ADNI4 Procedures Manual v2.0

ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE 4: IN-CLINIC

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Keck School of Medicine of USC
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CHAPTER 1: PROTOCOL SYNOPSIS

1.1 PROTOCOL SYNOPSIS

Title:	Alzheimer's Disease Neuroimaging Initiative 4 (ADNI4): In-Clinic
Study Description:	Non-randomized, natural history, non-treatment study
Objectives:	Primary Objectives: • Validation of biomarker measures • Inform clinical trial design • Increased inclusion of underrepresented populations (URPs) to improve generalizability of results and advance our understanding of health disparities across URPs. • Utility of web-based cognitive testing blood-based biomarkers to remotely identify and monitor those with AD biomarker pathology • Longitudinal changes in cognition and associated biomarkers • Prediction of cognitive decline • Discovery of novel risk and protective genes and pathways, and other known disease proteins found in AD brains.
Study Population:	Men and women aged 55-90 years across Cognitively Normal (CN), Mild Cognitive Impairment (MCI), and Dementia (DEM) populations. • Up to 750 new participants will be enrolled into the in-clinic cohort. Up to 750 will be rollover participants from ADNI3.
Phase:	N/A

Descriptions of Sites/Facilities Enrolling Participants:	Approximately 65 sites across the United States and Canada
Description of Study Intervention:	N/A
Study Duration:	5 years
Participant Duration:	The participant journey from initial visit to final visit may last up to 5 years

CHAPTER 2: SITE APPROVAL AND START-UP

Each site must meet start-up requirements before being granted approval to begin screening participants for the study. In order to meet these requirements, sites will work closely with several groups; please see the **ADNI4 Study Contact Sheet for contact information**.

- MRI Scanner Certification – Mayo MRI Group
- Personnel Requirements – ATRI Clinical Operations – ADNI4 Team
- PET certification is **not** required for ADNI4 if the same PET machine that will be used in ADNI4 is the same PET machine certified in ADNI3.
- IRB (central / local) approval, local radiation safety committee approval (if applicable), collection of applicable regulatory file documents – ATRI Regulatory Affairs (RA)

All of the requirements listed above must be met in order to receive full approval from ATRI to begin screening participants. We suggest working on the requirements in parallel.

- ATRI does not require a new executed ADNI4 contract for approval to start ADNI4 activities. See section 2.2 for more information.

2.2 CONTRACTS

An executed Master Contract, NIH Clinical Trial Agreement (CTA) is **not** required by ATRI but may be required by the site's institution prior to approval to begin screening. Prior to site approval to enroll, ATRI RA will need to confirm with each site if an executed (CTA) is required at their site. Please do not begin screening participants for ADNI4 until you have approval from ATRI to proceed. This ensures that your site is in compliance with all necessary start up pieces.

The Contracts & Budgets Team will be working with each site to make sure a master contract and a study signed agreement get completed as soon as possible.

2.3 PET SCANNER CERTIFICATION

If your PET scanner has been previously certified for ADNI3, certification is still valid. Recertification is only needed if your PET scanner has changed or has undergone a software or hardware upgrade. Please contact the PET Core team. For more information, refer to the PET Technologist Manual.

2.4 MRI SCANNER CERTIFICATION

Site MRI qualification requires a phantom scan and a volunteer scan. A volunteer scan may also be required if the scanner being used is NOT the same scanner that has been certified

previously by the Imaging Core for another similar study. **Volunteer scanning can be done for most sites before IRB approval because imaging data will not be stored**. **The Imaging Core Team will be in contact with your site to confirm which scanner will be used for this study and the certification requirements that are necessary**. For more information, refer to the MRI Technologist Manual.

2.5 PERSONNEL REQUIREMENTS

The following roles must be assigned in order to conduct the study. A single study team member can fill more than one role, if deemed appropriate by the Principal Investigator. Study-specific Personnel Sheets should be used to document which roles an individual will fill. The Personnel Sheet Instructions provides detail on how to complete the forms. Please review the instructions carefully and ensure all requirements have been delegated.

Ultimately it is the responsibility of the Principal Investigator to ensure all study team members are appropriately trained, qualified and able to perform responsibilities delegated to them in conduct of the study. A Training Log Template has been posted in the Document Repository under the Protocol folder for sites to use to document training of study team members if no other such mechanism for documentation of training exists at the site.

Role	Responsibilities may include, but are not limited to:
SITE PROTOCOL PRINCIPAL INVESTIGATOR (PI) The PI should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial	• Protect the rights and well-being of study participants • Conduct appropriate informed consent of study participants • Medical care of study participants • Supervise project personnel and ensure that clinical raters maintain a high level of skill and accuracy in conducting assessments • Perform or supervise clinical evaluation of all participants and ensure protocol adherence • Conduct the study in accordance with Federal Regulations, Internal Conference on Harmonization (ICH) and Good Clinical Practices (GCP) • Communicate with IRB • Maintain adequate and accurate source documents, study records and other study related reports (this includes data entered into the online EDC system) • Safety Reporting • Amyloid PET disclosure • **The Site PI may also serve as the study physician**
STUDY PHYSICIAN/SITE CLINICIAN This person must have credentials MD, DO, NP, APRN, MBBS, or PA-C.	• Conduct or supervise the clinical evaluation of all participants including physical and neurological exams, reviewing adverse events, and interpreting lab results at each study visit • Ensure that biological samples are correctly processed • Perform lumbar punctures unless another accredited individual is qualified to do so • Amyloid PET disclosure
STUDY COORDINATOR (SC)	• Manage the day-to-day conduct of the trial • Ensure accurate administration of all instruments at the site • Supervise accurate data collection and maintaining case report forms

	• Preparing, handling, and processing of all laboratory samples. • Coordinate clinic visits • Schedule visits at the MRI center, PET center and for LP procedures • Serve as a POC with the Coordinating Center/Clinical Monitor • Maintains contact with the Neuropathology Core Coordinator and coordinates contact between NPC and the site's Neuropath Lab or equivalent. This individual is fully informed on all procedures for brain donation at the site level. • May serve as the interviewer/psychometrician as long as he/she is properly trained • **Share communication from Coordinating Center with site staff as appropriate.** The Coordinating Center standard is to include PI and SC on all disseminated communication. The expectation is that SC will triage the communication further to applicable site staff.
REGULATORY	• Manage all regulatory related documents for the duration of the trial, including submitting all required regulatory documents to Regulatory Affairs • Ensure that all safety reports, protocol deviations, continuing review documents, protocol amendments and consent form modifications are submitted to the IRB in a timely manner and per the IRB's SOPs • Serve as the liaison between the site IRB and ATRI Regulatory Affairs
BILLING – REMITTANCE	• Accept and process payments from ATRI
BILLING – STATEMENT	• Review and verify payments from ATRI are in alignment with procedures completed
MRI CONTACT	• Conduct MRI scans per protocol for site qualification purposes and as needed to assess for drift or liaison with MRI Technician • Conduct participant MRI scans per protocol or liaison with MRI Technician • Upload MRI scans to LONI in a timely manner • Ensure that all MRI data is archived according to protocol
PET CONTACT	• Conduct PET scans per protocol for site qualification purposes and as needed to assess for drift or liaison with PET Technician • Conduct participant PET scans per protocol or liaison with PET Technician • Upload PET scans to LONI in a timely manner • Ensure that all PET data is archived according to protocol
LUMBAR PUNCTURE CONTACT	• Perform lumbar punctures
PROJECT INTERVIEWER / PSYCHOMETRIST/ RATER	• Have at least a bachelor's degree in healthcare psychology, social work or a related field, and/or well-documented experience in administering interviews and neuropsychological tests • This person may be responsible for administering the ADAS-Cog and CDR

RECRUITMENT CONTACT	• Manage recruitment for the duration of the study • Serve as the POC for the ATRI Recruitment Core and the Admin Core
COMMUNITY RESEARCH LIAISON	• Only applicable to ADNI4 Engagement Core Hub sites • Manage *URP-specific recruitment and engagement for the duration of the study • Serve as the POC for the Engagement Core

*Note: URP = Underrepresented Populations (e.g., Black or African American, Latino/a/x, Asian, Native Hawaiian/Other Pacific Islander, American Indian/Alaskan Native, persons with less than 12 years, and people who live in rural areas)

2.6 REGULATORY REQUIREMENTS

For sites in the US, Advarra is the IRB of record for the ADNI4 study. Documentation of Advarra IRB approval, local IRB reliance approval and local radiation safety approval (if applicable) will be required for site approval to enroll. Instructions on how to submit to Advarra is available in the document repository under Study Docs: Advarra IRB.

For sites in Canada, local REB approval and local radiation safety committee approval (if applicable) will be required for site approval to enroll.

For all sites, documentation of a completed regulatory file, verified by ATRI Regulatory Affairs, will be required for site approval to enroll. A regulatory file checklist, as well as template regulatory file documents, are available in the document repository under Study Docs: Regulatory Document Templates.

CHAPTER 3: CERTIFICATION, TRAINING AND EXPERIENCE

TRAINING AND CERTIFICATION MATERIALS ARE POSTED IN THE DOCUMENT REPOSITORY IN THE ADNI4 DATA PORTAL. NOT ALL STUDY TEAM MEMBERS (I.E., NEW PERSONNEL, PET TECHS, CLINICIANS, ETC.) HAVE ACCESS TO THE ADNI4 DATA PORTAL. STAFF THAT HAVE ACCESS TO THE DOCUMENT REPOSITORY (I.E., THE STUDY COORDINATOR (SC) OR SC BACK-UPS) SHOULD MAKE EDC STUDY TRAINING MATERIALS AVAILABLE TO OTHER TEAM MEMBERS AS NEEDED

It is the responsibility of the Site Principal Investigator (PI) to supervise delegated personnel and ensure clinical raters have the appropriate education, and experience to maintain a high level of skill and accuracy while conducting assessments. As required, certification must be completed prior to the administration of a cognitive instrument. All such training records, certifications etc. are maintained in your site's regulatory binder or study binder. Such documentation may need to be submitted to the ATRI Coordinating Center during start-up and throughout the course of the study as new personnel are trained.

Activities requiring certification:

- Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog)
- Clinical Dementia Rating Scale (CDR)
- EDC Access: EDC Certification is required for all individuals with access as requested

through the personnel sheet.

- Amyloid PET Disclosure: Certification is required for all appropriately delegated individuals prior to the first disclosure.

3.1 ADAS-COG CERTIFICATION

Only raters with current ADAS certification (granted via the process described here) may administer the ADAS-Cog. Certification procedures are detailed in the **ADAS Rater Certification Worksheet**.

NEW AND INEXPERIENCED ADAS RATERS:

New or inexperienced raters (less than one year of experience with the ADAS/or fewer than 10 ADAS administrations) must perform and document the completion of practice sessions prior to the real-time observation. Document five (5) ADAS administrations with at least two (2) under the supervision of an experienced ADAS rater in the ADAS Worksheet/Rater Worksheet. If the site does not have an experienced rater, contact ATRI Coordinating Center to set up observations. Certification will be provided after rater provides documentation of the following in the ADAS worksheet/Rater Worksheet to ATRI.

- Review of ADAS Manual (version dated October 10th, 2013)
- Review of Site-Specific Scoring Rules approved by ATRI Coordinating Center
- A real-time observation by an ADAS certifier of an ADAS testing session conducted by the rater

After observing the rater administering the ADAS, the ADAS certifier may require further practice sessions before certification is issued.

Once all requirements are fulfilled, a certification letter will be provided to the rater, indicating the period of validity (typically 1-2 years). Re-certification is required at the end of this period.

ADAS CERTIFIED:

Experienced ADAS raters and ADNI3 certified raters will complete the Expedited certification guidelines. Experienced Raters complete all steps except documentation of additional practice administration in the ADAS Worksheet/Rater worksheet is not required.

IF THE ADAS RATER WAS CERTIFIED FOR ANOTHER ATRI STUDY, THE ADAS CERT LETTER WILL SPECIFY IF IT IS STILL VALID. PLEASE REFER YOUR QUESTIONS TO ADNI-STUDY@ATRIHUB.IO

3.2 CLINICAL DEMENTIA RATING (CDR) CERTIFICATION

Ideally, the CDR rater will NOT be involved with any other cognitive or functional assessments and, if possible, the same CDR rater should administer the CDR for a given participant throughout the study. If it is anticipated that the CDR rater will be involved with other cognitive testing, then consult with the ATRI Coordinating Center prior to administration of the CDR so that the details can be discussed with study leadership.

All individuals administering the CDR must be certified through Washington University. Depending on previous CDR certification there are two separate requirements. CDR Certification and Refresher Course can be found online at the following url:

https://knightadrc.wustl.edu/cdr-public-training-path/

NEW AND INEXPERIENCED RATERS:

If a rater has **never** been CDR certified, full certification is required. The training includes nine (9) reliability tapes. The ratings/scores are compared to the Gold Standard and, if the rater passes, Washington University will issue a certificate.

CDR CERTIFIED:

For those raters who have been certified over 5 years ago, a refresher course is required. This refresher includes the review and scoring of five (5) reliability tapes. The ratings/scores are compared to the Gold Standard and, if the rater passes, Washington University will issue a certificate.

IF THE CDR RATER WAS CERTIFIED THROUGH WASHINGTON UNIVERSITY WITHIN THE PAST FIVE YEARS, THEIR CERTIFICATION IS VALID AND CERTIFICATION IS NOT REQUIRED AGAIN UNTIL EXPIRES. PLEASE ENSURE YOU PASS YOUR VALID CERTIFICATION TO ADNI-STUDY@ATRIHUB.IO

3.3 ADNI4 - ELECTRONIC DATA CAPTURE (EDC)

With the exception of PHI and scans, all data collected for ADNI4 must be entered into the EDC system. Therefore, ATRI EDC certification is required for anyone with access to the EDC. Account creation will be based on the access level selected on the ADNI4 Personnel Sheet. Please review the Personnel Sheet Instructions for additional guidance, available in the EDC Document Repository under the Personnel Sheet folder.

ATRI EDC certification can be completed as a self-study by reviewing the training slides available in the EDC Document Repository under the EDC Certification folder. Personnel must review the training presentation and sign the certificate (last page) of the presentation. Submit your signed certification to adni-study@atrihub.io and keep a copy on file at site.

PERSONNEL REQUESTING AN EDC ACCOUNT WITH EDIT/SIGN OFF ON PARTICIPANT ELIGIBILITY MUST HAVE CREDENTIALS MD, DO, NP, APRN, MBBS, OR PA-C.

Accounts are created within one week. Confirmation email includes a username and a link for establishing passwords. Personnel will need to complete confirmation of account as link expires within seven days.

For more information on how to enter study data, review the ADNI4 Data Entry Manual.

OTHER INSTRUMENTS ADMINISTERED FOR ADNI4 STUDY DO NOT REQUIRE FORMAL TRAINING CERTIFICATION. IT IS THE RESPONSIBILITY OF THE PI TO ENSURE EVERY RATER RECEIVES APPROPRIATE TRAINING.

3.4 ADNI4 – GLOBAL UNIQUE IDENTIFIER (GUID)

All ADNI4 participants must be assigned a GUID, per NIA. ADNI4 will use a different GUID tool than ADNI3. Therefore, a new GUID must be generated for every ADNI4 participant, including

rollovers. In order to generate the GUID, you will need to visit https://bricsguid.nia.nih.gov/portal/ and request an account. Please note it takes 2-4 business dates to get an account issued. Study personnel must obtain a GUID account prior to screening the first participant. Please return via email to adni-study@atrihub.io confirmation of GUID account being generated.

The new ADNI4 GUIDs include asking the participant for their city of birth. If any participant expresses concerns about providing this information, please reassure them that their personal information is not recorded as part of their ADNI4 data and will not be shared with anyone.

IF YOU HAVE ANY ISSUES OR NEED MORE ASSISTANCE SETTING UP YOUR GUID ACCOUNT, PLEASE EMAIL CUSTOMER SUPPORT-NIABRICSOPERATIONS@MAIL.NIH.GOV AND REACH OUT TO YOUR LOCAL IT.

3.5 ADNI4 – AMYLOID PET DISCLOSURE

In ADNI4, site PI or appropriately delegated site personnel may disclosure amyloid PET results to eligible participants. Eligible participants are those who have consented to receive their amyloid PET results and are deemed psychologically well by disclosing clinician at time of disclosure.

In order for a member of the study team to disclose a participant's amyloid status, that individual must:

- Have acceptable credentials – MD, DO, NP, PA, RN, PsyD, PhD and have site PI permission to disclose amyloid PET results;
- Read the disclosure process as described in the ADNI4 Disclosure Training Manual; and
- Agree to following personal attestation: "I am comfortable disclosing Amyloid PET results to ADNI participants who are cognitively normal or have diagnoses of mild cognitive impairment (MCI), dementia, and Alzheimer's disease.

If a member of the study team meets all of the criteria above, they must return an Amyloid Disclosure Certification to the ADNI4 Clinical Operations Support Team (adni-study@atrihub.io).

CHAPTER 4: RECRUITMENT AND RETENTION

4.1 OVERALL ADNI4 RECRUITMENT AND RETENTION

ADNI4 will use multiple sources for recruitment and retention efforts: ATRI Recruitment and Retention, referrals from the Remote Digital and Remote Blood cohorts via the Ebisu ADNI online portal, and assistance from Alaniz marketing. Hub Sites will receive additional referrals from Community Research Liaisons, and should refer to their Engagement Core Hub Site SOP manual for additional details.

Recruitment of ADNI3 participants (termed rollovers) into ADNI4: A major priority for each clinical site is to encourage as many ADNI3 participants to continue in the ADNI study by

enrolling in ADNI4. These individuals are termed rollovers. Special emphasis should be given to encouraging URPs from ADNI3 to enroll in ADNI4. It is the responsibility of clinical site staff to contact ADNI3 participants and explain the importance of ADNI4. Specific materials are provided by the ATRI staff to the site for this purpose.

