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

### 7.3.2.3 CLINICAL READ OF MRIS

The research site is responsible to obtain a read from a local radiologist following local standards of care for each MRI completed in the ADNI protocol.

### 7.3.2.4 DATA MANAGEMENT AND QUALITY CONTROL

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

## 7.4 BIOSPECIMENS

Local labs, National Cell Repository for Alzheimer's Disease (NCRAD), and University of Pennsylvania (UPENN) will analyze all laboratory samples. Lab reports will be reviewed, signed and dated by the Site PI (or a medically-qualified individual delegated by the PI). Site clinicians will indicate whether abnormal lab results are clinically significant or not, with additional review by ATRI

Medical Monitoring group. Those results that are deemed clinically significant may need to be repeated and follow up with the participant's treating physicians will be recommended by study personnel.

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## 7.4.1 BLOOD DRAW

The relevant study manual will provide detailed instructions for the collection, processing and shipment of all biofluid samples. Samples will be collected to accommodate the assay of the broadest range of the best antecedent biomarkers/analytes. Fasting overnight (minimum 6 hours) is required for plasma, serum and CSF sample collection. Only water is permitted (no food but water is encouraged) until blood draws and the LP procedure are completed. ADNI4 will continue to measure A $\beta$ 1-42, A $\beta$ 1-40, total tau, and phosphorylated tau181 in CSF samples.

Methods used for blood draw will continue as in ADNI3 for longitudinal biomarker and genetic data with the addition of PBMC collection.

### 7.4.1.1 BASELINE BLOOD SAMPLES FOR PBMC AND CELL LINE BANKING

Whole blood samples will be collected at baseline for all participants and used for extraction of peripheral blood mononuclear cells (PBMCs). For newly enrolled participants and rollovers who have not yet provided this sample, an additional blood sample will also be used to derive immortalized cell lines. Whole blood will be collected and shipped overnight under ambient conditions to NCRAD. It is important to ship samples drawn for PBMCs the same day they are drawn and that they are received at NCRAD the next day; any delay will affect the viability of the cells. The Genetics Core will request a re-sampling if the condition of the sample on arrival prevents processing.

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

#### 7.4.1.1.1 Longitudinal Blood Samples for Genomic Analysis and Related Bioassays

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

#### 7.4.1.1.2 Genetic and Genomic Analyses

APOE and genome-wide genotyping will be completed for newly enrolled participants. For participants whose samples have not already undergone whole genome sequencing, resources will be sought during ADNI4 to perform these analyses.

#### 7.4.1.1.3 Plasma and Serum Collection for Biomarkers

Plasma, serum, and buffy coat will be collected at Baseline from newly enrolled participants, and at the initial ADNI4 visit from rollover participants, and then ongoing during follow-up at In-Clinic Visits for all participants. All samples will be collected in the morning before breakfast and after an overnight fast (minimum 6 hour fast). Plasma and serum must be prepared at the site, frozen and then sent overnight on dry ice to the Biomarker Core at the UPENN. As above, buffy coat and red blood cells will be extracted from blood at the site and shipped overnight under ambient conditions to NCRAD.

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## 7.4.2 LUMBAR PUNCTURE

The Lumbar Puncture procedure is optional for all participants. Should a newly enrolled or rollover participant agree to the optional LP, they will have CSF samples collected at Baseline and again every 2 years through the course of the ADNI4 study. All samples will be collected in the morning before breakfast and after an overnight fast (minimum 6 hours fast).

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

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

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

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### 7.4.3 NEUROPATHOLOGY

Participants at all sites will be approached to register in ADNI's brain donation program. At the time of death, a participant's next of kin may be asked to agree to a brain-only autopsy. Participants are encouraged to discuss their wishes with family members in advance of their passing. The participants/families will be approached by an investigator at an appropriate time to discuss registration in the brain donation/autopsy program. Interested participants/study partners will be given informational, site-specific materials about the brain donation program and whom to contact at their site at the time of death. A protocol is contained within the relevant study manual for the processing of brain tissue from all participants that come to autopsy, provision of the tissue to the Neuropathology Core, and documentation required that accompany that tissue. Participants enrolled in other studies may still register for ADNI's brain donation program. The Neuropathology Core will make arrangements with the other study for tissue sharing.

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## 7.5 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS FOR IN-CLINIC COHORT

### 7.5.1 ADVERSE EVENT (AE) DEFINITION

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

All AEs are to be documented, regardless of relationship to study procedures, commercial, or investigational products used in this study (amyloid (Florbetapir, Florbetaben, NAV4694) or tau (Flortaucipir, MK6240, PI2620) PET tracers), beginning from the time the participant signs the Informed Consent Form (ICF) through the last study visit or last assessment.