Recruitment of new participants into ADNI4: ADNI has set an overall recruitment goal aiming for 50-60 % of all new enrollments to come from Underrepresented Populations (URPs) including: Black/African American, Hispanic/Latino, Asian, American Indian/Alaska Native, Native Hawaiian, Pacific Islander adults, persons with less than 12 years of education, and people who live in rural areas. Furthermore, the goal is to enroll across the AD spectrum, with ADNI aiming for 20% of new enrollments with dementia, 40% with MCI and 40% who are Cognitively Normal. All new participants will be screened and enrolled by the clinical site staff. There are two major ways that these participants can be identified, and a third pathway for ADNI4 Hub Sites:

(1) Direct recruitment by clinical site staff: Site staff may identify and recruit ADNI4 participants from patients who come to their clinic for assessment, or from the variety of recruitment approaches being used by their clinical site. The following groups of participants can be directly screened and enrolled by the clinic site staff: All URPs (CN, MCI, Dementia), and non-Hispanic white adults with MCI and Dementia. The clinical sites are strongly discouraged from enrolling Cognitively Normal non-Hispanic white adults. Highest priority should be given to URPs with MCI and Dementia, with secondary priority given to URPs who are CN. ATRI can provide sites with recruitment and informational materials about ADNI4, and additional materials can be created with the help of Alaniz Marketing. If your site is interested in receiving tailored marketing materials, please contact: site.support@adni4.org

(2) Referral to clinical site staff from Remote Digital and Remote Blood cohorts: In addition to direct recruitment by the clinical site staff, ADNI4 will recruit participants to join the Remote Digital and Remote Blood cohorts. These Remote cohorts will be pre-screened to identify a curated group of participants that site staff will be able to contact and consider for on-site screening. The Admin Core is operating the Ebisu ADNI Online platform (see Chapter 4.3) which is where participants will complete remote questionnaires and assessments. Clinical site staff will have access to an Ebisu ADNI Online Investigator Portal where pre-screened referrals from Remote cohorts will be visible to site staff. Clinical site staff will have the ability to update the ADNI4 Administrative Core about the timing and tempo of referrals from the Remote cohorts via the ADNI Online Investigator Portal. The Admin Core may also directly reach out to sites to communicate about the referral process from Remote cohorts (Admin Core staff can be reached at: site.support@adni4.org). A new CRF has been developed to record/assign an Ebisu ADNI ID to all individuals that sites screen and/or rollover. This CRF is critical for connecting data across the Remote and In-clinic participation pathways and for ensuring high-quality referrals to clinical sites.

a. 1-888-299-ADNI (2364) will connect ADNI participants to Community Research Navigators (CRNs), who can assist with all ADNI Online activities (note: this phone line does not connect participants with clinical sites or site staff)

(3) For ADNI4 Hub Sites - Recruitment by Community Research Liaisons (CRLs): About a third of ADNI4 sites will be designated as 'Hub Sites', which are provided with additional resources including funding to hire CRLs. The CRLs are site staff who will focus on community-sourced URP recruitment and retention. CRLs will help to identify individuals who can be screened at their site, especially focusing on URPs who are likely impaired.

4.2 ATRI RECRUITMENT AND RETENTION SUPPORT

ADNI4 Clinical Core Recruitment and Retention (R&R) efforts will be led by the ATRI ADNI4 R&R team. The focus of the R&R efforts will be support across all ADNI4 sites regarding (a) recruitment efforts to enroll the Mild Cognitive impairment (MCI) and Alzheimer's disease (AD) cohorts, (b) guidance and support for all ADNI3 rollover participants into ADNI4, and (c) retention support for all ADNI4 participants, in close collaboration with the ADNI4 Engagement Core.

Resources, materials and engagement provided by the ATRI R&R team will be made available to all ADNI4 sites.

The ATRI R&R team will continually engage with all ADNI4 sites throughout the study R&R efforts. This will be done through email and/or phone communication, R&R specific site webinars, and more.

Sites can reach out to the ATRI ADNI4 R&R team at any time using the study email: ADNI-participate@usc.edu

4.2.1 ATRI R&R MATERIALS

The ATRI ADNI4 R&R team will maintain a "toolkit" of documents and other resources, including recruitment materials, educational tools, and templates for the recruitment of the MCI and AD cohorts, as well as supportive materials for rollover participants and the retention of participants. Materials will be made available throughout the study in English and Spanish.

All materials produced by the ATRI ADNI4 R&R team will be submitted to the IRB on record (Advarra) by the ATRI ADNI4 R&R team, on behalf of sites. Sites will have access to approved materials within the Advarra portal, as well as the Docs Tool within the EDC. Sites are also welcome to create and submit their own materials to the IRB for review.

Examples of the types of materials that will be available for site use include:

- **Flyers**
- **Tri-fold Brochures**
- **Dear Colleague Letter**
- **Draft Press Release**
- **Thank You Letter**
- **Certificate of Completion**
- **Appreciation Gifts**
- **Participant Newsletters**

If a site experiences challenges in study recruitment and/or retention, a site specific recruitment and retention plan will be developed in collaboration with the ADNI4 R&R teams across all cores.

4.3 ADDITIONAL RECRUITMENT SUPPORT

Additional recruitment support is available in ADNI4 from the Administrative and Engagement Core teams. Site enrollment goals will also be assisted by referrals from the Remote cohorts, which will focus on URP recruitment. For assistance related to referrals from the Remote cohorts, or if your site is interested in developing marketing materials for local URP recruitment (in conjunction with Alaniz), please contact the Admin Core at: site.support@adni4.org.

4.4 ALANIZ MARKETING

ADNI4 is contracting with the Alaniz marketing firm to assist with marketing materials, especially for the recruitment and retention of URPs. All sites that are interested can request to have tailored informational and/or marketing materials, including local-site branded ADNI websites, created for them with the help of the Administrative and Engagement Cores and Alaniz. Sites can reach out to site.support@adni4.org to receive more information about Alaniz marketing.

Alaniz marketing has helped create social media campaigns and digital advertisements that will drive people to an adni4.org recruitment webpage to enroll into the Remote Digital cohort, with the goal of screening individuals before referral to clinical sites. Alaniz will also create various 'microsites' (tailored websites) aimed at recruiting specific groups for ADNI4 (Black/African-American, Hispanic/Latino, etc.) residing in geographies specific to clinical sites. These websites will provide information about the entire ADNI4 study, and encourage people to join ADNI by first enrolling in the ADNI4 Remote Digital Cohort. Participants who join the Remote Digital cohort will be screened (demographic questions, some inclusion/exclusion criteria questions, and subjective and objective cognitive assessments), and a subset will be referred to the Remote Blood cohort. Participants in the Remote Blood cohort will visit a Quest Diagnostics clinic and provide a blood sample for AD biomarker analysis. Ultimately, the information collected on Remote Digital and Remote Blood cohort participants will be used to provide Clinical Site Staff with a curated list of 'pre-screened' participants that site staff can then use as a recruitment source to populate their ADNI4 In-Clinic cohort.

4.5 REFERRALS FROM EBISU – ADNI INVESTIGATOR PORTAL

One of the new approaches that we believe will help site efficiency in recruitment efforts are the ADNI4 Remote Digital and Remote Blood cohorts. These participant cohorts will be used as a referral source for ADNI Clinical Site staff to draw upon. This referral program will be managed by the ADNI Admin Core via the Ebisu ADNI Online platform – a secure and encrypted platform that includes the Ebisu ADNI Investigator Portal (IP).

For detailed instructions with screenshots of how to claim referrals and update referral status, please see the "ADNI4_Ebisu Investigator Portal Guide" document in the "Ebisu ADNI Online" folder in the EDC Document Repository.

The Ebisu ADNI IP is entirely online and can be accessed by visiting:
https://ebisu.adni4.org/login

Each clinical staff user (recruiter, study coordinator, etc.) will have their own account. Users will only have access to the studies/sites that they are approved to work on. Furthermore, users will only have access to site information at the site where they work. For any Ebisu IP account questions, contact site.support@adni4.org.

ACCESSING/"CLAIMING" REFERRALS FROM THE EBISU ADNI IP FOR IN-CLINIC SCREENING:

1. Site staff will tell Admin Core (site.support@adni4.org) the number of new referrals per month that you can support.
2. You will receive an email notification when a new Remote referral is available for your site. You can access the referral's contact information for In-Clinic cohort screening via the Ebisu ADNI IP. **We request that site staff make initial contact with a referral within 4 weeks.**
3. Log onto https://ebisu.adni4.org/login
4. Select your study: ADNI4
5. On the left black navigation bar, click Referrals, then Unclaimed from the drop down.
6. Within the Unclaimed Referrals table, you will see a list of participants that have not been "claimed"/contacted by your site.
7. To retrieve the contact information for a referral, click the blue Claim button (note only one referral can be claimed at a time).
8. This will take you to the Subject page where you can view contact and other basic information for this referral and find their Ebisu ADNI Online ID.
9. Once claimed, the referral will move from the Unclaimed table to the Claimed table.
10. A claimed Remote referral can then be screened by site staff to join the In-Clinic cohort.
11. If a referred participant is screened by site staff at the clinic, then site staff will record the Ebisu ADNI Online ID for that individual on the new Ebisu ADNI Online ID CRF during the screening visit (see Chapters 5.1.3 and 6.2).
12. Site staff should regularly update the "Eligibility" status of the referrals that they have contacted from the Remote cohorts. On the Ebisu IP, site staff can search for the participant's name to view their Subject page. On the upper right corner under "Interested" there is an option to "Update Eligibility." See the Ebisu Investigator Portal Guide for detailed instructions.

The Ebisu ADNI IP will also be used by site staff to register ADNI3 rollovers and new ADNI4 participants who do not come to the site via the Remote Digital or Blood cohorts, for **remote longitudinal monitoring** activities (see Remote and In-Clinic protocols and Chapter 5.1.3 and 14.1).

CHAPTER 5: GENERAL INFORMATION

5.1 STUDY SUPPLIES

5.1.1 ATRI PROVIDED SUPPLIES

ATRI will provide some administrative supplies and supplies required for collection of genetic, biomarker, and CSF samples.

INITIAL SUPPLIES:

Regulatory staff will notify sites by email when they are approved to launch study activities. All ATRI supplies are shipped within two weeks of site activation and may be expedited if prior arrangements have been made. An email notification will be sent out on the date that supplies are shipped.

FOLLOW-UP SUPPLIES:

There are no automatic shipments of ATRI supplies. To order additional supplies, please use the ADNI4 Supply Order Form which can be found in the Document Repository under ATRI order form folder. Please be sure to order supplies far enough in advance of scheduled visits (at least 8-10 business days prior).

SUPPLIES PROVIDED BY ATRI

- Research Lab and CSF collection kits – refer to the sample collection and CSF collection chapters of the Procedures Manual as well as the Lab manuals for more detail.
- Regulatory binder inserts – provided by ATRI Regulatory Affairs.
- Participant binder inserts/tabs, spine and covers. (The cost of the actual participant binders has been factored into the startup fund distributed at the beginning of the study; therefore, actual participant binders will **NOT** be provided by ATRI at all).
- Neuropsychometric Testing Supplies:
    - ADAS kits if needed (sites are encouraged to access the kits they may have on hand from other ATRI studies; word lists can be ordered separately)
- Hard copies of the MMSE Worksheet
    - Due to copyright restrictions, the MMSE will not be included in the source document worksheet packets. The number of hard copies of the MMSE included in the initial shipment from the ATRI will be based on the number of potential participants prescreened at your site. The online supply order form will need to be used to order additional copies of the MMSE.

DO NOT MAKE PHOTOCOPIES OF THE MMSE WORKSHEET AT ANY TIME. HARD COPIES SHOULD BE ORDERED DIRECTLY FROM THE ATRI.

- Electronic copies of the study documents like the following are available in the study folder of the Document Repository: Protocol, Procedures Manual, Worksheets, Data Entry Manual

5.1.2 LABORATORY SUPPLIES PROVIDED BY URMC

URMC will provide supplies for safety/clinical labs. Note, in ADNI4, safety/clinical labs will be collected at all visits, not just screening/initial. For more information about kits, please refer to the URMC Lab manual available in the doc repository under the Labs – Clinical Safety folder.

There are no automatic shipments after the initial set of supplies are sent to the site. To request additional specimen collection kits, please use the kit re-supply form, found in the URMC lab manual, and fax or email it accordingly. Please refer to the URMC Lab Manual for more information about the lab reports and alerts, specimen collection, packaging, and shipping.

5.1.3 OVERVIEW OF SYSTEMS

ATRI ADNI4 DATA PORTAL (EDC)

Once ATRI site approval to begin screening participants for the study, key study team members will be provided access to the EDC data portal. Accounts will be created for the remaining team members based on completion of the Personnel Sheet (PSheet), indicating the required level of access. See Personnel Sheet Instructions for details on how to complete and submit the form.

New accounts following site initiation will be set up following completion of the Psheet. Please allow a 5-day turn-around time for the set-up of new accounts.

NEVER SHARE YOUR PASSWORD WITH ANOTHER PERSON

EVERY INTERACTION IN THE STUDY DATA PORTAL IS TIME/DATE STAMPED AND CAN BE TRACED BACK TO THE USER WHO COMPLETED THE TRANSACTION

The study data portal consists of the following systems and activities. Access to individual tools is dependent on PSheet specifications:

- **EDC** – View and/or Enter eCRFs, including:
  - Register participants / obtain participant IDs
  - Enter study data
  - Electronic sign off on participant eligibility
  - Record protocol deviations
  - Upload source documents

REMOVE ALL PARTICIPANT IDENTIFIERS (INCLUDING NAME, INITIALS, MEDICAL RECORD NUMBER) ON ANY FORMS UPLOADED IN THE EDC.

IDENTIFY THE SUBJECT ONLY BY: STUDY PARTICIPANT ID, VISIT NAME AND DATE

- **Query Management** - Create, view, and respond to queries (tab within the study portal)
- **Doc Tool** - Access to study documents including the Procedures Manual, Imaging Technologist Manuals, Safety Lab Manual, Supply Order Form, Source Doc Worksheets, Training Materials.

FOR ADDITIONAL INFORMATION ON ACCESSING THE DATA PORTAL AND THE SYSTEMS AND ACTIVITIES WITHIN THE DATA PORTAL, REFER TO THE POSTED MATERIALS

ADMINISTRATIVE CORE: EBISU ADNI ONLINE

The Ebisu ADNI Online platform serves as the data collection website for **all** participants who complete Remote longitudinal monitoring activities as part of ADNI4. This novel part of the ADNI4 study will allow us to test new methods to remotely monitor eligible participants and their cognitive state by asking them to complete activities such as the ECog 12-item questionnaire and the Novoic Storyteller memory test, online remotely every six months.

The Ebisu ADNI Online is equipped with an Investigator Portal (IP) which will be used by site staff:

1. to register rollover and direct recruit participants for longitudinal remote activities
2. to collect and update status of referrals from the Remote Digital and Remote Blood cohorts (see Chapter 4.5)
3. to obtain an ADNI Ebisu ADNI Online ID for **all** in-clinic participants

All participants must have an Ebisu ADNI Online ID entered into the Ebisu ADNI Online ID CRF. Remote referrals have an existing ID by way of Remote participation. Site staff must register participants who are direct (non-Remote) recruitments or rollovers in order to generate an ID. DEM/AD participants will not be asked to join remote longitudinal monitoring, but still need to have an Ebisu ADNI Online ID assigned to them.

SITE STAFF WILL ASSIGN/RECORD AN EBISU ADNI ONLINE ID TO ALL PARTICIPANTS AT THEIR INITIAL OR SCREENING VISIT VIA THE EBISU ADNI ONLINE ID CRF

INSTRUCTIONS CAN BE FOUND IN THE EBISU IP GUIDE ON EDC AND BELOW

Registering rollover and direct recruit (non-Remote referral) participants

- For participants who rollover from ADNI3 to ADNI4 or new participants that site staff directly recruit and enroll in the ADNI4 In-clinic cohort, site staff will log into the Ebisu ADNI Investigator Portal and 'register' the participant's information at the initial or screening visit, respectively (see Chapter 14.1). This will generate an Ebisu ADNI Online ID which needs to be entered into the ADNI Online ID CRF.
- At the initial or screening visit, site staff should provide all in-clinic participants with the "ADNI Online Participant Information" sheet, which is located in the EDC document repository in the Ebisu ADNI Online folder.
- For detailed instructions, see the "Ebisu Investigator Portal Guide" in the EDC document repository Ebisu ADNI Online folder.

Claiming remote referral participants

- One of the new approaches that we believe will help site recruitment efforts are the ADNI4 Remote Digital and Remote Blood cohorts. These will be a referral source for

ADNI Clinical Site staff to draw upon (see Chapter 4.5).

- For detailed instructions, see the "Ebisu Investigator Portal Guide" in the EDC document repository Ebisu ADNI Online folder.

Any questions that In-Clinic participants have about the ADNI Online activities can be answered by our Community Research Navigator team at info@adni4.org or at 1-888-299-ADNI (2364).

USE OF MULTIPLE LOCATIONS AT A SINGLE CENTER

The following guidelines have been developed to facilitate the decision-making process with respect to the use of additional locations at a single center. These guidelines apply to multiple locations of the main clinic and do not apply to ancillary services/centers (e.g. pharmacies, MRI, PET centers etc.).

- The Site PI must take responsibility for all locations
- No additional contracts will be provided for other locations affiliated with the center
- A single study coordinator must be used for all locations. This individual must be available to Clinical Monitors to answer any questions about data entered in the EDC System from any location. The Coordinating Center should be immediately notified if the study coordinator changes
- Monitoring visits must be conducted at a single location
- All source documents must be maintained at a single location in order to avoid the expenses associated with additional travel by the Clinical Monitors

Any plan to use more than one (1) location to conduct the study must be approved by ATRI.

CHAPTER 6: NEW ENROLLEES – SCREENING PROCEDURES

6.1 SCREENING OVERVIEW

The purpose of the ADNI4 Screening Visit is to determine eligibility and to collect measures that will be used as a reference to assess change. Only newly enrolled participants, including those directly identified by the site and those referred from the Remote Digital or Remote Blood cohorts will have a screening visit. A standardized evaluation will be performed at each clinical site.

Prescreening participants during telephone scheduling does not require Informed Consent. However**, Informed Consent must** be obtained before any portion of the screening visit is initiated. Eligibility will be determined according to the Inclusion/Exclusion criteria outlined later in this section before the participant can be brought back for Baseline.

The following items will be covered in this section:

1. PARTICIPANT INDENTIFIERS
2. DATAFLOW
3. SCREEN FAILURES AND RESCREENS
4. INCLUSION CRITERIA
5. EXCLUSION CRITERIA
6. EXCLUDED MEDICATIONS

7. PERMITTED MEDICATIONS
8. SCREENING ASSESSMENTS
9. SCREENING BLOOD DRAWS

KEY REMINDERS:

- 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.
- Participants must meet all inclusion/exclusion criteria. Exceptions can be made on a case-by-case basis with approval from Medical Monitors and Leadership. Please see the study contact sheet available in the EDC Document Repository under the study contact sheet folder.
- Complete Data Entry within 1-2 business days of the screen, including Laboratory Reports. This is extremely important because it is the only way that ADNI4 leadership can monitor enrollment progress.

PARTICIPANT IDENTIFIERS

There will be two different formats of Participant ID (PTID) in ADNI4

- Rollover PTID: consists of the ATRI 3-digit site number, a single character identifier (S for 'Subject' or P for 'Phantom'), followed by a sequential 4-digit subject number reflecting the chronological order in which the ID's are assigned across sites. Participants from participants enrolled into ADNI2 began at 4001, participants enrolled into ADNI3 began at 6000.
    - XXX-Y-ZZZZ
- New participant PTID: consists of the ATRI 3-digit site number, a single character identifier (S for 'Subject' or P for 'Phantom'), followed by a sequential **5-digit** subject number reflecting the chronological order in which the ID's are assigned across sites. New participants in ADNI4 will begin at 10000.
    - XXX-Y-**ZZZZZ**

Use the Participant ID for all study documents, source documents, MRI/PET scans and biologic samples. Phantom IDs are not assigned on the ADNI Clinical Data Portal. Assign Phantom IDs following instructions in the MRI and PET technologist manuals. If the participant is a rollover, diagonally line through the empty 5th digit on all documentation and labels.

IMPORTANT: PARTICIPANT ID'S MAY ONLY BE ASSIGNED ONCE CONSENT IS SIGNED. ASSIGN THE ID ON THE DAY OF SCREENING WHENEVER POSSIBLE. ONCE ASSIGNED, IDS CANNOT BE REMOVED FROM THE ADNI4 DATA PORTAL.

To Assign an ADNI PTID for New Participants:

- Log on to the ATRI ADNI4 data portal

- From the EDC tab in the participant list menu click “Add Participant”
- Indicate language (English or Spanish), and if previously enrolled (yes/no) in ADNI
- The new participant ID will be displayed on the following screen

Enter Registry as soon as possible after a visit is initiated.

1. Indicate participant status as active (even for participant who screen fail).
2. Visit type as standard for those that complete their first ADNI4 visit (even if the participant screen fails).
3. The examination date is the date the first part of the ADNI4 screening visit was completed.
4. If a participant is a rescreen, indicate, “yes” for “Is this a screen” and enter the previous participant ID in the subsequent field.

Please remember any participant who is a rescreen requires prior approval and at minimum 2 months between original screen and rescreen.

REMINDER: IN THE REGISTRY ECRF A ‘STANDARD’ VISIT SHOULD BE SELECTED WHEN MOST PRIMARY OUTCOME MEASURES WERE CONDUCTED. A ‘NONSTANDARD’ VISIT SHOULD BE SELECTED WHEN MOST OF THE PRIMARY MEASURES WERE NOT CONDUCTED.

6.2 DATA FLOW

PRESCREENING:

- Review participant’s medical history, medications, and any past diagnoses for eligibility
- Review prior MRI and PETs to help determine eligibility
- Pencil in a slot for the 3T MRI 7-10 days from Screening Visit. If the MRI cannot be scheduled that quickly, then perform as soon as possible.

SCREENING VISIT

- Screen visit completed by Study Coordinator
- Consent must be obtained prior to assigning a Participant ID.
- Explain Study and Obtain consent
- Assign and record Ebisu ADNI Online ID. See section 14.1 for more information.
- Demographics (Participant and Study Partner)
- Hollingshead Index Score (embedded in the Demographics questionnaire – not a separate assessment)
- Family History
- Inclusion and Exclusion Criteria
- Medical History

- Physical Exam
- Neurological Exam
- Vital Signs
- Height (only taken during screening visit)
- Screening labs (hematology, chemistry panel, urinalysis, B12, TSH, HgbA1c, high sensitivity CRP)*
- Mini Mental State Examination (MMSE)
- Logical Memory I and II
- Geriatric Depression Scale
- Clinical Dementia Rating Scale
- Concomitant Medications
- Adverse Events
- Diagnostic Summary
- Brain Donation discussion
- GUID creation
- 3T MRI Imaging (only to be conducted after confirmation from clinician that the subject has met all other inclusion/exclusion criteria).

*New participants must have safety labs to aid in assessing eligibility. Safety lab kits are provided by URMC; please refer to the clinical laboratory samples section in the Samples Collection chapter of this Procedures Manual and the URMC Laboratory Manual for details.

ENTER ALL DATA AND UPLOAD WORKSHEETS IN THE ADNI4 DATA PORTAL WITHIN 3 BUSINESS DAYS OF SCREENING VISIT

DEMOGRAPHICS:

- Education: use the following guidelines to determine years of education completed
    - These guidelines should be use for all subjects, regardless of where education was received (US, Canada, Mexico, etc.).
    - Code 16 years only if BA/BS has been completed
    - Code 18 years only if MA/MS completed in one year. If participant has MA/MS and one year towards PhD, code 19 years. Only code 20 years if PhD and/or MD have been completed
    - If participant has technical or college training beyond high school, but has not completed a degree, add the additional years of education to 12 (high school).

Example: If a high school graduate has completed 1 year of technical school, education – 13 years.

DEGREE	YEARS
GED	12
High school diploma	12
AA	14
BA/BS	16
MA/MS	18
Law Degree	19
MD, PhD, or both	20

MONITOR REVIEW:

- ATRI Clinical Monitors will review all data and uploaded study document in the EDC.
- Clinical Monitor enters all queries in the ADNI4 Data Portal.
- Resolve and reply to all queries.

3T MRI SCAN:

- PI to confirm eligibility requirements are met BEFORE moving participant forward to the MRI step (including review of cognitive testing, lab results, etc); clinical monitor approval is required after MRI is completed.
- Ensure Participants and Study Partner are provided appointment reminder and directions. Lyft or taxi services may be available to assist with participant transportation, please reach out to adni-study@atrihub.io for further assistance.
- Ensure that MRI Center has current MRI Technologist Manual and MRI Scan Information Form for the participant.
- Upload Scan to LONI day of scan (see MRI Tech Manual and LONI instructions for more details)
- Enter MRI Scan Information form in EDC on day of scan.
- Ensure that MRI is read by a radiologist at the site, locally, in order to identify any medical condition (e.g., brain tumor) which requires attention. ADNI does not provide clinical reads of MRI.

ENSURE ANY IDENTIFIERS ARE BLACKED OUT ON THE COPY UPLOADED TO THE ATRI EDC INCLUDING MEDICAL RECORD NUMBERS, TELEPHONE NUMBERS, AND DATE OF BIRTH

IF A SIGNIFICANT ABNORMALITY IS SEEN BY THE LOCAL RADIOLOGIST OR THE MRI CORE (E.G. HEMISPHERIC INFARCTION), THE PATIENT IS EXCLUDED. IF A QUESTIONABLE ABNORMALITY IS SEEN, THE RADIOLOGICAL FINDINGS WILL BE REVIEWED WITH THE MEDICAL MONITOR FOR INCLUSION/EXCLUSION DETERMINATION

6.3 CLINICIAN AND MONITOR REVIEW DURING SCREENING

MRI QC REVIEW

Each site is responsible to obtain a read from a local radiologist for each MRI completed in the ADNI protocol. In addition, MRI Quality Control at Mayo Clinic (MRI QC) will review the scan uploaded to LONI and confirm eligibility; however, review of the central read report for eligibility is not required. In order for Mayo to QC the scan, it is imperative that the MRI Scan Information form is entered online and that the scan date is accurate. If either of these have not been completed or are not correct, the QC results will not make it in the EDC system and will require prompt attention from site staff.

CLINICIAN VERIFICATION

Prior to Baseline, a Site Clinician must complete the Clinician Eligibility eCRF verifying eligibility only after reviewing the local 3T MRI Radiology Report/Clinical Read.

MONITOR REVIEW AND MONITOR APPROVAL:

A Clinical Monitor will review data entered into the EDC and all study documents uploaded from Screening Visit(s). They will then complete the Monitor Eligibility eCRF.

Important Reminders:

- 3T MRI may NOT be conducted until screen is approved by both the clinical monitor and site clinician
- Baseline may NOT be conducted until 3T MRI local radiologist read report has been reviewed and eligibility has been confirmed by both the clinical monitor and site clinician
- Baseline visit (in-clinic assessment) must start within 30 days of screening visit. There are an additional 2 weeks to complete other Baseline procedures. (e.g. PET, LP, Neuropsych). If additional time is required to complete procedures, please reach out to adni-study@atrihub.io to provide rationale which will be approved by leadership.

DO NOT CONTINUE TO BASELINE UNTIL MONITOR ELIGIBILITY IS CONFIRMED!

SCREEN FAILURES

All participants who sign consent must be assigned an ADNI4 PTID and an Ebisu ADNI Online ID, even if a Screening Visit is not completed. All data obtained must be entered into the EDC. Indicate whether a participant is a screen fail on the Clinician Verification form. All data collected should be entered into the EDC system for every screen fail. As soon as a participant is identified as a screen fail, **enter the Study Visits Summary eCRF** to see the more limited set of minimally required forms that require data entry.

Enter all data collected for screen fails. At a minimum these forms are required:

- Registry (Reminder: For all participants, even those who screen fail).
- Participant Demographics
- Ebisu ADNI Online ID
- Clinician Verification

REFER TO THE DATA ENTRY MANUAL FOR COMPLETE DETAILS ON HOW TO CAPTURE AND ENTER DATA FOR A SCREEN FAIL

RESCREENS

According to the protocol, unless otherwise approved by the Project Director, only one re-screen is allowed, should the original screen be a failure. A minimum of 3 months will be required between the original screen and the re-screen. Before scheduling a rescreen, contact your clinical monitor for approval. Rescreens must be assigned a new ADNI4 Participant ID (PTID). Ensure Clinician Verification for initial screen is entered as 'ineligible'.

- All rescreen data must be entered under the new subject ID number.
- Discuss with your clinical monitor whether the alternate Logical Memory story should be used for the rescreen.

6.4 ELIGIBILITY CRITERIA

STUDY POPULATION

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

Please refer to the Inclusion and Exclusion criteria from the protocol.

EXCEPTIONS TO THESE GUIDELINES MAY BE CONSIDERED ON A CASE-BY-CASE BASIS AT THE DISCRETION OF THE PROTOCOL DIRECTOR & MEDICAL MONITOR

6.5 PROHIBITED AND CAUTIONARY MEDICATIONS

Please refer to the Prohibited and Cautionary Medications document for a full list of medications that are acceptable or excluded during participation in ADNI4, available in the Procedures Manual and Excluded Medications folder in the Document Repository.

CHANGE IN MEDICATION AFTER ENROLLMENT

Record any change in medication (including dose or frequency) on the Concurrent Medications Log for the visit the change is reported. If a participant begins an excluded medication, report this as a protocol deviation.

If a participant begins a cholinesterase inhibitor or memantine after being approved for enrollment into the study, this should be documented by completing the Protocol Deviation Form.

6.6 PRIVATE MD NOTIFICATION

CONSENT FROM THE PARTICIPANT IS REQUIRED BEFORE SENDING INFORMATION TO THEIR PRIVATE MD.

If the participant agrees, send a letter to each participant's private MD as soon as the participant has completed screening and has been approved to be enrolled into the study. The letter will serve to notify the MD of the participant's involvement in the ADNI4 study and outline the study procedures, as well as state the participant's wishes to register in brain donation, if applicable. A letter template for registration in brain donation can be found, and modified for distribution to the MD, in the ADNI Neuropathology Procedures Manual in the Document Repository of the EDC in the Neuropathology folder. In the letters, include the name and telephone number of a clinician at the site who will be available to answer any questions about the study. Do not copy any personnel from ATRI on the letter to the private MD.

CHAPTER 7: NEW ENROLLEES – BASELINE

CONDUCT THE BASELINE VISIT ONLY IF A PARTICIPANT MEETS ALL INCLUSION CRITERIA AND NONE OF THE EXCLUSION CRITERIA AS DETERMINED DURING THE SCREENING PHASE

7.1 BASELINE OVERVIEW

The baseline visit for new participants may only be initiated following completion of all screening assessments and required approvals and must start within 30 days of Screening. Once the baseline visit has started, there is an additional 2 weeks to complete all baseline procedures. The baseline visit procedures may be completed over multiple days and will typically require at least two visits.

Once the visit begins, all imaging, biofluid collection, and clinical/cognitive assessments must take place within the next 2 weeks. Note, ECGs have been removed in ADNI4.

BASELINE PROCEDURES

Per protocol, the following are baseline visit procedures for new participants:

- Cognitive assessments (should be done prior to, or at least 24 hours after any procedure that requires fasting).

- Functional assessments
- Behavioral assessments
- Safety assessments (review of concurrent medications and adverse events)
- Review of concurrent medications and adverse events
- Biospecimen samples – All samples will be collected in the morning before breakfast and after an overnight fast (minimum 6 hour fast)
- LP very desirable, but optional for participants in ADNI4. If the participant consents to LP, then CSF samples for participants should be collected after a 6-hour fast, preferably in the morning. Only water is permitted (no food but water is encouraged)
- In **no** instance should cognitive assessments be performed while the subject is in a fasted state. After the blood tests and/or LP are done the participant should either be provided with a meal, or given time to obtain a meal, prior to beginning assessments.
- At Baseline only, whole blood samples will be collected for peripheral blood mononuclear cell (PBMC) banking for genetic analysis.
- Amyloid PET imaging, Tau PET imaging, and LP for CSF (for participants who have consented to LP) starts at Baseline
    - We are offering Amyloid PET disclosure in ADNI4 to all participants. ADNI participants are eligible to receive their results if they have signed consent and the site PI deems them psychologically well to receive their results. Review section 9.2 of the procedures manual for more information about the amyloid disclosure process.
- Each PET scan must be done on a separate day or at least 12 hours after a prior scan
- Brain Donation program will be discussed at each visit

Provide participant the “ADNI Online Participant Instructions,” if applicable. This is only given to new participants who did not come to the site via referral from the Remote Digital or Remote Blood cohorts (those Remote referral participants are already part of the ADNI Online longitudinal monitoring study). The “"ADNI4 Online Participant Instructions” sheet is available on the EDC Document repository in the "Ebisu ADNI Online” folder. Site staff will write the “ADNI Online Participant Code” on the sheet (which is listed on the Ebisu ADNI Online Investigator Portal; see Chapters 4 and 5, above), before giving the sheet to the participant. Note the ADNI Online longitudinal monitoring activities are also only for participants who are in the CN or MCI diagnostic groups of the study.

Special ADNI4 Baseline highlights

- FDG PET Scans have been dropped in ADNI4
- ECGs have been dropped in ADNI4

CHAPTER 8: ROLLOVERS – INITIAL

ROLLOVERS DO NOT RECEIVE A SCREENING VISIT. THE PROCEDURES COMPLETED AT THEIR INITIAL VISIT WILL DEPEND ON THEIR FINAL VISIT IN ADNI3.

8.1 ROLLOVER INITIAL VISIT OVERVIEW

Consent must be obtained before any portion of the initial ADNI4 visit begins. There is no screening visit for continuing participants and no prior approval necessary before the MRI scan is conducted.

KEY REMINDERS

- 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. If participants are no longer willing or able to travel to the clinic for annual visits, as much information should be collected via telephone and ebisu as possible.
- New procedures/assessments in ADNI4 to be done at initial visit for rollovers:
    - Assign/record Ebisu ADNI Online ID (new CRF)
    - Perceived Stress Scale (PSS)
    - Perceived Ethnic Discrimination Questionnaire (PEDQ)
    - Area Deprivation Index (ADI): For US Sites only
    - Rural-Urban Commuting Area (RUCA) & Rural Urban Continuum Codes (RUCC): For US sites only
    - **For participants who identify as Hispanic/Latinx only:** Abbreviated Multidimensional Acculturation Scale (AMAS)
    - Provide rollovers with the "ADNI4 Online Participant Information" sheet (available on the EDC Document Repository in the Ebisu ADNI Online folder). If the rollover participant is known to have a clinical diagnosis of DEM/AD, they do need to receive this information sheet and will not complete Remote longitudinal monitoring study tasks.

ROLLOVER PARTICIPANTS IN THE CN COHORT

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. **However, they will still need to come into clinic to provide consent and blood for labs.** Assessments can be completed in clinic when the participant comes in to provide blood and consent, or they can be completed virtually.

If a CN rollover participant did not have an Amyloid or Tau PET scan during their last year of ADNI3, then their initial visit will be fully in-clinic and include MRI and Amyloid and Tau PET scans for their first year of ADNI4.

Rollover participants in the CN cohort will be assigned an Ebisu ADNI Online ID by site staff, using the Ebisu ADNI Investigator Portal (see Chapters 5 and 14.1). Site staff will also provide an "ADNI4 Online Participant Information" sheet at the initial visit, which is available on the EDC

Document repository in the Ebisu ADNI Online folder. This sheet provides information to the participant about the ADNI Online study for the Remote longitudinal monitoring aspect of ADNI4.

ROLLOVER PARTICIPANTS IN THE MCI AND DEM COHORT

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. MCI and DEM cohorts that had either an Amyloid or Tau PET scan during their last year of ADNI3, will not have PET scans at their first visit in ADNI4 because PET scans are done on alternate years. No participants should have an amyloid or a tau PET scan two years in a row.