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

The investigator is obliged to follow participants with AE's until the events have subsided, the conditions are considered medically stable, or the participants are no longer available for follow up. Participants who discontinue due to Adverse Events will be treated and followed according to established medical practice. All pertinent information will be entered into the eCRF.

AEs the site PI (or medically qualified designee) deems related to study procedures or investigational products used in this study and serious adverse events (SAEs) occurring within 24 hours of PET tracer administration, regardless of causality, are to be documented beginning from the time the participant signs the ICF through the last study visit or last assessment.

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

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### 7.5.2 SERIOUS ADVERSE EVENT (SAE) DEFINITION

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

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

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

Upon notification of a participant's death, the Neuropathology Core will reach out to the next of kin and the site to request additional information regarding brain donation and autopsy.

For more information, refer to the Code of Federal Regulation Title 21 Part 312.

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### 7.5.3 EVENT ASSESSMENT, REPORTING, AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of clinical site personnel during study visits; as a result of laboratory report and/or imaging read findings; through other interactions with the participant, caregiver, and/or study partner/knowledgeable informant; or as a result of clinical monitor review of study records. Solicitation of specific events will not be required (i.e., the participant will not be asked if they have experienced any specific adverse events).

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

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### 7.5.4 SERIOUS ADVERSE EVENT REPORTING AND FOLLOW-UP

Any such experience due to any cause, which occurs during the course of the investigation or within 30 days of the last study visit, must be reported to the ATRI Coordinating Center within 24 hours after learning of the event. This in turn will trigger an alert to the appropriate ATRI Coordinating Center personnel, which will lead to the initiation of the creation of a report. Sites will report SAEs based on the IRB/IEC and local institutional requirements.

A serious adverse event (SAE) reported to have occurred within 24 hours of amyloid (FBP, FBB, NAV4694) or tau (FTP, MK6240, PI2620) PET tracer administration will be reported, regardless of the investigator's opinion of causation. Thereafter, sites must continue to report any serious or life-threatening adverse event whether or not it is related to study procedures. A subset of those SAEs may then be reported to Avid, Life Molecular Imaging (LMI) and Cerveau for events related to florbetaben, florbetapir, NAV4694, flortaucipir, MK6240, PI2620.

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

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

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

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

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

#### 7.5.4.1 EXPEDITED REPORTING

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

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### 7.5.5 EVENT CLASSIFICATION

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

### 7.5.5.1 SEVERITY

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

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

### 7.5.5.2 RELATIONSHIP TO INVESTIGATIONAL PRODUCTS AND STUDY PROCEDURES

The site PI (or medically qualified designee) will assess the relationship of an adverse event (AE) to NAV4694, MK6240, and PI2620 and study participation/procedures based on temporal relationship and clinical judgment. The degree of certainty about causality will be graded using the categories below and recorded in the CRF.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration). However, other factors may have contributed to the event (e.g., the participant’s clinical condition, other concomitant events). Although an AE may rate only as “possibly related” soon after discovery, it can be flagged as requiring more information and later be upgraded to “probably related” or “definitely related”, as appropriate.
- Unlikely Related – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the investigational PET tracer product) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant’s clinical condition, other concomitant treatments).
- Not Related – The event is completely independent of investigational product administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

### 7.5.5.3 EXPECTEDNESS

The Data and Coordinating Center in consultation with the IRB/IEC, will be responsible for determining whether an adverse event (AE) is expected or unexpected based on information provided by the clinical site or through central review activities. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

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## 7.5.6 REPORTING EVENTS TO PARTICIPANTS

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

MRI Clinical Read – Each research site is responsible for obtaining a clinical interpretation following local clinical practice for each MRI scan to make a determination whether additional follow-up and contact with the subject and their primary physician is indicated.

PET Clinical Read – Amyloid PET scans will be read by the PET Core; results will be reported to Site investigators, which in turn can be provided to the participant if the participant requests the result and to support clinical decision-making with regard to approved therapeutics such as aducanumab.

## 8 STATISTICAL CONSIDERATIONS

### 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 Alzheimer’s Therapeutic Research Institute (ATRI) as the Data and Coordinating Center.