If they did not have an Amyloid or Tau PET scan during their last year of ADNI3, then their initial visit includes Amyloid and Tau PET scans for their first year of ADNI4.

Rollover participants in the MCI cohort will be assigned an Ebisu ADNI Online ID by site staff, using the Ebisu ADNI Investigator Portal (see Chapters 5 and 14.1). Site staff will also provide an "ADNI4 Online Participant Information" sheet at the initial visit, which is available on the EDC Document repository in the Ebisu ADNI Online folder. This sheet provides information to the participant about the ADNI Online study for the Remote longitudinal monitoring aspect of ADNI4.

Rollover participants in the DEM cohort should not be provided with an "ADNI Online Information" sheet, the remote longitudinal monitoring activities will only be part of the CN and MCI cohort experience. However, rollover participants in the DEM cohort should have an Ebisu ADNI Online ID assigned to them at their initial visit (site staff should complete the corresponding CRF).

BE SURE TO REVIEW ADNI3 SCHEDULES TO ENSURE THE ROLLOVER PARTICIPANT IS FOLLOWING THE CORRECT VISIT SCHEDULE IN ADNI4

RESOURCES FOR ROLLOVER PARTICIPANT SCHEDULES

- EDC: When registering rollover participants in the EDC, you will be prompted to answer whether they completed PET scans during their final visit in ADNI3. Your answer will generate their visit schedule based on the outline above.
- Schedule of events spreadsheet in the Document Repository: You can also refer to the schedule of events spreadsheet broken down by cohort for new participants, rollovers who did have PET scans in their last year of ADNI3, and rollovers who did NOT have PET scans in their last year of ADNI3.
- You can always reach out to your monitor or the ATRI study team at adni-study@atrihub.io to clarify any questions.

CHAPTER 9: LONGITUDINAL VISIT ASSESSMENTS AND PROCEDURES

9.1 LONGITUDINAL FOLLOW-UP ASSESSMENTS / PROCEDURES

In general, the ongoing In-clinic Visits (follow-up visits) will be timed every 12 months from the Baseline/initial visits; exceptions to this are CN participants who are seen in the clinic every other year (see guidance on CN participant scheduling in section 10.1). Ongoing In-Clinic visits include:

- Cognitive assessments
    - Including the remote longitudinal monitoring procedures via the Ebisu ADNI Online portal
- Functional assessments
- Behavioral assessments
- Review of concurrent medications and adverse events
- Blood collection for longitudinal DNA and RNA genetic analyses at each In-clinic follow-up visit
- Biomarker – Plasma, Serum and buffy coat will be collected at each In-clinic follow-up visit. All samples will be collected in the morning before breakfast and after an overnight fast (minimum 6 hour fast)
- MRI is conducted at each ongoing In-Clinic visit. The MRI scan should be conducted prior to the LP to rule out intracranial mass for safety. In instances where this is not possible, the study MRI can be performed 72 hours after the optional LP.
- Amyloid and Tau PET scans and LPs (LPs are optional in ADNI4) are conducted every two years
    - We are offering Amyloid PET disclosure in ADNI4 to all participants. ADNI participants are eligible to receive their results if they have signed consent and the site PI deems them psychologically well to receive their results. Review section 9.2 of the procedures manual for more information about the amyloid disclosure process.
- Brain donation program should be discussed every 6 months until the participant passes or decides to not donate
- ADI, RUCC, RUCA: only need to be collected once unless the participant has moved. Sites will prompt the participant to confirm if they are at the same address at every subsequent visit.

9.2 AMYLOID PET DISCLOSURE

Participants are eligible to receive their amyloid results once they have provided amyloid disclosure consent. At the time of consent and at future disclosure visits, the sites will provide the participant with educational materials available in the EDC under the Amyloid PET Disclosure folder. Sites will collect information on all eligible participants prior to the PET scan visit, at the time of the disclosure visit, after the disclosure visit, and longitudinally. If the participant has decided not to receive their results, this information will not be collected. For more information about amyloid PET disclosure, please review the ADNI Disclosure Manual in the Amyloid PET disclosure folder.

Site PI and/or the disclosing clinician are required to complete Amyloid PET disclosure training and be appropriately delegated on the psheet. The training certificate for the Amyloid PET disclosure is available in the Amyloid PET disclosure folder in the Doc Repository.

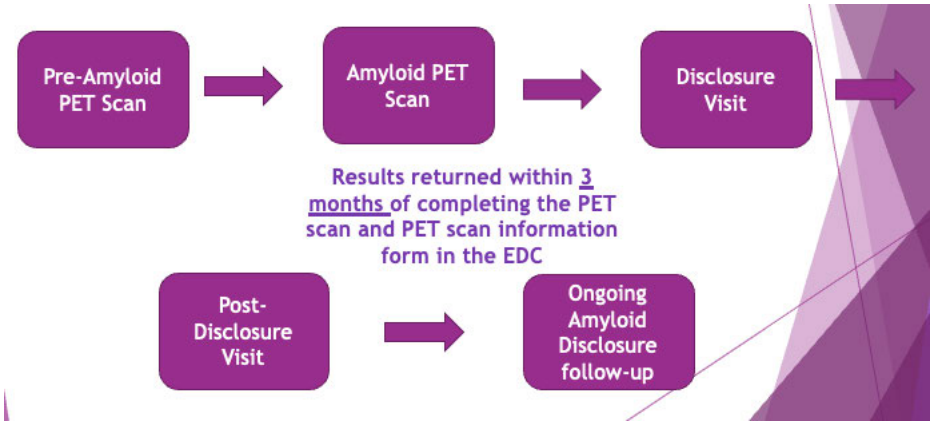
Pre-Amyloid PET Disclosure: Prior to an eligible participant's PET scan visit, the site is required to collect pre-amyloid PET scan assessments to learn about the participant's previous knowledge and understanding of their Amyloid PET result, their anticipated result, and the confidence of their result. Eligible participants in CN and MCI cohorts will review their perceived risk of Dementia.

After these assessments are collected on eligible participants, sites will perform the Amyloid PET scan and complete data entry necessary for the PET Core team to conduct a clinical read on the scan. Once results are available, sites are to disclose the results to eligible participants within 3 months of completed data entry. Disclosure may be delayed if data entry is delayed.

Amyloid PET Disclosure: The disclosure visit can occur in-person or virtually and must be performed by the site PI or qualified clinician. For eligible participants in MCI and DEM cohorts, it is required that the participant's study partner, or someone who is available and has a personal, supportive relationship with the participant, attends the disclosure visit. At the site PI/clinician's discretion, the results should not be disclosed if the participant appears psychologically distressed. The site will collect information during the visit. Additional optional assessments of well-being may be administered based on the site PI/clinician's discretion. These additional optional assessments include: mini-STAI and questions from the C-SSRS.

Post-Amyloid PET Disclosure: Sites are to meet with the eligible participants 1 week after the disclosure visit either in-person or virtually. At the site PI/clinician's discretion, the post-disclosure visit can be completed by a site coordinator who has completed amyloid disclosure training. The site will collect information about the participant's recall and understanding of their result as well as any post-disclosure behavior changes.

Ongoing Disclosure Assessments: The site will collect information about the participant's recall and understanding of their result as well as any post-disclosure behavior changes, Impact of Events, and Ryff Psychological Well-Being Purpose in Life.



BE SURE TO REVIEW RESOURCES OUTLINED BELOW FOR AMYLOID PET DISCLOSURE AVAILABLE IN THE DOCUMENT REPOSITORY

RESOURCES FOR AMYLOID PET DISCLOSURE PROCESS

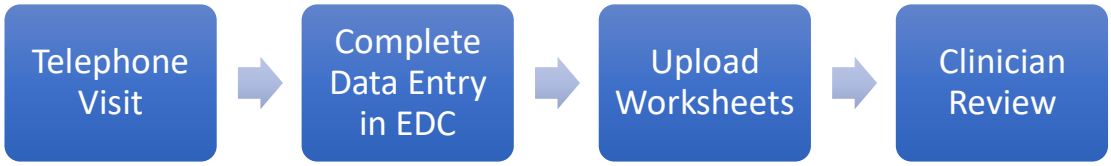
- Amyloid PET Disclosure Training Manual in the Amyloid PET Disclosure folder
- Contact information for the Amyloid PET disclosure team in the Study Contact Sheet folder
- Amyloid PET Disclosure Packet in the Worksheets, Visit Packets folder

CHAPTER 10: TYPES OF TELEPHONE VISITS

10.1 TELEPHONE CHECKS

CN participants are seen in the clinic every other year (biennially). A Phone Check Visit is conducted on the "off-years" where no In-clinic Visit is called for by protocol. It is very important to get as much information as possible about the status of each participant by telephone, ideally by both direct contact with the participant and/or with the study partner.

DATA FLOW



Complete Data entry within 5 business days of the telephone visit. Scan and Upload worksheets to the ADNI4 Data Portal:

CN TELEPHONE CHECK ASSESSMENTS:

- Concurrent Medication Review
- Adverse Event Review
- Neuropsychiatric Inventory Q
- Brain Donation Discussion
- Diagnostic Summary Review

- ADNI Online tasks: 12-Item ECog and Novoic Storyteller**
- Asking if the participant has moved since last visit
    - If so, re-collect the ADI and RUCC & RUCA scores using new address.

PLEASE COMPLETE THE DIAGNOSTIC SUMMARY FORM IN-PERSON FOR THE INITIAL VISIT FOR ROLLOVER CN'S WHO HAD A PET SCAN IN THEIR FINAL YEAR OF ADNI3

10.2 BRIEF BRAIN DONATION TELEPHONE CHECK INS

Obtaining brain tissue after a participant passes away is a vital aspect of ADNI. Therefore, discussion about autopsy and brain donation with the participant and study partner is a priority in ADNI4. An ADNI site clinician will discuss autopsy brain donation with each participant (CN, MCI, and AD) during the consent process, at Initial/Screening visit and at every In-clinic Visit thereafter until registration is captured or the participant indicates refusal. Additionally, annual follow-up Brain Donation Phone Check Visits for those who have provisionally registered to neuropathology or are undecided will continue through the end of the study. These phone calls are crucial for a successful brain autopsy. These phone calls serve to assess the participants whishes regarding brain donation, reiterate the value of brain donation, to answer any questions they may have regarding brain autopsy and review the plan for making the donation at the time of death. The site should update contact information for the individual and re-evaluate donation plans if the participant has moved. For more information about discussing the brain donation program, please refer to the Neuropathology Core Procedures Manual.

10.3 TELEPHONE IN REPLACEMENT OF IN-CLINIC VISIT OPTION

Participants eligible for telephone-only follow-up:

1. Any rollover participant that is not willing or not able to return for in-clinic visits
2. ADNI4 new enrollees, who have completed all, or most, baseline assessments under ADNI4 but then after this visit, are only available by phone
3. Individuals being followed for brain donation only are not participating in the full ADNI4 protocol

It is a priority in this study to track each participant's cognition and activities of daily living longitudinally, over as long a period of time as possible. The intent of the phone visit is to obtain as much information as possible over the phone in cases where the participant is unable or unwilling to come into the clinic. We are offering this information because the longitudinal data on such participants is extremely valuable. For example, has the participant's cognitive state decline? Has the participant lost independence? You should offer the phone visit option to any eligible participant who is no longer able to come to the clinic for annual visits. Obtaining information from the study partner by phone is also extremely useful.

THESE PHONE VISITS ARE IN REPLACEMENT OF THE ANNUAL IN-CLINIC VISITS AND ARE SEPARATE FROM THE INTERIM PHONE CHECKS, WHERE REVIEW OF CONCURRENT MEDICATION, ADVERSE EVENTS AND NPI-Q ARE CONDUCTED

TELEPHONE VISIT REPLACEMENT OF IN-CLINIC VISIT TELEPHONE ASSESSMENTS:

- Clinician Dementia Rating Version 2*
- Geriatric Depression Scale
- Neuopsychiatric Inventory
- Functional Assessment Questionnaire
- Concurrent Medication Review
- Adverse Event Review
- Clinician Review
- ADNI Online tasks: 12-Item ECog and Novoic Storyteller**

*Full interview with only informant. Used in cases where an annual telephone visit is being conducted in replace of the in-person clinic visit.

** ADNI Online tasks may also be completed by participants who are on the telephone-only follow-up schedule. These tasks include the 12-Item Everyday Cognition assessment and the Novoic Storyteller assessment, which are collected remotely via the Ebisu ADNI Online portal (see Chapters 4 and 5, above for more details and how to connect participants with the Ebisu ADNI Online portal).

IF A CHANGE IN COGNITIVE STATUS IS APPARENT DURING THE TELEPHONE VISIT, THIS SHOULD BE DOCUMENTED IN THE VISIT COMMENT FORM.

CHAPTER 11: EARLY TERMINATION

According to the protocol the investigators at each site will make every reasonable effort to maximize participant retention. Participants who discontinue early from the study will be encouraged to have an Early Termination Visit at the point of discontinuation.

The Early Discontinuation Visit will contain the same assessments as the complete annual visit, to allow collection of the main outcome measures. **Depending on when the last study visit was conducted, certain procedures (e.g. LP, MRI or PET scan) may not be required at the Early Discontinuation Visit.** For guidance, please inquire by emailing ADNI team email adni-study@usc.edu.

If an in-person visit is not possible, site personnel will complete as much of the Early Discontinuation Visit as possible by telephone.

FOR DATA ENTRY GUIDELINES REGARDING EARLY DISCONTINUATION, CONSULT THE DATA ENTRY MANUAL

Highlight the possibility of long-term follow-up for the purposes of brain donation by autopsy with the participant and the family.

11.1 ENROLLMENT CRITERIA AND PARTICIPANT DISCONTINUATION

Enrollment criteria must be followed explicitly. If a Site Clinician identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, the Project Director must be notified. If the Clinical Monitor identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, the Site PI and Project Director will be notified. The Investigator must obtain approval from the Project Director (and/or Medical Monitor) in order to allow the inadvertently enrolled participant to continue in the study. Considerations will be made on a case-by-case basis, with sites first contacting the Coordinating Center for guidance. When special cases arise, the ATRI team/Coordinating Center will alter the Administrative Core, who will route the request to the appropriate parties and leadership to make a decision.

11.2 LOST TO FOLLOW-UP

According to ICH 4.3.4, “Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject’s rights.”

In order for a participant to be considered “lost to follow-up”, at least 3 attempts must be made to contact the participant: 2 phone calls and 1 certified letter.

ENSURE EACH ATTEMPT IS DOCUMENTED APPROPRIATELY IN THE PARTICIPANT’S RESEARCH CHART AND PROVIDE THE FINAL DISPOSITION IN THE EDC SYSTEM

CHAPTER 12: CLINICAL MONITORING

The International Conference on Harmonization/Good Clinical Practice (ICH/GCP) defines monitoring as, “The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded and reported in accordance with the protocol, standard operating procedures (SOP), GCP and the applicable regulatory requirements.”

The purposes of monitoring is to ensure that:

- The rights and well-being of human participants are protected
- The reported trial data are accurate, complete, and verifiable from source documents
- The conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with the applicable regulatory requirement(s).

All activities will be conducted in accordance with the ICH/GCP guidelines.

12.1 MONITORING FREQUENCY

The first onsite-monitoring visit will be conducted within 2 months of the first successful Baseline Visit. During this visit the clinical monitor will confirm eligibility as well as verification that Informed Consent (ICF) has been properly signed and dated, and will perform Source Document Verification (SDV) for completion and accuracy.

The second on-site monitoring visit will be conducted a year after the first baseline subject. Additional monitoring visits may take place for sites if deemed necessary. The monitor will be responsible for remote monitoring between on-site visits to ensure compliance and safety standards.

THE FREQUENCY OF ON-SITE VISITS MAY BE ADJUSTED TO ACCOMMODATE A SITES' ENROLLMENT FREQUENCY, COMPLIANCE WITH THE PROTOCOL, AND/OR AT THE DISCRETION OF THE PROJECT DIRECTOR AND PROGRAM MANAGER

12.2 MONITORING RESPONSIBILITY

The Clinical Monitor (CM) is responsible for activities pertaining to on-site monitoring and follow-up of action items resulting from an on-site visit. The Clinical Monitor will:

- Be the primary contact person for the sites and main line of communication between ATRI and participating sites
- Verify that the Investigator has the appropriate qualifications, resources and facilities including laboratories, equipment and staff, to safely and properly conduct the trial, and that these remain adequate throughout the study
- Conduct ongoing training of site personnel as needed
- Confirm that all participants screened have signed the appropriate ICF and that no study related procedure was conducted prior to obtaining consent
- Review and approve all potential participants for enrollment in the trial
- Confirm that all assessments are conducted per protocol.
- Verify the proper handling and storage of lab specimens
- Review all serious and non-serious adverse events for completeness and accuracy
- Ensure that participant enrollment, data verification, and query resolution are taking place on schedule
- Verify that all regulatory documents are accurate, current, properly stored and maintained and confirm that all required communication with the IRB is on file and are current
- Verify the Personnel Sheets or similar delegation of authority log at every on-site visit to ensure the appropriate personnel are performing assessments as delegated

CHAPTER 13: ASSESSMENTS AND PROCEDURES

All assessments and procedures are administered at the times shown in the Study Schedule of Events.

13.1 NEW ASSESSMENTS AND CASE REPORT FORMS IN ADNI4

EBISU ADNI ONLINE ID

As part of novel remote longitudinal monitoring of In-Clinic participants in ADNI4 as well as the new Remote cohort referral efforts, we need a way to connect the data collected from the Ebisu

ADNI Online platform (remote ADNI activities) with participant's In-Clinic data. To do this we are asking site staff to complete a new CRF at the screening (new participants) or initial (rollover participants) visit, called the Ebisu ADNI Online ID CRF, which records this important deidentified, unique code which ADNI Investigators will use to connect data on LONI.

Referrals who come through the Remote cohorts will already have an existing Ebisu ADNI Online ID associated with them. Site staff will use their Investigator Portal (https://ebisu.adni4.org/login) to access that participants' Ebisu ADNI Online ID and enter it on this CRF (see Chapter 4.5).

Rollover participants and new participants who have not come through the Remote Digital or Remote Blood cohort will need to be assigned an Ebisu ADNI Online ID by site staff. To do that, site staff will log into their Ebisu Investigator Portal and register the participant, which will generate a new Ebisu ADNI Online ID for that participant.

- **Registration process for Rollovers and new participants (who do not come via the Remote cohorts):**
  1. Site staff log onto https://ebisu.adni4.org/login
  2. Click the register subject icon (human with a plus (+) sign; at the top of the webpage) and under "Register Subject," select ADNI4
  3. Complete the registration page (indicate that the participant signed the ADNI4 In-Clinic consent, provide participant name and contact information) and hit 'register.'
  4. You will be taken to the Subject page which displays an Ebisu ADNI Online ID. **Site staff need to enter this ID on the Ebisu ADNI Online ID CRF.**
  5. In the days/weeks following, the Ebisu ADNI Online system will send eligible participants an email to complete their registration (and electronically consent) for remote longitudinal ADNI study tasks at home. DEM/AD participants will not be asked to join remote longitudinal monitoring and will not receive an email, but those participants still need to be registered by site staff in the Ebisu Investigator Portal so that they have an Ebisu ADNI Online ID assigned to them.
  6. Provide the participant an "ADNI Online Participant Information" sheet. The "ADNI4 Online Participant Information" sheet is available on the EDC Document repository in the Ebisu ADNI Online folder.

For detailed instructions, see the "ADNI4 Ebisu Investigator Portal Guide" document on the EDC document repository (in the Ebisu ADNI Online folder).

If site staff receive an error message when completing the Ebisu ADNI Online ID CRF, please promptly contact the Admin Core staff at: site.support@adni4.org

ABBREVIATED MULTIDIMENSIONAL ACCULTURATION SCALE (AMAS)

Administration

The *AMAS* should only be administered to **participants at US sites who identify as Latinx**. The questionnaire asks about the participant's culture of origin and native language. "Culture of origin" refers to the culture (other than culture of [site location: United States or Canada]) that the participant identifies with/is a part of. "Native language" refers to the language of that other culture.

Instructions

- For pts who express concern about being asked about [site location: American/Canadian] cultural identity vs culture of origin, here are example replies:
    - IF FROM Puerto Rico (or other US territory): "(You're right), Puerto Rico (or other territory) is part of the USA. However, we would like to understand how strongly you identify with each culture; that is, Puerto Rican culture, as well as U.S. mainland culture."
    - "People often identify with more than one culture, so we want to understand how strongly you identify with both [site location: American/Canadian] culture, as well as your culture of origin, i.e., _____" and fill in that blank with the culture they previously identified (e.g., Dominican culture).

AREA DEPIVATION INDEX SCORE (ADI)

Administration

The *ADI* should be administered once for all participants at baseline for new participants and at initial for rollovers unless participants have moved since their last visit. Sites should inquire if a participant's address has changed at every visit.

Instructions

Instructions are available as additional resources for this assessment in the Document Repository in the EDC under the Cognitive Testing Materials folder. Please be sure **not** to write down the participant's full address on source documents that will be uploaded to the EDC. PHI should never be uploaded to the EDC.

MODIFIED HOLLINGSHEAD INDEX SCORE

Administration

The *Hollingshead Index Score* should be administered once for all participants at screening for new participants and at initial for rollovers. This assessment is embedded in the Demographics case report form. Please **do not** write down the name of participant's companies or locations of work on source documents. This is identifiable information and should never be uploaded to the EDC.

Instructions

Using the ACTC Modified Hollingshead Occupation categories below, please select the most appropriate category based on the description of participant's primary occupation during most of their adult life.

Categories	
Professional and Higher Executive Occupations, Chief Executives	Accountants Agricultural and Food Scientists Anesthesiologists

	Anthropologists and Archeologists Architects Astronomers Biochemists and Biophysicists Chemists Chief Executives (Pres, VP, CEO, DFO, COO) Computer and Information Research Scientists Computer Systems Analysts Commissioned Military Officers Dentists Economists Epidemiologists Financial Specialists, Accountants, Auditors Information Security Analysts Internists Lawyers/Judges Legislatures Mathematicians, Statisticians Music Directors/Composers Physicians, Surgeons, Chiropractors, Orthodontists Physicists Professor/University Teachers Psychiatrists Psychologists Scientists/PhD Sociologists Veterinarians

	Zoologists
Middle Professional Occupations/Small Business Owners	Advertising Executives, Marketing and Sales Mangers Air Traffic Controllers Airline Pilots Budget Analysts Business Owners- Small Businesses Clergy Compliance Officers Contractors- Major Computer Network Architects Education Administrators Educational, Guidance and Vocational Counselors- MA degree Engineers- MA level First-line Supervisors of Police and Detectives and Firefighters Geographers Historians Human Resource Specialist Librarians Multimedia Artists and Animators Nurse Practitioners- MA level Occupational Therapists-MA level Physical Therapists- MA Level Physician Assistants- PA certified Podiatrists Political Scientists Producers/ Directors Public Relations, Fund Raising Manager Therapists/ Counselors- all other MA level Restaurant Owners Social Workers- MA Level Tax Preparers
Managers	Actuaries Administrative Services Managers Athletic Trainers- Professional Broadcast News Analysts Choreographers Claims Adjusters, Insurance Appraisers, Examiners and Investigators Coaches- Professional Community and Social Service Occupations Compensation and Benefits Managers Computer and Information Systems Managers Computer Programmers Construction Managers Credit Analysts Database Administrators Dental Hygienists Editors and Technical Writers Emergency Management Directors Farm Labor Contractors

	Farmers, Ranchers and Agricultural Managers Fashion and Floral Designers Financial Managers Fine Arts, Painters, Sculptures, and Illustrators Firefighters First Line Supervisors or Mechanics, Installers and Repairers Fundraisers Funeral Service Managers Government Officials Graphic Designers Hotel and Food Service Managers Human Resource Managers Industrial Production Managers Interior Designers Labor Relations Specialists Loan Officers Medical and Health Service Managers Meeting, Convention and Event Planners Musicians/ Singers/ Dancers/ Actors- Professional Network and Computer Systems Administrators Operations Research Analysts Optometrists Pharmacists Police and Sheriff Patrol Officers Postmasters and Mail Superintendents Property, Real Estate and Community Association Managers Purchasing Managers Religious Education Directors Self-Enrichment Teachers Social and Community Service Managers Social Workers- BA level Software Developers Substitute Teachers Surveyors Tax Examiners, Collectors, Revenue Agents Therapists- BA level, OT, PT, Training and Development Managers Transportation, Storage and Distribution Managers Urban and Regional Planners Web Developers
Support Personnel, Drafters, Technicians	Aerospace Operations Technicians Agricultural and Food Technicians Ambulance Drivers Architectural and Civil Drafters Archivists Chefs and Head Cooks Civil Engineering Technicians Clinical and Laboratory Technicians

	Computer Network Support Specialist Computer User Support Specialist Court Reporters Curators Dieticians/ Nutritionists Editors and Technical Writers Electrical and Electronics Engineering Technicians Flight Attendants Hearing Aid Specialists Interpreters/ Translators Mechanical and Electrical Drafters Medical Assistants Medical Records and Health Information Technicians Medical Technologists and Technicians Merchandise Displayers and Window Trimmers MRI Technicians Paralegal Assistants Pharmacy Technicians Photographers Private Detectives and Investigators Reporters and Correspondents Research Assistants Respiratory Technicians Surgical Technologists Teacher Assistants Technicians- all others Title Examiners, Title Searchers Transit and Railroad Police Veterinary Technologists and Technicians
Arts, Design, Entertainment, Sports Occupations – Non-Professional	Actors- Non-Professional Coaches- Nonprofessional Licensed Practical Nurses Massage Therapists Musicians/ Singers/ Dancers- Non-Professional Opticians Radio and Television Announcers Radio Operators Reporters and Correspondents Singers- Non-Professional Umpires/ Referees/ Other Sports Officials- Non-Professional
Aides/Assistants/Clerks	Animal Control Workers Computer Operators Crossing Guards Dental Assistants Dressmakers Health Care Support Workers- all others Home Health Aide Laboratory Animal Caretakers Library Assistants Lifeguards Mail Carrier Mechanics Medical Assistants Meter Readers- Utilities Nursing Assistants Office and Administrative Support Assistants

	Orderlies Parking Enforcement Workers Pharmacy Aides Phlebotomists Postal Service Clerks Protective Service Workers Psychiatric Aide Receptionists Secretaries Security Guards Tailors Ticket Agents Transportation Security Screeners Typists
Laborers	Agricultural workers Animal Breeders Automotive and Body Mechanics Bakers Brick layers Bus Drivers Carpenters Cement masons Construction Helpers Conveyor Operators Fisherman Food Processing Workers Insulation Workers Iron and Rebar Workers Jewelers Locomotive Engineers Logging Operators Maids and Cleaners Misc. Repairers Paper Hangers Parking Lot Attendants Plasterers Pipe Layers Roofers Sewing Machine Operators Sheet Metal Workers Stone masons Taxi Drivers, Chauffeurs, LYFT, Uber Drivers Tile and marble setters Truckers Welders

PERCEIVED STRESS SCALE (PSS)

Administration

The *PSS* should be administered once for all participants at baseline for new participants and at initial for rollovers.

Instructions

Instructions, scoring and frequently asked questions are available as additional resources for this assessment in the Document Repository in the EDC under the Cognitive Testing Materials folder.

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

Administration

The *RUCA & RUCC* should be administered once for all participants at baseline for new participants and at initial for rollovers unless participants have moved since their last visit. Sites should inquire if a participant's address has changed at every visit.

Instructions

Instructions are available as additional resources for this assessment in slides of the site webinar protocol v2.0 training on April 26, 2023 in the document repository in the webinar folder.

13.2 COGNITIVE / CLINICAL ASSESSMENTS

GENERAL COGNITIVE / CLINICAL TESTING GUIDELINES

Neuropsychological testing is not a mechanical process. The examiner encounters a wide range of emotional and physical problems that can interfere with testing. The skill and judgment of the examiner, the examiner's perceived level of cultural competence, and even the environment in which assessment is taking place often affect the Participant's willingness to be tested and the effort he/she invests. An office devoid of racial or ethnic diversity in staff, for instance, might make some participants feel out of place or reduce trust. The following guidelines are intended to maintain inter-rater reliability and ensure standard administration of cognitive tests.

Although guidelines are presented below as a sequence of tests, during an actual test session the examiner must simultaneously administer tests, observe and assess Participant behavior and make necessary adjustments. Following these guidelines at your site will help generate valid and accurate measurements with a minimum of stress and discomfort for test Participants.

CREATING A PRODUCTIVE TESTING ENVIRONMENT

Due to the many ways in which the examiner can influence testing, it is helpful if the same rater administers the instrument for a study participant throughout the course of this protocol. Additionally, to eliminate variability due to the time of day, every effort should be made to conduct testing sessions at approximately the same time of day each time the battery is administered. Testing should occur in a quiet location with as few distractions as possible. Examiners should, to the extent possible, be mindful of any relevant sociocultural or religious factors that might affect the interaction.

Strive for consistent administration. Provide instructions as consistently as possible.

INTRODUCING THE TESTING

Before testing, question both the Participant and the study partner about the Participant's ability to hear and see. Make sure the Participant is wearing needed corrective eyeglasses or hearing aids.

The general orientation to the day's activities should include the study partner. Explain the purpose of the testing, what the test(s) will be like, how long testing will take, and what the day's schedule will be, including when the Participant may take breaks. Consider this a cultural competency and humility-infused period of rapport building with the participant. The better the connection, the more likely the participant is to feel comfortable and invested in the process.

After answering any questions, instruct the study partner to wait outside the test room in the designated waiting area (most Participants test better if they are not observed by people they know). If the Participant will comply only with a study partner present, the study partner should be instructed not to provide answers, and to sit in an area of the room where the Participant will not easily turn to him/her for feedback.

MANAGING TESTING TIME

The tests should be given in the order indicated in the protocol on page 44, with adherence to time limits and standardized instructions.

This may be challenging with Participants who interrupt testing or digress into excessive conversation. In these cases, the examiner must regain control of the testing session and "reorient" the Participant back to the task at hand.

KEEPING PARTICIPANTS FOCUSED

If the Participant is exhibiting signs of frustration or requests to terminate the test, the examiner should acknowledge the Participant's concerns, and take note of any reported or expressed physical symptoms (*e.g.*, pain, fatigue) that could be interfering with test performance. It may become necessary to differentiate the Participant who *refuses* to continue a task from the Participant who *cannot* continue a task due to severe impairment. (This is made more difficult by the fact that a Participant may refuse testing due to frustration over their inability to perform a task.)

Whether a Participant is fatigued, frustrated or merely distracted, there is no one approach that will work with all Participants, but the examiner should have a flexible style that acknowledges the Participant's concerns, while gently diverting their attention back to the task.

ASSESSING PARTICIPANT COMPREHENSION

The examiner's responsibility is to see that the Participant understands the instructions before each test is started and that he/she maintains this understanding throughout the test. Instructions may be repeated or simplified according to the instructions for each task during the test session, taking care not to provide any new information, hints or answers. Some culturally/linguistically diverse participants may be unfamiliar or have a differing understanding of testing-related constructs, so it is imperative that they receive a clear, jargon-free explanation of the evaluation.

FEEDBACK AND PROMPTING

Provide only neutral feedback to the Participant, without indicating if their answers are right or wrong, *e.g.*, "okay" or "you are doing fine." Reward all good effort, not just good performance.

Often a Participant will give more than one answer. If that should occur, encourage the Participant to choose one of them, without cueing for a specific response. “Which one is it?” or “Choose one” can be useful prompts to get a Participant to choose a single answer.

SCORING AND RECORDING

Since it is better to score an incorrect response than no response, participants should be encouraged to give an answer even if they are unsure. “What’s your best answer?” or “try” can be helpful prompts. An incorrect response can give some evidence that the participant understood the question.

Record the participant’s responses in full and verbatim. More notes are better than too few notes. Many examiners prefer to tape record their participant’s response, and then transcribe any words they may have missed after the session. **This is acceptable if appropriate consent has been obtained.**

Many tests are auto-scored on the eCRF forms. Please review the **eCRF Completion Guidelines** for guidance on how to complete eCRFs and to learn which tests are auto-scored.

PLEASE REMEMBER THAT THE PARTICIPANT’S NAME NOR THEIR INITIALS SHOULD NOT BE WRITTEN ON THE WORKSHEET NOR SHOULD ANY PERSONAL IDENTIFIERS (E.G. MEDICAL NUMBER, SS#, ADDRESS ETC.)

ALZHEIMER’S DISEASE ASSESSMENT SCALE-COGNITIVE (ADAS-COG13)

The ADAS-Cog is to be conducted by a **certified ADAS-Cog rater**. For information about ADAS-Cog certification and training, refer to the Certification, Training, and Experience chapter of this procedures manual.

For ADAS administration instructions see ADAS Manual (version October 2013) available in the study document folder.

ADAS-cog sub scores and total score will be automatically calculated on the electronic case report form based on the item level data entered.

Since visits are annually, there is less of a concern for a learning effect. Therefore, ADAS Word List 1 will be used at each annual In-Clinic Visit. There are four-word lists that can be used in this study; it is recommended that if there is a concern for a learning effect, that ADAS Word List 2 be used.

MINI-MENTAL STATE EXAMINATION (MMSE)

The Mini-Mental State Examination (MMSE) is a widely used, well-validated and reliable screening tool for evaluation of cognitive impairment, as well as course of cognitive change over time. The brief assessment measures orientation to time and place, immediate recall, short-term verbal memory, calculation, language, and construct ability.

- It is strongly recommended that the same rater administer the MMSE for the same Participant at all visits that include MMSE.
- If the Participant is unable to perform any item, the item should be scored as “Incorrect”
- Prior to administration, ensure that eyeglasses (if needed) are being worn and hearing

aids (if needed) are adjusted appropriately.

- If the Participant is anxious, it can be helpful to periodically say, “you’re doing fine”

[redacted]

INSTRUCTIONS	SCORING
ORIENTATION TO TIME: [redacted]	**SCORING:** [redacted]

If [redacted] [redacted] [redacted] [redacted] [redacted] **ORIENTATION TO PLACE:** [redacted] [redacted] [redacted] [redacted] "[redacted]	[redacted] [redacted] **SCORING:** [redacted] [redacted]
REGISTRATION/ IMMEDIATE RECALL: [redacted] [redacted]	**SCORING:** [redacted]

ATTENTION AND CALCULATIONS: [redacted]	**SCORING:** [redacted]
DELAYED RECALL: [redacted]	**SCORING:** [redacted]
NAMING: [redacted]	**SCORING:** [redacted]
REPETITION: [redacted]	**SCORING:** [redacted]
COMPREHENSION: [redacted]	**SCORING:** [redacted]

READING: [redacted]	**SCORING:** [redacted]
WRITING: [redacted]	**SCORING:** [redacted]
DRAWING: [redacted]	**SCORING:** [redacted]

FUNCTIONAL ASSESSMENT QUESTIONNAIRE (FAQ)

Administration

The questionnaire is administered by clinic personnel to the study partner on their impression of the participant's performance on each activity (outlined in the questionnaire) **during the past 4 weeks**, as well as the level of performance are rated.

Scoring

A total score is derived by summing scores across items, and ranges from 0 (maximal impairment) to 78 (maximally independent function). Scores will be calculated as needed prior to analysis and will not be reported back to sites during the study.

CLINICAL DEMENTIA RATING SCALE (CDR)

Administration

For information about CDR certification and training, refer to the Site Approval and Start-Up chapter of this procedures manual.

The interview is to be conducted by a **certified CDR rater** with the informant and study participant. Supplementary information may be added to the existing questions on the worksheet to support the assigned box scores.