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

#### 9.1.1 ADNI CORES

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

##### 9.1.1.1 ADMINISTRATIVE CORE

The overall goal of the Administrative (Admin) Core is to ensure the success and impact of the entire ADNI study. The Administrative Core developed and oversees the Ebusu platform used for data collection on the 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, see ADNI4: Remote protocol. The Administrative 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, see ADNI4: Remote protocol.

##### 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, including clinical site start-up and monitoring, regulatory oversight and data management. Safety oversight and reporting to the ATRI DSMB will be managed by the ATRI Medical Safety section. All ADNI4 in-person data collection will utilize the ATRI Electronic Data Capture (EDC) System<sup>48</sup>, with nightly uploads to LONI for sharing. The Clinical Core will collaborate closely with the Engagement Core and Admin Core on all recruitment and retention activities, assuring that 50-60% of new participants will be from URPs. 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 all 30,000 in the remote digital cohort, 6000 in



the remote blood cohort, the 750 roll-over ADNI-3 participants, and all study partners through every step of the remote activities for the ADNI4 study. 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. We anticipate 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 ADNI PET Core is to standardize the acquisition, quality control, processing, and analysis of multicenter PET data to provide a flexible dataset for analysis of longitudinal measurement of A $\beta$  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 guidelines documents on the ADNI/LONI website.

#### 9.1.1.7 GENETICS CORE

The mission of the Genetics Core is to identify and validate genetic markers for use in drug discovery and clinical trials. APOE genotype contributes to clinical trial stratification and enrichment as it influences onset age, A $\beta$  deposition/clearance, and susceptibility to adverse effects of anti-amyloid treatment. The Core will continue its focus on advances in genetics and related omics to discover, validate, and implement novel genetic markers that can improve the precision and power of AD clinical trials. The Core will provide APOE genotype, polygenic risk scores, increase statistical power for all analyses, and include new phenotypes to enable novel questions. New bioinformatics strategies will be used to analyze the growing 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. Neuropathology data will be interpreted to better understand the influence of non-AD pathologies on AD biomarkers and is essential for deciphering antemortem biomarker data accurately.

#### 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.

## 9.1.2 DATA AND COORDINATING CENTER

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

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

All communication to and from the data system is encrypted. All user and study data transmissions occur through a secure internet connection-HTTPS over TLS 1.2 and higher (Hypertext Transfer Protocol within a connection encrypted by Transport Layer Security) using secure 256 bit and stronger ciphers. All study data stored is encrypted at rest. Access is controlled on a per-user basis and access logs are kept and monitored on an ongoing basis to ensure data security and integrity, keeping data protected from improper use and disclosure. Each user of the system has an individual account with a password which is required to be reset at set intervals to comply with USC ATRI password requirements. Users are logged out of the system after a period of inactivity.

## 9.2 REGULATORY CONSIDERATIONS

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

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

## 9.3 INFORMED CONSENT

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

Informed consent will be obtained and documented in accordance with applicable local and regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and in adherence to ICH GCP.

Informed consent is a process that is initiated prior to an individual agreeing to participate in the study and it continues throughout an individual’s study participation. The informed consent process will be documented in the source document (including the date).

### 9.3.1 INFORMED CONSENT

The informed consent form (ICF) will be approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC). The ICF will be used to explain the study, potential risks and benefits of study participation in simple terms and to document that the participant (or surrogate/LAR) and study partner/knowledgeable informant are satisfied with their understanding and agree to participate in the study. Prior to signing, the participant (or surrogate/LAR) and study partner/knowledgeable informant will be given the opportunity to carefully review the ICF and ask questions.

The investigator is responsible to ensure the participant (or surrogate/LAR) and the study partner/knowledgeable informant understand the nature of the study, the procedures involved, the expected duration, the potential risks and benefits, potential alternative procedures(s) or course(s) of treatment available to the participant, the extent of maintaining confidentiality of the participant’s records, and their rights as research participants. The investigator (or designee) will answer any questions the participant and study partner/knowledgeable informant have throughout the study and will share, in a timely manner, any new information that may be relevant to their willingness to continue their participation. Communication of this information will be documented. Each participant and study partner/knowledgeable informant will be informed that participation in the study is

voluntary, that they may withdraw from the study at any time, and that withdrawal of consent will not affect their subsequent medical treatment or relationship with the treating physician.

The investigator (or designee) will provide a verbal explanation of the study, potential risks, and the participant's rights to the participant and study partner/knowledgeable informant that is suited to their comprehension.

The study partner/knowledgeable informant will document agreement to support the participant's participation in the study and will be provided with an ICF (or equivalent as per local requirements) specific to their participation in the study. This agreement (ICF or equivalent) must be signed prior to the study partner/knowledgeable informant participating in any further aspects of the study.