Consistent with CDR administration guidelines, **the CDR rater should not consider data outside of the CDR assessment. Ideally, the CDR rater will NOT be involved with any other cognitive or functional assessments and, if possible, the same CDR rater should administer the CDR for a given participant throughout the study.** If it is anticipated that the CDR rater will be involved with other cognitive testing, then consult with the ATRI prior to administration of the CDR so that the details can be discussed with study leadership.

Monitors will review the worksheets for each CDR. If they feel the information on the worksheet does not support the CDR score, they will review it with the CDR rater or other personnel at the site. This review will focus on the information for each box score. If additional information results from this review, it should be noted on the worksheets and signed by the site personnel.

If the monitor and the site personnel do not come to agreement, the Protocol PI will resolve the scoring. If needed, the Protocol PI will contact Dr. John Morris at Washington University for guidance. The Protocol PI, in conjunction with the consultant, will make the final decision.

- Use all information and make the best judgment. Score each category (M, O, JPS, CA, HH, PC) as independently as possible.
- Mark in only one box, rating impairment as decline from the **person's usual level due to cognitive loss alone**, not impairment due to other factors, such as physical handicap, depression, or personality change.
- Occasionally the evidence is ambiguous and the clinician's best judgment is that a category could be rated in either one of the two adjacent boxes, such as mild (1) or moderate (2) impairment. **In that situation, the standardized procedure is to check the box of greater impairment.**

Scoring

The **global CDR** is derived from the scores in each of the six categories ("box scores"):

1. Memory
2. Orientation
3. Judgment and Problem Solving
4. Community Affairs
5. Home and Hobbies
6. Personal Care

MEMORY (M) IS CONSIDERED THE PRIMARY CATEGORY AND ALL OTHERS ARE SECONDARY.

CDR = GLOBAL BOX SCORE

M = MEMORY BOX SCORE

CDR = M IF AT LEAST THREE SECONDARY CATEGORIES ARE GIVEN THE SAME SCORE AS MEMORY.

- When M = 0.5, CDR = 1 if at least three of the other categories are scored 1 or greater.
- If M = 0.5, CDR cannot be 0; it can only be 0.5 or 1.
- If M = 0, CDR = 0 unless there is impairment (0.5 or greater) in two or more secondary categories, in which case CDR = 0.5.

Whenever three or more secondary categories are given a score greater or less than the memory score, CDR = score of majority of secondary categories on whichever side of M has the greater number of secondary categories. In the unusual circumstance in which three secondary categories are scored on one side of M and two secondary categories are scored on the other side of M, CDR = M. The above rules do not cover all possible scoring combinations.

Unusual circumstances are scored as follows:

1. With ties in the secondary categories on one side of M, choose the tied scores closest to M for CDR (e.g. M and another secondary category = 3, two secondary categories = 2, and two secondary categories = 1; CDR =2).
2. When only one or two secondary categories are given the same score as M, CDR = M as long as no more than two secondary categories are on either side of M.
3. When M = 1 or greater, CDR cannot be 0; in this circumstance, CDR = 0.5 when the majority of secondary categories are 0.

Aphasia is taken into account by assessing both language and non-language function in each cognitive category. If aphasia is present to a greater degree than the general dementia, the participant is rated according to the general dementia. Supply evidence of non-language cognitive function.

TO VERIFY THE GLOBAL CDR, YOU MAY ALSO ACCESS THE WASHINGTON UNIVERSITY CDR WEB PAGE:

HTTPS://NACCDATA.ORG/DATA-COLLECTION/TOOLS-CALCULATORS/CDR

The **Sum of Boxes CDR** is derived from the summation of scores from each of the six categories (“box scores”).

Both the Sum of Boxes and Global CDR scores will be calculated automatically by the eCRF.

GERIATRIC DEPRESSION SCALE

Administration

The assessment is administered by clinic personnel to the study participant and consists of 15 questions that the participant is asked to answer yes or no on the basis of **how they felt over the past week**. Answers to 5 of the items are negatively oriented for depression (e.g., Do you feel full of energy?) and 10 positively oriented (e.g., Do you often feel helpless?).

If the Participant becomes aphasic, use a pointboard or a board with the scale and yes/no next to the items and have the participant point out the correct answers.

If the Participant does not comprehend the first 5 questions adequately enough to give answers, then stop the assessment and indicate on the form that the participant is unable to complete the GDS based on the clinician’s best judgment.

Scoring

One point is given for each appropriate positive or negative answer indicative of a symptom of depression, for a possible total of 15 points. Although differing sensitivities and specificities have been obtained across studies, for clinical purposes a total score of 0-5 are considered likely to be normal and scores of 6-15 are considered to be more likely to be depressed.

The score will be automatically calculated by the eCRF after the form is submitted. If the manually calculated score differs from the automatically calculated score, there was either a transcription error on the item-level data entered into the eCRF or an error in the manual calculation of the score. Review both to identify the source of the discrepancy.

NEUROPSYCHIATRIC INVENTORY (NPI)

Administration

The purpose of the NPI is to obtain information on the presence of psychopathology in participants with brain disorders. The NPI was developed for application to participants with Alzheimer's disease and other dementias, but it may be useful in the assessment of behavioral changes in other conditions. The NPI is an interview by a site clinician (certification is not required) with the study partner. As with all interviews with the study partner it is best conducted in the absence of the participant to facilitate an open discussion of behaviors that may be difficult to describe with the participant present.

The NPI evaluates both the frequency and severity of 12 neuropsychiatric features, including delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor behavior, sleep and appetite/eating disorders.

Several points should be made when you begin the NPI interview with the study partner

- Purpose of the interview
- Ratings – frequency, severity, distress (described below)
- Answers apply to behaviors that are new since the onset of the disease and have been present for the past four weeks or other defined period
- Questions usually can be answered with "yes" or "no" and responses should be brief

Questions should be asked exactly as written

- Clarification should be provided if the study partner does not understand the question.
- Acceptable clarifications are restatements of the questions in alternate terms.

The questions pertain to changes in the participant's behavior that have appeared since the onset of the illness

- Behaviors that have been present throughout the participant's life and have not changed in the course of the illness are not scored even if they are abnormal (e.g., anxiety, depression).
- Behaviors that have been present throughout life but have changed since the illness are scored (e.g., the participant has always been apathetic but there has been a notable increase in apathy during the period of inquiry).

The NPI is typically used to assess changes in the participant's behavior that have appeared in a defined period of time (e.g., in the past four weeks). For all visits, ask the study partner to indicate whether the participant behaviors changed **during the previous 4 weeks**.

The SCREENING QUESTION is asked to determine if the behavioral change is present or absent.

- If the answer to the screening question is negative, mark NO and proceed to the next screening question without asking the subquestions
- If the answer to the screening question is positive or if there are any uncertainties in the study partner's response or inconsistencies between the response and other information known by the clinician (e.g., the study partner responds negatively to the euphoria screening question, but the participant appears euphoric to the clinician), the category is marked YES and is explored in more depth with the subquestions.
- If the subquestions confirm the screening question, the severity and frequency of the behavior are determined according to the criteria provided with each behavior. When determining the severity and frequency, use the behaviors identified by the subquestions as most aberrant.

For example: If the study partner indicates that resistive behavior is particularly problematic when you are asking the subquestions of the agitation section, then use resistive behavior to prompt judgments regarding the frequency and severity of agitation.

- If two behaviors are very problematic, use the frequency and severity of both behaviors to score the item.

For example: If the participant has two or more types of delusions, then use the severity and frequency of all delusional behaviors (all types) to phrase the questions regarding severity and frequency.

In some cases, the study partner will provide a positive response to the screening question and a negative reply to all subsections. If this happens, ask the study partner to expand on why they responded affirmatively to the screen.

- If they provided information relevant to the behavioral domain but in different terms, the behavior should be scored for severity and frequency as usual.
- If the original affirmative response was erroneous, leading to a failure to endorse any subquestions, then the behavior is changed to "NO" on the screen.

Some sections, such as the questions pertaining to appetite, are framed so as to capture whether there is an increase or decrease in the behavior (increased or decreased appetite or weight). If the study partner answered "yes" to the first member of the paired question (such as has the participant's weight decreased?), do not ask the second question (has the participant's weight increased?) since the answer to the second question is contained in the answer to the first.

If the study partner answers "no" to the first member of the pair of questions, then the second question must be asked.

Determining Frequency

Tell the study partner "Now I want to find out how often these things [define using the description of the behaviors they noted as **most problematic** on the subquestions] occur."

Some behaviors, such as apathy, eventually become continuously present, and then "are constantly present" can be substituted for "every day."

Determining Severity

Tell the study partner "Now I would like to find out how severe these behaviors are. By severity, I mean how disturbing or disabling they are for the participant." "Would you say that [the behaviors] are mild, moderate, or severe?"

Additional descriptors are provided in each section that may be used to help the interviewer clarify each grade of severity.

In each case, be sure that the study partner provides you with a definite answer as to the frequency and severity of the behaviors.

Do not guess what you think the study partner would say based on your discussion.

We have found it helpful to provide the study partner with a cue card on which is written the frequency and severity descriptions to allow them to visually see the response alternatives.

Frequency Descriptions:	Severity Descriptions:
Less than once per week	Mild
About once per week	Moderate
Several times per week	Severe
Daily or continuous	

In very impaired participants or in participants with special medical circumstances, a set of questions may not be applicable.

For example: Bed-bound participants may exhibit hallucinations or agitation but could not exhibit aberrant motor behavior.

If the clinician or study partner believes that the questions are inappropriate, then the section should be marked No, and no further data are recorded for that section. Likewise, if the clinician feels that the responses are invalid (e.g., the study partner did not seem to understand the particular set of questions asked), No should also be marked. When each domain is completed and the study partner has completed the frequency and severity rating, you may want to ask the associated study partner distress question.

The study partner must rate his/her own distress on a five-point scale:

0 – No Distress

1 – Minimal

2 – Mild

3 – Moderate

4 – Severe

5 – Very Severe or Extreme

Scoring

Frequency assessments range from 1 (occasionally, less than once per week) to 4 (very frequent, continuously present); severity from 1(mild), 2 (moderate) and 3 (severe) and distress from 0 (no distress) to 5 (very severe/extreme distress). For each behavioral domain there are 4 scores: frequency, severity, domain score (frequency x severity) and caregiver distress. **The total score is the sum of all domain scores. The distress score is not included in the total NPI score**. Scores will be calculated as needed prior to analysis and will not be reported back to sites during the study.

MULTI-LINGUAL NAMING TEST (MINT)

Administration

The rater will administer the assessment by showing the participant images of 32 items.

Scoring

There is 1 point for each correct answer Uncued or Semantic columns. 0 points for correct answer under Phonemic column. Sum of all total correct uncued, semantic are needed to calculated the total correct score.

13.3 SAFETY MEASURES

All safety assessments described in this section are administered according to the times shown in the schedule of events in the protocol.

PHYSICAL AND NEUROLOGICAL EXAMINATION

A Site Clinician will perform a brief physical and neurological examination. The physical examination will consist of a review of the major body systems (i.e., skin, head, eyes, ears, nose, throat, cardiovascular, pulmonary, abdomen, musculoskeletal, edema and skin). Physical examination will be performed as clinically indicated and according to the schedule of events. The neurological examination will include an assessment of cranial nerves, motor strength, coordination, reflexes, sensation, tremor, gait, and mental status. If necessary, a neurologist may be consulted in the event of any clinically significant findings.

VITAL SIGNS

Vital signs, including temperature and weight, will be measures at all in-clinic visits. Blood pressure, respiration, and pulse will be measured in the sitting position. Height will only be measured at Screening Visit 1a. Oxygen saturation will be measured at all in-clinic visits.

MEDICAL HISTORY

A comprehensive medical systems review of the following will be conducted to ensure that the participant is clinically appropriate for the study:

- Past medical history
- Current medical conditions, signs and symptoms present at the time of screening
- Any other abnormal / clinically significant findings from Screening (i.e., ECG, MRI, physical / neurological etc.)

It is the PI's discretion as to which findings are considered abnormal and/or clinically significant and should therefore be recorded.

ONGOING SAFETY LABS

In ADNI4, safety labs will be collected during screening and at all ongoing clinic visits. Please review chapter 15 in the procedures manual and refer to the URMC lab manual for instructions on collecting, handling and shipping safety labs.

CHAPTER 14: SAMPLE COLLECTIONS, PROCESSING AND SHIPMENT

THE FOLLOWING TOPICS WILL BE COVERED IN THIS SECTION:

- Biofluids Collection Schedule
- Sample Identification and Tracking
- Sample Quality Checks
- Clinical Safety Laboratory Samples
- Plasma sample collection (samples shipped to UPENN)
- Buffy Coat sample collection (samples shipped to NCRAD)
- Whole blood for long read sequencing (samples shipped to NCRAD)
- PBMC sample collection (samples shipped to NCRAD)
- Serum sample collection (samples shipped to UPENN)
- RNA sample collection (samples shipped to NCRAD)
- CSF sample collection (samples shipped to UPENN)
- Brain Tissue: Formalin fixed and fresh/frozen brain tissue (samples shipped to Washington University)

For more information on any of these topics, please review the Biomarker and Genetics Lab Manual and the Neuropathology Core Procedures Manual available in the Document Repository.

BIOFLUIDS GLOSSARY

BLD	Blood (Whole)
CSF	Cerebrospinal Fluid
PL	Plasma
URN	Urine
EDT	EDTA (ethylenediaminetetraacetic acid)
SER	Serum
BLD EDT	Whole blood collected in a lavender-top tube
BLD SER	Whole blood collected in a plain red-top tube

LP	Lumbar Puncture
NCRAD	National Centralized Repository for Alzheimer's Disease and Related Dementias
PBMC	Peripheral blood monoclear cell

All samples described in this section are collected according to the times shown in the Schedule of Events in the ADNI4 protocol.

For NCRAD related questions, please visit www.NCRAD.org, please go to 'Tools for active studies' which provides various resources including buffy coat instructions, guidance for blood drawn on Friday's, holiday closures, and shipping instructions for ambient, frozen, and RNA PAXgene samples.

It is recommended, but not required that study personnel responsible for shipping should be certified in biospecimen shipping. If not available at your university, training and certification is available through the CITI training site (Course titled "Shipping and Transport of Regulated Biological Materials" at https://www.citiprogram.org/.

14.1 BIOSPECIMEN COLLECTION SCHEDULE

NEWLY ENROLLED PARTICIPANTS									
	Safety / Clinical Labs	CSF	Plasma	Serum	Buffy Coat	PBMC	Whole blood (long read)	RNA	Brain Tissue
Screening	✓								
Baseline	✓	✓	✓	✓	✓	✓	✓	✓	
Ongoing Annual Visits	✓	✓*	✓	✓	✓			✓	
Time of Death									✓
Ship samples to:	**URMC**	**UPENN Biomarker Lab**			**NCRAD**				**WUSTL**

*LP to be performed every two years from Baseline (New Participants) / Initial Visit (Rollover Participants).

ROLLOVER PARTICIPANTS									
	Safety / Clinical Labs	CSF	Plasma	Serum	Buffy Coat	PBMC	Whole blood (long read)	RNA	Brain Tissue
Initial Visit	✓	✓*	✓	✓	✓	✓	✓	✓	
Ongoing Annual Visits	✓	✓*	✓	✓	✓			✓	
Time of Death									✓
Ship samples to:	**URMC**	**UPENN Biomarker Lab**			**NCRAD**				**WUSTL**

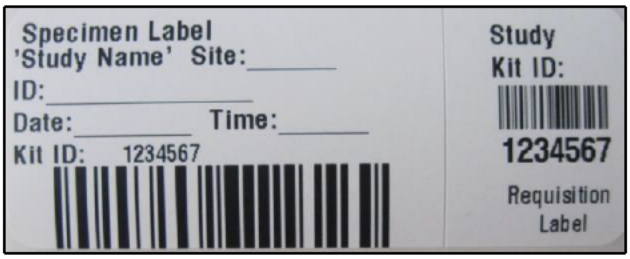
*LP to be performed every two years from Baseline (New Participants) / Initial Visit (Rollover Participants).

14.2 SAMPLE IDENTIFICATION AND TRACKING

PLEASE CONFIRM YOU HAVE LABELS FOR EACH VISIT BEFORE SCHEDULING THE VISIT.

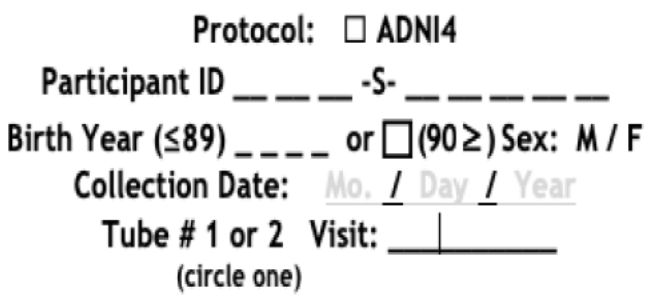
Clinical Laboratory Samples (URMC)

Done through Kits provided by ***URMC***. Laboratory samples at screen will use URMC's barcode system.



All genetic samples (NCRAD): Whole Blood long read sequencing, RNA, PBMC, and Buffy Coat

Must be identified using the ***NCRAD*** Sample Identification label provided by the ATRI.



Annual Visit Codes	
CODE	**LABEL**
BL	New Participant Baseline Visit
INIT	Rollover Participant Initial Visit
M12	ADNI4 Month 12 Visit
M24	ADNI4 Month 24 Visit
M36	ADNI4 Month 36 Visit
M48	ADNI4 Month 48 Visit

All biomarker samples (UPENN): plasma, serum and CSF

Must be identified using the ***UPENN*** biomarker Identification label provided by the ATRI.

14.3 SAMPLE TRACKING

IT IS VERY IMPORTANT TO DOUBLE CHECK THAT ALL SAMPLES ARE SENT TO THE APPROPRIATE LABORATORY:

- All biomarker samples (plasma, serum, and CSF) are shipped to UPENN
- All genetic samples (whole blood long read sequencing, RNA, Buffy coat, PBMC) are shipped to NCRAD
- All brain tissue (formalin fixed and fresh/frozen) is shipped to Washington Univeristy in St. Louis, Missouri

All samples will be tracked online using the FedEx Tracking number (except for the screening clinical laboratory samples that are sent to URMC).