The original, signed ICF(s) (or equivalent for study partner/knowledgeable informant) will be kept on file according to local procedures.

The investigator (or designee) will provide a verbal explanation of the study, potential risks, and the participant's rights to the participant and study partner/knowledgeable informant that is suited to their comprehension.

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.

## 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 and the release of any tracer to the site (ICH E6, Section 4.4).

## 9.5 SAFETY OVERSIGHT

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

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

## 9.6 CLINICAL MONITORING

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

- Monitoring for this study will be performed by the Data and Coordinating Center.
- A combination of on-site and centralized monitoring will be performed for initial assessment of clinical sites readiness to screen and enroll participants and throughout the study to verify adherence to the protocol, completeness and accuracy of data, and adherence to applicable regulatory requirements and GCP. A risk-based approach will be taken to determine the extent of data review and verification focusing on eligibility as well as key endpoint and safety data variables. Site PIs are expected to cooperate in the monitoring process. Site PIs will be required to ensure the availability of source documents (as defined by ICH E6, Section 1.52) and other study records (including participants corresponding medical records) as requested, promptly address any matters brought to their attention by the Clinical Monitor, and meet in-person with the Clinical Monitor during certain site visits when requested.
- Clinical sites will be provided copies of post-visit letters. Monitoring Visit Reports (MVRs) will be maintained centrally.
- Details of clinical site monitoring will be documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Audits may be conducted by the Data and Coordinating Center (or designee) to ensure monitoring practices are performed consistently across all participating clinical sites and that Clinical Monitors are following the CMP.

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 PI will cooperate in the monitoring process by ensuring the availability of the eCRFs, source documents and other necessary documents at the time of the monitoring visits. The site PI will promptly address any matters brought to his/her attention by the monitor. The Site PI may also be asked to meet in-person with the site monitor during certain visits.

## 9.7 QA/QC

Data collected remotely via the Ebisu 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 Ebisu platform and database in compliance with the protocol.

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

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

Following written Standard Operating Procedures (SOPs), the Clinical Monitors will verify that the clinical trial is conducted 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)).

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

The Site Investigator and site personnel are responsible for maintaining the site master file containing all study-related regulatory documents as outlined by the Data and Coordinating Center. The site master file will be suitable for inspection at any time by the Data and Coordinating Center, its designees, and/or regulatory agencies. Inspections of site facilities (e.g., pharmacy, laboratories) may occur to evaluate study conduct and compliance with the protocol.

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

## 9.8 PROTOCOL DEVIATIONS

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

These practices are consistent with ICH GCP:

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

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

## 9.9 DATA HANDLING AND RECORD KEEPING

### 9.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES – EBISU

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

#### 9.9.1.1 DATA COLLECTION AND STORAGE

Study data will be collected remotely in the following ways:

- via Ebisu

The Ebisu software platform (Ebisu) is developed and operated by the University of California, San Francisco, and takes security and data security very seriously. Ebisu uses a cloud provider, Microsoft Azure, to assure that all servers and infrastructure used are in professionally-managed data centers with sophisticated intrusion detection, security perimeter management and robust firewalls. All data collected through this web-based platform including audio recordings will be stored on secure servers. While participating in research lends itself to a loss of privacy, every effort will be made to avoid this. Ebisu data system for 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. The Novoic Ltd. Testing Platform uses cloud providers (Amazon World Services and Google Cloud Platform), and assures that all servers and infrastructure used are in a professionally-managed data center with sophisticated intrusion detection, security perimeter management, and robust firewalls. Further, all software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data and communications are encrypted on the wire when transmitted over any network. All data stored are encrypted at rest. All Ebisu staff desktops and laptops make use of full disk encryption, virus scanner, and intrusion detection software. Participant information will be available only to the study PI and ADNI4 research staff, including Admin Core and Engagement Core staff.

#### 9.9.1.1.1 Remotely Collected Data: Ebisu

In order to provide the data generated from this project to ADNI investigators, pharmaceutical industry and the public through LONI in an anonymized manner (free of any identifying information such as name, address, or phone number), these 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 Ebisu 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).

Speech recordings, transcripts, and speech-derived measures generated by Novoic Ltd. for the ADNI4 study will be transferred to LONI at quarterly intervals, and may be made available for us by other researchers including those outside the study. Sharing of speech recordings and other identifiable data extracted from speech recordings will be subject to a separate speech-data use agreement that specifies the appropriate handling of the data. A participant's name will never be shared with those researchers. Deidentified data extracted from the speech recordings, including transcripts, will be more broadly available on LONI via ADNI's standard data use agreement.

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

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

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

All data for remote components of ADNI4 will be transmitted securely via the Internet to ADNI4 Admin Core. Access to the Ebisu 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. 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.

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## 9.9.2 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES – IN-CLINIC DATA

The Data and Coordinating Center is responsible for overseeing in-clinic data collection, standardization, data management, data transfer, and quality control.

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

### 9.9.2.1 DATA COLLECTION AND STORAGE

Study data will be collected in the following ways:

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

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

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

Except where otherwise specified in the relevant study manual, data will be collected on the CRFs and entered into ATRI EDC, a 21 CFR Part 11 compliant data management system provided by the ATRI Data and Coordinating Center. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent,

incomplete, or inaccurate. All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements.

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

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

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

#### 9.9.2.1.1 In Clinic Cohort Data: ATRI/LONI

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

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

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

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

All data will be transmitted securely via the Internet to ATRI at USC. Access to the database is role-based and will be limited to key personnel at sites and USC. Access is granted to study team members based on role. Each user of the system has an individual account with a password that is required to be reset at set intervals to comply with USC password requirements. Users are logged out of the system after a period of inactivity. All communication to and from the data system is encrypted.

Data transmission will occur through a secure internet connection. The ATRI Clinical Operations and Informatics Cores will also provide real-time web-based reporting on data flow; assure optimal data security and redundant data backups.

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

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

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

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

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

#### 9.9.2.1.3 Cohort Biomarker Data and Material Storage: UPENN

Blood samples from the in-clinic cohort and the remote cohorts will be maintained in the same way 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 with a bar code reading system. Bar code labels affixed to each sample vial will contain a Global Specimen Number which is a unique number that when used with the 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, and 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 the high-level protection with the UPHS Enterprise class perimeter firewall that includes a default deny policy. Access to LDMS has 4 layers of security: controlled building access, controlled laboratory access, PC password and LDMS password. VPN access is disabled so data are available only locally. The data are backed-up daily with 256-bit encryption and a copy is stored in a secure location.

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

#### 9.9.2.1.4 In Clinic Cohort Imaging Data Storage: LONI

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

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### 9.9.3 STUDY RECORDS RETENTION

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

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

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

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

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



## 9.10 CONFIDENTIALITY AND PRIVACY

The contents of this protocol and any amendments and results obtained during the study are to be kept confidential by the study staff, site PI, clinical site staff, and IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the Data and Coordinating Center. Data and biospecimens collected as part of the study shall only be used in accordance with the terms and conditions set forth in the Clinical Trial Agreement executed between the institution/site PI and the Data and Coordinating Center.

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

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

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

Clinical Monitors, other authorized representatives of the Data and Coordinating Center and/or the regulatory sponsor representatives of the IRB/IEC, may inspect all documents and records required to be maintained by the site PI, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical site will permit access to such records.

Any data, specimens, forms, reports, and other records that leave the clinical site will be identified by a PTID to maintain confidentiality. All physical records will be kept in a locked file cabinet. All computer entry and networking programs will be done using PTIDs only. Information will not be released without written permission of the participant, except as necessary for monitoring by the IRB/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, or Data and Coordinating Center and/or the regulatory sponsor requirements.

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

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### 9.10.1 HIPAA

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 the study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research participant to revoke their authorization for use of their PHI

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

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### 9.10.2 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.

## 9.11 FUTURE USE OF STORED SPECIMENS AND DATA

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

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

Audio recordings, transcripts, and speech-derived measures are also stored by Novoic Ltd. and LONI, on HIPAA compliant servers located in the USA. Sharing of speech recordings and other identifiable data extracted from speech recordings will be subject to a separate speech-data use agreement to better safeguard participant privacy. Deidentified data extracted from the speech recordings, including transcripts, will be more broadly available via LONI under ADNI's standard data use agreement.

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

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

## 9.12 PUBLICATION AND DATA SHARING POLICY

### 9.12.1 PUBLICATION OF RESULTS

The results of this study will be published in accordance with the 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.

### 9.12.2 SHARING OF STUDY DATA, BIOSPECIMENS, AND GENETIC MATERIAL

All ADNI data will be shared on the USC LONI ADNI website to all qualified scientists who complete the Data Use Agreement. 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 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.