The NCRAD/genetic sample collection worksheet (collects data related to whole blood long read sequencing, RNA, Buffy coat, and PBMC), and UPENN/Biomarker sample collection worksheet (collects data related to plasma and serum) must be completed on the day of each visit. These forms include information used to track the sample, confirm receipt of the sample, and information essential to processing and analysis. Additionally, the corresponding eCRF in the ADNI4 EDC must be completed on the day of each visit.

Genetic samples (NCRAD): whole blood long read sequencing, RNA, Buffy coat, and PBMC

Please email or fax a copy of the sample form to NCRAD before shipping so the lab knows to expect the sample.

Note, the shipping address has changed from ADNI3

NCRAD Shipping Address:

ADNI4 at NCRAD
National Centralized Repository for ADRD
351 W. 10th Street
TK-217
Indianapolis, IN 46202

NCRAD HELPDESK: ALZSTUDY@IU.EDU
TEL: (800) 526-2839

Biomarker samples (UPENN): plasma, serum and CSF

UPENN (ADNI BIOMARKER CORE LABORATORY) SHIPPING ADDRESS:

ADNI Biomarker Core Laboratory
7 Maloney South
University of Pennsylvania Medical Center
3400 Spruce Street
Philadelphia, PA 19104

For questions regarding biomarker shipping or packaging please contact the UPENN biomarker core help desk.

UPENN HELPDESK: ADNI@UPHS.UPENN.EDU

Brain Tissue (WUSTL): formalin fixed, fresh/frozen

***Prior to shipping tissue**, please coordinate shipment with the ADNI Neuropathology Core Coordinator. Shipping containers and prepaid airway bills will be provided by the NPC*

NEUROPATHOLOGY CORE (WUSTL) SHIPPING ADDRESS:

ADNI4 Neuropathology Core
c/o Haley Bernhardt
Washington University School of Medicine
Dept. of Path West Bldg Rm. 4713
425 S. Euclid Ave.
Saint Louis, Missouri 63110

For questions regarding biomarker shipping or packaging please contact the UPENN biomarker core help desk.

NPC CONTACT: ADNI-NPC@EMAIL.WUSTL.EDU

14.4 QUALITY CHECKS

In addition to being tracked online in the ADNI4 EDC, the condition and amount of samples received will be tracked by UPENN and NCRAD.

- Sites are responsible to ensure the requested amounts of each fluid are collected, to the best of their ability
- If a sample is not obtained at a particular visit, this should be recorded on the appropriate worksheet and eCRF (Sample Collection: UPENN Samples (serum/plasma); Sample Collection: NCRAD Samples (RNA, long read blood sequencing, Buffy coat, PBMC); Sample Collection (CSF)). Please ensure the reason why the sample was not obtained is provided.

IMPORTANT TO USE THE APPROPRIATE SAMPLE LABELS FOR EACH SAMPLE TYPE

- **NCRAD labels:** for Whole blood long read sequencing, RNA, Buffy Coat, and PBMC samples
- **UPENN Labels:** for plasma biomarker sample, serum biomarker sample and CSF

14.5 CLINICAL LABORATORY SAMPLES (URMC)

URMC – Safety Labs

URMC will provide laboratory kits for the ADNI4 Study. All other laboratory supplies are provided by the ATRI. Lab kit supplies are sent out by URMC to sites within two weeks of the Site Approval Notification email from Regulatory Affairs. Samples are collected according to the schedule of events. The URMC Laboratory Manual is available under the Labs – Clinical Safety folder in the document repository .

ALL CLINICAL LABORATORY SPECIMENS MUST BE SHIPPED ON THE DAY OF COLLECTION

CLINICAL LABORATORY REPORTS

URMC will fax or email a laboratory report to each center within 36 hours after receipt of the specimens.

- For each laboratory test, the participant's test result will be provided, as well as the reference range for that test
- All results that are out of range will be flagged as high or low by URMC
- For all out-of-range results, the PI or the clinician at the center must indicate clinical significance (yes or no) by checking the appropriate box on the report with additional review by medical monitoring

- Those results that are deemed clinically significant may need to be repeated and follow up with the patient's treating physician will be recommended by the study personnel
- The clinician must also initial and date each page of the report. All clinically significant out-of-range lab values should be entered as an Adverse Event online

FOR SPECIMENS MAILED ON A FRIDAY, BE SURE TO CHECK "SATURDAY DELIVERY" ON THE SHIPPING LABEL

If vitamin B12 level is ≤ 211 pg/mL at screening, a message will be printed on the lab report provided by URMC. The participant should return for homocysteine and methylmalonic acid testing to confirm they are eligible for the study. These kits are provided, including tailored lab requisition forms, and processed by URMC.

A LOW B12 IS EXCLUSIONARY, UNLESS FOLLOW-UP LABS (HOMOCYSTEINE [HC] AND METHYLMALONIC ACID [MMA]) INDICATE THAT IT IS NOT PHYSIOLOGICALLY SIGNIFICANT

For more information about safety lab collection kits, packaging, shipping, and safety sample collection kit resupply, refer to the URMC Laboratory Manual posted in the study documents folder.

ORDER ADDITIONAL CLINICAL LABORATORY KITS BY FAXING A COMPLETED URMC LAB KIT RE-SUPPLY FORM TO 585-4861376 OR IF YOU HAVE ANY QUESTIONS ABOUT HOW TO USE THE CLINICAL LABORATORY KITS, CONTACT URMC: URCENTRALLABS@URMC.ROCHESTER.EDU

14.6 BIOMARKER (UPENN), GENETIC (NCRAD) SAMPLES, BRAIN TISSUE (WUSTL)

SAMPLES COLLECTED BY VISIT

The following samples will be collected and shipped to the NCRAD or UPENN for analysis:

ORDER	SAMPLE TYPE		TUBE TYPE	# TUBES x VOLUME (ml)	TOTAL AMOUNT (ml)	SHIPPING TEMP	LAB FOR SHIPPING
1	Blood draw for **Plasma**		Lavender top EDTA	2 x 10	20	Frozen	**UPENN**
	Buffy Coat	Extracted from plasma sample tube	Cryovials	2 x 2	4	Ambient/ Frozen	**NCRAD**
2	Blood draw for **Long Read Sequencing***		Lavender top EDTA	1 x 3	3	Frozen	**NCRAD**
3	Blood draw for **PBMC****		Green top NaHep	2 x 10	20	Ambient	**NCRAD**
4	Blood draw for **Serum**		Red top serum	1 x 10	10	Frozen	**UPENN**
5	Blood draw for **RNA**		PAXgene	2 x 2.5	5	Ambient/ Frozen	**NCRAD**
6	**CSF**	Cryogen vials are for local testing	Clear top Sarstedt	2 x 13	20	Frozen	**UPENN**
7	**Fresh, frozen brain tissue*****		Container with dry ice	n/a	n/a	Frozen	**WUSTL**
	Formalin fixed brain tissue***		Rigid watertight container	n/a	n/a	Ambient	**WUSTL**

***Collected at the time of death. Place the bag with the wrapped fixed hemisphere in the cardboard box inside the insulated cooler box (both provided). Place extra packing material inside the box to secure the brain tissue within the box. Place the frozen hemisphere in the insulated box full of dry ice. It is critical that you **do not** transport the frozen and fixed brain in the same container. This will produce artifacts on the slides used for diagnostic purposes.

**PBMC collected once upon entry. New Participants at Baseline & Rollovers at Initial Visit.

*Whole blood for long read sequencing collected once upon entry. New Participants at Baseline & Rollovers at Initial Visit.

BIOMARKER AND GENETIC LAB SUPPLIES

Supplies required for the collection and shipment of the biomarker / genetic samples will be provided by the ATRI. Startup/initial supplies will be sent as outlined in the Site Approval Notification email from ATRI Regulatory and no later than two weeks from site activation. To order supplies beyond startup/initial shipment, please use the supply order form in the Document Repository. Please allow up to 7-10 business days to receive supplies.

14.7 PLASMA (UPENN) AND BUFFY COAT (NCRAD)

PLASMA SAMPLES (UPENN)

Plasma will be collected at Baseline (New Participants) / Initial Visits (Rollovers) and Ongoing (Yearly) In-clinic follow-up visits.

FASTING OVERNIGHT (MINIMUM 6 HOURS) IS REQUIRED FOR PLASMA, SERUM, AND CSF SAMPLE COLLECTION. ONLY WATER IS PERMITTED UNTIL THESE BLOOD DRAWS AND THE LP ARE COMPLETED.

Begin by confirming the subject consented to biomarker collection per their informed consent.

Next, complete the information on the BLD Plasma Biomarker label, and ensure all fields on the label are complete, and securely place the label onto the 13 mL transfer tubes (lavender top tubes for plasma) PRIOR to transfer of biomarker samples.

- ➲ **The Sample Identification label must be placed on the transfer tube prior to freezing!**

NOTE: Please use a ballpoint pen or permanent marker when completing the biomarker label.

BLOOD COLLECTION:

2 x 10 mL Lavender top tubes for plasma

1. Write the Subject Identification Number on the side of the tubes prior to drawing blood.
2. Collect blood until each tube is full.
3. **Immediately after collection,** gently invert/mix (180 degree turns) the tubes 10-12 times.
4. Estimate blood volume and record on the ADNI Biomarker Samples form.
5. Centrifuge samples for **15 minutes** using the Sorvall T 6000D Centrifuge (rotor H-1000B swinging bucket rotor) at 1500 rcf (3000 rpm for this specific centrifuge) with the brake on, or in another centrifuge and rotor at a comparable rcf.
6. Recommendations for sample processing times:
    a. Time from blood draw to centrifuge – **30 minutes**
    b. Time from start to centrifuge to transfer plasma into transfer tube – **20 minutes**
    c. Time for transfer tube to be placed on dry ice – **5 minutes**

TOTAL TIME FOR THE ENTIRE PROCESS FROM DRAW TO FREEZE AFTER PLACEMENT ON DRY ICE IS 60 MINUTES

1. Write in the Subject Identification Number, the time and date of collection and circle M or F to indicate subject gender, on the bar code label specific for BLD PLASMA and place this on one 13ml plastic transfer tube (lavender top screw cap) standing in a tube rack in the vertical position.
2. Using a pipette carefully transfer plasma from each of the two lavender- top blood tubes into the bar code-labeled 13ml plastic transfer tube, and firmly cap with the lavender screw cap.
3. After the plasma has been transferred to the plastic labeled tube and capped, place the lavender screw-capped BLD PLASMA - labeled tube upright in dry ice and allow to completely freeze until shipment to **UPenn**.

4. Ensure all fields on the Biomarker Samples worksheet (plasma) located in the visit packet are complete
5. Ensure name of the individual who packaged and shipped the blood specimen, along with their phone number and email is listed on the worksheet.
6. List in the comments section of the worksheet any issues that occurred during the blood draw, with packaging or any temperature excursions.
7. Email the completed Biomarker Sample Collection worksheet: Plasma, Serum, CSF to **ADNI@uphs.upenn.edu** on the day of collection**.**
8. Complete the Biomarker Sample (serum/plasma) eCRF located in the ADNI4 web portal immediately after sample collection. Remember to include any issues that occurred during the collection.

BUFFY COAT SAMPLES (NCRAD)

Buffy coat extraction should follow each biomarker (plasma/EDTA) lab blood draw. For all participant types, buffy coat will be extracted at the Baseline / Initial Visit and then at each Ongoing In-clinic visit.

Prior to collection, complete the information on the NCRAD labels, and ensure all fields on the label are complete. Then attach to cryogenic vials ensuring that labels are dovetailed so as to not obscure any information on the labels.

- **Complete this process for both 2mL buffy coat cryogenic vials**

NOTE: Please use a ballpoint pen or permanent marker when completing the biomarker label.

BLOOD COLLECTION:

1. After plasma has been removed from the BLD PLASMA labeled EDTA (Lavender-top) Blood Collection tubes, extract the buffy coat layer.
2. Using sterile gloves and a sterile pipette, extract the buffy coat from one of the lavender-top BLD PLASMA labeled EDTA tubes and aliquot it into one of the 2ml cryogenic vials. Repeat for 2nd set of tubes. Do not combine them.


3. If shipping same day, store upright at room temperature. If Friday draw, store tubes at -80ºC in a wire rack until frozen shipment to **NCRAD.**

YOU WILL GET SOME OF THE RED BLOOD CELLS WHEN PULLING OFF THE BUFFY COAT. GENERALLY, IF YOU DON'T SEE RED THEN YOU HAVEN'T GONE FAR ENOUGH DOWN THE TUBE. AFTER EXTRACTING THE BUFFY COAT, HOLD ONTO REMAINING CELLS.

4. Ensure all fields on the NCRAD Sample Collection worksheet located in the visit packet are complete.
5. Ensure name of the individual who packaged and shipped the blood specimen, along with their phone number and email is listed on the worksheet.
6. List in the comments section of the worksheet any issues that occurred during the blood draw, with packaging or any temperature excursions.
7. Email the completed NCRAD Sample Collection worksheet: DNA, PBMC, RNA, Buffy Coat and Whole blood for long read sequencing to alzstudy@iu.edu.
8. Complete the NCRAD Sample eCRF located in the ADNI4 portal immediately after sample collection. Remember to include any issues that occurred during the collection.

14.8 LONG READ SEQUENCING/DNA (NCRAD)

Blood samples for long read sequencing (DNA) will be collected for long read sequencing at the Baseline Visit for Newly Enrolled Participants and at Initial Visit for Rollover Participants.

Begin by confirming the subject consented to DNA testing.

Next, complete the information on the NCRAD label for the EDTA (lavender top) tube and 2mL aliquot tubes for Whole Blood. Ensure all fields on the label are complete, and attach to tubes ensuring that labels are dovetailed so as to not obscure any information on the labels

- **The Sample Identification label must be placed on the transfer tube prior to freezing!**

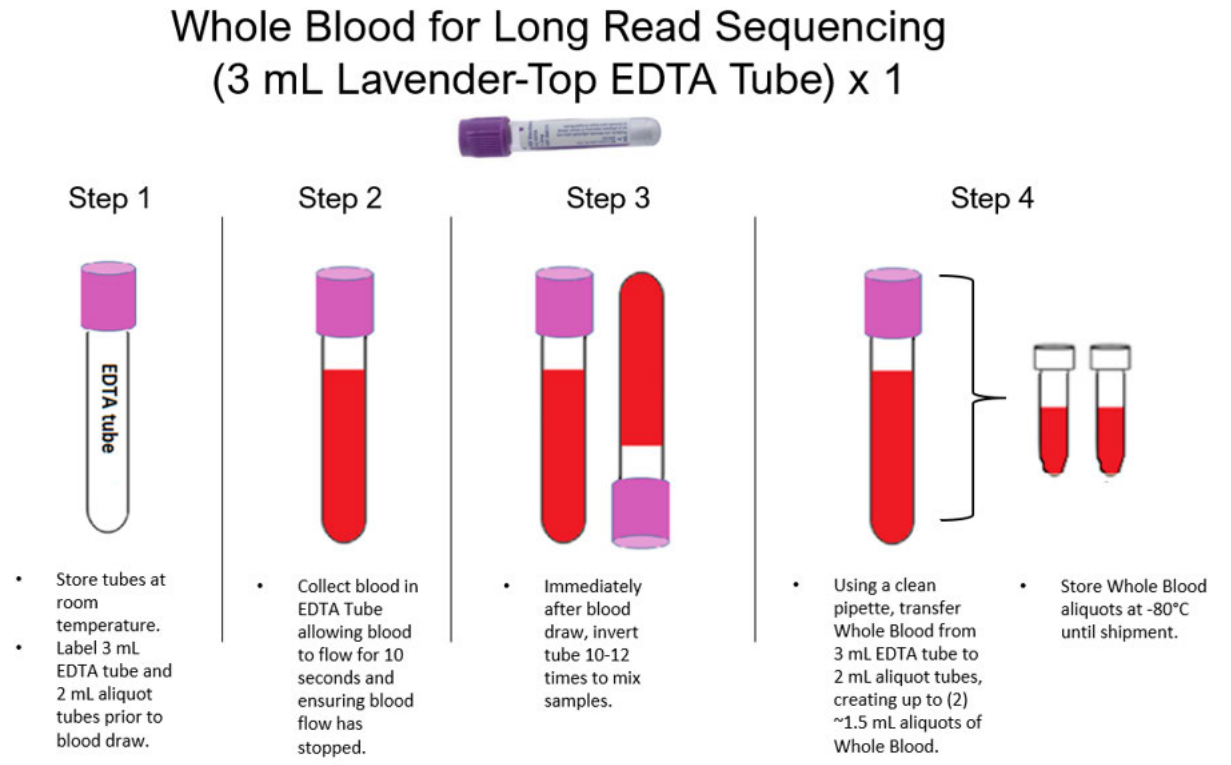
NOTE: Please use a ballpoint pen or permanent marker when completing the biomarker label.

BLOOD COLLECTION:

1 x 3 mL EDTA Lavender top tube and 2 x 2mL aliquot tubes

1. Allow at least 10 seconds for a complete blood draw to take place in each tube. Ensure that the blood has stopped when draw is complete.
2. **Immediately after blood collection**, gently invert/mix (180 degree turns) the tube 10-12 times.
3. **Without processing the EDTA tube**, transfer the whole blood from the EDTA tube using a clean pipette into both 2ml aliquot tubes creating ~1.5ml aliquots of Whole Blood. Both 2ml aliquot tubes with ~1.5ml of Whole Blood are to be shipped to NCRAD frozen, without processing at the collection site.
4. Store Whole Blood aliquots at -80°C until shipment to NCRAD.
5. Ensure all fields on the NCRAD Sample Collection worksheet located in the visit packet are complete

6. Ensure name of the individual who packaged and shipped the blood specimen, along with their phone number and email is listed on the worksheet.
7. List in the comments section of the worksheet any issues that occurred during the blood draw, with packaging or any temperature excursions.
8. Email the completed NCRAD Sample Collection worksheet: DNA, PBMC, RNA, Buffy Coat and Whole blood for long read sequencing to alzstudy@iu.edu
9. Complete the NCRAD Sample eCRF located in the ADNI4 portal immediately after sample collection. Remember to include any issues that occurred during the collection.