Speech recordings and transcripts generated by Novoic Ltd. for the ADNI4 study will be transferred to LONI at quarterly intervals. Audio files may be shared with other researchers. To access that data, researchers must submit a research proposal for review, and would only obtain access if a proposal is approved and a speech-data use agreement is signed that specifies the appropriate handling of the data.

### 9.13 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this study will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this 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.

### 9.14 STUDY DISCONTINUATION AND CLOSURE

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

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

If the Data and Coordinating Center decides to suspend or terminate the study, written notification, documenting the reason for study suspension or termination, will be provided by the Data and Coordinating Center or suspending or terminating party to site PIs and regulatory authorities. If the study is suspended or prematurely terminated, the site PI will promptly inform study participants and the 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.

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

## 10 ABBREVIATIONS

|               |  |
|---------------|--|
| <b>AE</b>     | Adverse Event                              |
| <b>ANCOVA</b> | Analysis of Covariance                     |
| <b>CFR</b>    | Code of Federal Regulations                |
| <b>CLIA</b>   | Clinical Laboratory Improvement Amendments |

|                |   |
|----------------|---|
| <b>CMP</b>     | Clinical Monitoring Plan                            |
| <b>COC</b>     | Certificate of Confidentiality                      |
| <b>CONSORT</b> | Consolidated Standards of Reporting Trials          |
| <b>CRF</b>     | Case Report Form                                    |
| <b>CRLs</b>    | Community Research Liaisons                         |
| <b>CRNs</b>    | Community Research Navigators                       |
| <b>DCC</b>     | Data Coordinating Center                            |
| <b>DHHS</b>    | Department of Health and Human Services             |
| <b>DSMB</b>    | Data Safety Monitoring Board                        |
| <b>DRE</b>     | Disease-Related Event                               |
| <b>EC</b>      | Ethics Committee                                    |
| <b>eCRF</b>    | Electronic Case Report Forms                        |
| <b>FDA</b>     | Food and Drug Administration                        |
| <b>FDAAA</b>   | Food and Drug Administration Amendments Act of 2007 |
| <b>FFR</b>     | Federal Financial Report                            |
| <b>GCP</b>     | Good Clinical Practice                              |
| <b>GLP</b>     | Good Laboratory Practices                           |
| <b>GMP</b>     | Good Manufacturing Practices                        |
| <b>GWAS</b>    | Genome-Wide Association Studies                     |
| <b>HC</b>      | Health Canada                                       |
| <b>HIPAA</b>   | Health Insurance Portability and Accountability Act |
| <b>IB</b>      | Investigator's Brochure                             |
| <b>ICH</b>     | International Conference on Harmonisation           |
| <b>ICMJE</b>   | International Committee of Medical Journal Editors  |
| <b>IDE</b>     | Investigational Device Exemption                    |
| <b>IND</b>     | Investigational New Drug Application                |
| <b>IRB</b>     | Institutional Review Board                          |
| <b>ISM</b>     | Independent Safety Monitor                          |
| <b>ISO</b>     | International Organization for Standardization      |
| <b>ITT</b>     | Intention-To-Treat                                  |
| <b>LSMEANS</b> | Least-squares Means                                 |
| <b>MedDRA</b>  | Medical Dictionary for Regulatory Activities        |
| <b>MOP</b>     | Manual of Procedures                                |
| <b>MSDS</b>    | Material Safety Data Sheet                          |
| <b>NCT</b>     | National Clinical Trial                             |
| <b>NIH</b>     | National Institutes of Health                       |
| <b>NIH IC</b>  | NIH Institute or Center                             |
| <b>OHRP</b>    | Office for Human Research Protections               |
| <b>PI</b>      | Principal Investigator                              |

|            |                              |
|------------|------------------------------|
| <b>QA</b>  | Quality Assurance            |
| <b>QC</b>  | Quality Control              |
| <b>SAE</b> | Serious Adverse Event        |
| <b>SAP</b> | Statistical Analysis Plan    |
| <b>SMC</b> | Safety Monitoring Committee  |
| <b>SOA</b> | Schedule of Activities       |
| <b>SOC</b> | System Organ Class           |
| <b>SOP</b> | Standard Operating Procedure |
| <b>UP</b>  | Unanticipated Problem        |
| <b>US</b>  | United States                |

## 11 PROTOCOL AMENDMENT HISTORY

| Version | Date      | Description of Change | Brief Rationale |
|---------|-----------|-----------------------|-----------------|
| 1.0     | 12Jul2022 | N/A                   | Initial         |
|         |           |                       |                 |
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