14.9 PBMC (NCRAD)

Blood for PBMC is collected at Baseline for all Newly Enrolled Participants and at Initial Visit for Rollover Participants, **if not previously collected in ADNI3**. PBMCs will not be collected in Ongoing Annual Visits.

Begin by confirming the subject consented to creation of cell lines.

Next, complete the information on the NCRAD label for the genetic tube (NaHep top) tube. Ensure all fields on the label are complete, and securely place label on NaHep tube.

- ➲ **No processing is required for this tube. The single tube is to be shipped to NCRAD, without processing at the site.**

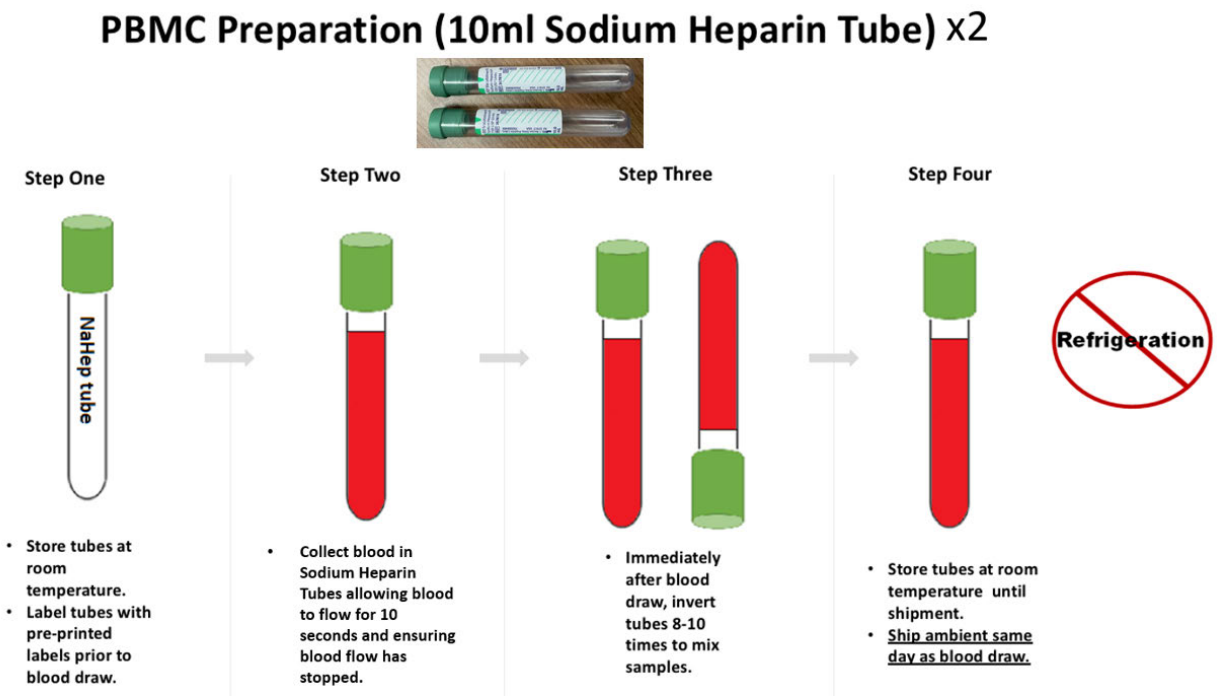
NOTE: Please use a ballpoint pen or permanent marker when completing the biomarker label.

BLOOD COLLECTION:

2 x 10mL Sodium Heparin (NaHep) Green top tube

1. Using a blood collection set and a holder, collect blood into the Sodium Heparin (Green-Top) Blood Collection Tubes (10 ml) using your institution's recommended procedure for standard venipuncture technique.
2. Allow at least 10 seconds for a complete blood draw to take place in the tube. Ensure that the blood has stopped flowing into each tube before removing the tube from the holder. The tube with its vacuum is designed to draw 10 ml of blood into the tube.
3. **Immediately after blood collection**, gently invert/mix (180-degree turns) each tube 8-10 times.
4. Ship the unprocessed tubes ambient to **NCRAD** the day of the participant visit.
5. Ensure all fields on the NCRAD Sample Collection worksheet located in the visit packet are complete
6. Ensure name of the individual who packaged and shipped the blood specimen, along with their phone number and email is listed on the worksheet.
7. List in the comments section of the worksheet any issues that occurred during the blood draw, with packaging or any temperature excursions.
8. Email the completed NCRAD Sample Collection worksheet: DNA, PBMC, RNA, Buffy Coat and Whole blood for long read sequencing to alzstudy@iu.edu
9. Complete the NCRAD Sample eCRF located in the ADNI4 portal immediately after sample collection. Remember to include any issues that occurred during the collection.

UNDER NO CIRCUMSTANCES CAN PBMC SAMPLES BE DRAWN AND SHIPPED ON A FRIDAY. MUST BE DRAWN ON MONDAY-THURSDAY.



14.10 SERUM (UPENN)

Serum will be collected at Baseline (New Participants) / Initial Visits (Rollovers) and Ongoing (Yearly) In-clinic follow-up visits.

FASTING OVERNIGHT (MINIMUM 6 HOURS) IS REQUIRED FOR PLASMA, SERUM, AND CSF SAMPLE COLLECTION. ONLY WATER IS PERMITTED UNTIL THESE BLOOD DRAWS AND THE LP ARE COMPLETED.

Begin by confirming the subject consented to biomarker collection per their informed consent.

Next, complete the information on the BLD SERUM Biomarker label, and ensure all fields on the label are complete, and securely place the label onto the 13 mL transfer tubes (red top tubes for lavender top tubes for plasma) PRIOR to transfer of biomarker samples.

- **The Sample Identification label must be placed on the transfer tube prior to freezing!**

NOTE: Please use a ballpoint pen or permanent marker when completing the biomarker label.

BLOOD COLLECTION:

1 x 10mL Red top tube

1. Write the Subject Identification Number on the side of the tubes prior to drawing blood.
2. Collect blood until each tube is full.
3. **Immediately after collection**, gently invert/mix (180 degree turns) the tubes 10-12 times.

4. Estimate blood volume and record on the ADNI Biomarker Samples form.
5. Allow the blood to clot for 30 minutes at room temperature in a vertical position.
6. Within one (1) hour of collection, centrifuge samples for 15 minutes using the Sorvall T 6000D Centrifuge (rotor H-1000B swinging bucket rotor) at 1500 rcf (at 3000 rpm for this specific centrifuge) with the brake on, or in another centrifuge and rotor at a comparable rcf.
7. Recommendations for sample processing times:
    a. Time for blood draw to centrifuge – **60 minutes**
    b. Time from start to centrifuge to transfer serum into transfer tube – **20 minutes**
    c. Time for transfer tube to be placed on dry ice – **5 minutes**

TOTAL TIME FOR THE ENTIRE PROCESS FROM DRAW TO FREEZE AFTER PLACEMENT OF DRY ICE IS BELOW 90 MINUTES

8. Write in the Subject Identification Number, the time and date of collection and circle M or F to indicate subject gender, on the bar code label specific for BLD SERUM and place this on one 13ml plastic transfer tube (red top screw cap) standing in a tube rack in the vertical position.
9. Using a pipette carefully transfer serum from each of the two red-top blood tubes into the bar code-labeled 13ml plastic transfer tube, and firmly cap with the red screw cap.
10. After the serum has been transferred to the plastic labeled tube and capped, place the red screw-capped BLD SERUM-labeled tube upright in dry ice and allow to completely freeze until shipment to **UPenn**.
11. Ensure all fields on the Biomarker Samples worksheet (serum) are complete.
12. Ensure name of the individual who packaged and shipped the blood specimen, along with their phone number and email is listed on the worksheet.
13. List in the comments section of the worksheet any issues that occurred during the blood draw, with packaging or any temperature excursions.
14. Email the completed Biomarker Sample: Plasma, Serum, CSF worksheet to **ADNI@uphs.upenn.edu** on the day of collection.
15. Complete the Biomarker Sample (serum/plasma) eCRF located in the ADNI4 portal immediately after sample collection. Remember to include any issues that occurred during the collection.

14.11 RNA (NCRAD)

An RNA sample will be collected at Baseline and Ongoing Annual Visits across all Newly Enrolled Participants. Rollover Participants will have an RNA sample collected at the Initial Visit and then Ongoing at annual follow-up visits. Whole blood will be collected in two 2.5 ml PAXgene™ Blood RNA tubes.

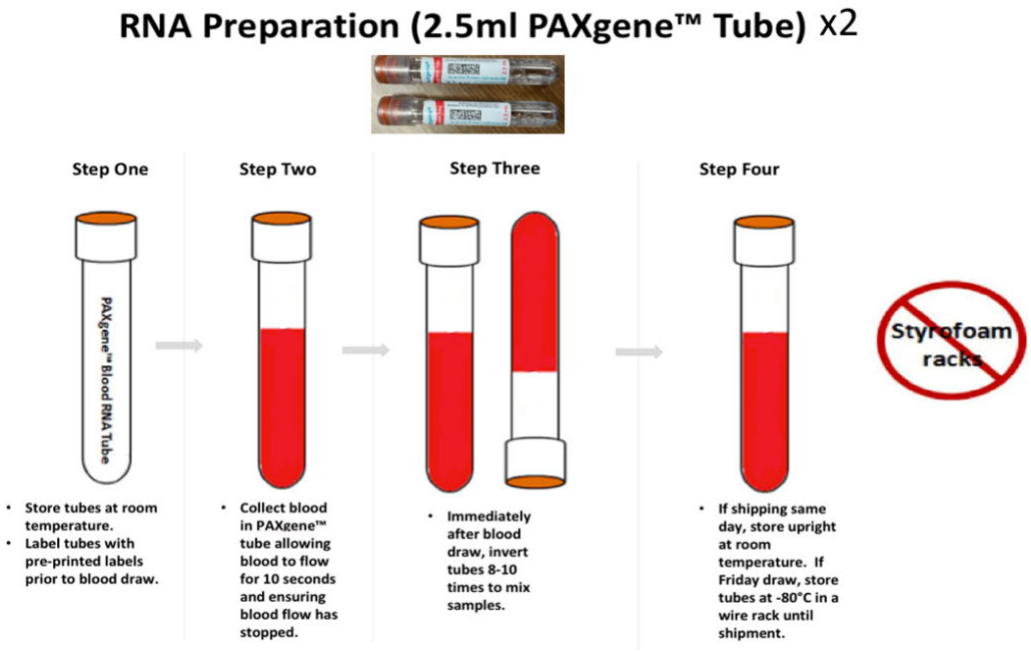
Begin by confirming the subject consented to RNA testing.

Next, complete the information on the NCRAD label for each of the PAXgene™ blood RNA tubes. Ensure all fields on the label are complete, and securely place label on each tube.

NOTE: Please use a ballpoint pen or permanent marker when completing the biomarker label.

BLOOD COLLECTION:

1. PAXgene Blood RNA tubes are provided by the ATRI.
2. Ensure that the PAXgene™ Blood RNA tube is at room temperature prior to use.
3. If the PAXgene™ Blood RNA tube is the only tube to be drawn, a small amount of blood should be drawn into a "discard tube" prior to drawing blood into the PAXgene™ Blood RNA tube. Otherwise, the PAXgene™ Blood RNA tube should be the **LAST** tube drawn in the phlebotomy procedure. (Discard tube is included in the RNA collection kit provided by ATRI).
4. Using a BD (Becton, Dickinson and Company) Vacutainer™ Safety-Lok Blood Collection Set, collect blood into the PAXgene™ Blood RNA tube using your institution's recommended standard procedure for venipuncture.
5. Hold the PAXgene™ Blood RNA tube vertically, below the blood donor's arm, during blood collection.
6. Allow at least 10 seconds for a complete blood draw to take place. Ensure that the blood has stopped flowing into the tube before removing the tube from the holder.
7. Gently invert the PAXgene™ Blood RNA tube 8 to 10 times.
8. Store the PAXgene™ Blood RNA tube upright at room temperature.
9. If Friday draw, stores tubes at -80ºC in a **wire rack** until shipment to **NCRAD**.
10. Ensure all fields on the NCRAD Sample Collection worksheet located in the visit packet are complete
11. Ensure name of the individual who packaged and shipped the blood specimen, along with their phone number and email is listed on the worksheet.
12. List in the comments section of the worksheet any issues that occurred during the blood draw, with packaging or any temperature excursions.
13. Email the completed NCRAD Sample Collection worksheet: DNA, PBMC, Whole blood long read, RNA, and Buffy Coat to alzstudy@iu.edu
14. Complete the NCRAD Sample eCRF located in the ADNI4 portal immediately after sample collection. Remember to include any issues that occurred during the collection.



14.12 CSF (UPENN)

LP in the ADNI4 study is performed only on subjects consented to LP and exceptions will be made for participants that decline LP under certain circumstances: medical exclusion including anticoagulation or back surgery; unsuccessful LP procedure; or participant had a bad experience with LP in the past. Always confirm participant consented to LP before scheduling the procedure and again prior to performing the procedure.

For all participants, CSF will be collected at Baseline / Initial Visit and every two years thereafter.

FASTING OVERNIGHT (MINIMUM 6 HOURS) IS REQUIRED FOR PLASMA, SERUM, AND CSF SAMPLE COLLECTION. ONLY WATER IS PERMITTED UNTIL BLOOD DRAWS AND THE LP ARE COMPLETED.

Begin by confirming the subject consented to CSF collection per their informed consent.

Next, complete the information on the CSF label, ensure all fields on the label are complete, and securely place the label onto each of the 13 mL polypropylene tubes (clear screw cap) PRIOR to collection of CSF samples.

- ➲ **The Sample Identification label must be placed on the transfer tube prior to freezing!**

NOTE: Please use a ballpoint pen or permanent marker when completing the biomarker label.

CSF COLLECTION:

1. Collect CSF in 13ml polypropylene collection tubes (or 5cc syringes if using the suction method), for a total of 20 ml.

2 . To clear any blood from minor trauma associated with needle insertion; the first 1-2 ml (or more if needed) of CSF from the total 20 ml CSF collected in Step 1 should be discarded.

3 . Aliquot (via pipette) 1ml of the approximately 18 ml CSF left over from Step 2 into a 2ml cryogenic vial provided by ATRI. Repeat this same process with a second 2ml cryogenic vial. The two (2) 2ml cryogenic vials will be used for standard tests done locally. There should be approximately 16 ml of CSF left after performing Steps 1 – 3.

4 . **Freeze the remaining CSF in the 13ml tubes immediately by placing the tubes in an upright position for 20 minutes on dry ice until frozen. Make sure cap is properly closed on the tube. Ship to UPenn.** Follow **frozen** shipping instructions in Chapter 10.

5 . Set aside the two (2) x 2.0ml cryogenic vials of CSF and store temporarily at room temperature. Deliver these cryogenic vials (or ship overnight at ambient temperature) to your local lab for standard tests (total red and white blood cell counts, total protein and glucose).

6. Remember CSF sample shipped to your local lab for testing is NOT to be frozen and is shipped ambient.

DO NOT ALLOW SAMPLES TO THAW AT ANY POINT AFTER THEY HAVE BEEN FROZEN

7. Ensure all fields on the biomarker samples worksheet are complete.

8. Ensure the Bar Code License Plate and FedEx tracking number are included on the worksheet.

9. Additionally, list in the comments section of the worksheet any issues that occurred during the CSF collection, with packaging or any temperature excursions.

14.13 BRAIN TISSUE (WUSTL)

Information about brain tissue collection is available in the Neuropathology Core Procedures Manual in the Document Repository of the EDC in the Neuropathology folder.

14.14 GENERAL SHIPPING INSTRUCTIONS

Ensure all fields on the Biomarker Samples worksheet and the NCRAD Samples worksheet located in the visit packet are complete, and that the name of the individual who packaged and shipped the blood specimen, along with their phone number and email is listed on the worksheet. Additionally, list in the comments section of the worksheets any issues that occurred during the blood draw, with packaging or any temperature deviations.

SAMPLE TYPE	SHIP TO	SHIPPING TEMP.	SHIPPING NOTES	IF FRIDAY DRAW…
Whole Blood for Long Read Sequencing (Lavender-Top EDTA)	NCRAD	Frozen	Store frozen until ready to ship.	Store frozen – can be shipped Monday – Wednesday.
PBMC (Green-Top NaHep)	NCRAD	Ambient	Ship same day.	No Friday Draws.
RNA (PAXgene™ Tubes)	NCRAD	Ambient (unless drawn on Friday)	Must be received by NCRAD with 24 hours of draw.	Store frozen and ship out Monday.
Buffy Coat (From Plasma EDTA tubes going to UPENN)	NCRAD	Ambient (unless drawn on Friday)	Must be received by NCRAD with 24 hours of draw.	Store frozen and ship out Monday.
Plasma (Lavender-Top EDTA)	UPENN	Frozen	Ship frozen same day.	Store frozen and ship out Monday.
Serum (Plain Red Top)	UPENN	Frozen	Ship frozen same day.	Store frozen and ship out Monday.
CSF	UPENN	Frozen	Ship frozen same day.	Store frozen and ship out Monday.
Fresh/Frozen Brain Tissue	WUSTL	Frozen	Store frozen until ready to ship.	n/a
Formalin Fixed Brain Tissue	WUSTL	Ambient	Must sit in formalin for two weeks prior to shipping	n/a

NOTIFYING NCRAD:

The day the blood sample is shipped to **NCRAD** you must FIRST email a copy of the completed NCRAD Sample Collection worksheet to NCRAD at **alzstudy@iu.edu.**

NOTIFYING UPENN:

The day the serum, plasma, and CSF are collected and shipped to **UPenn**, you must FIRST email the completed Biomarker Sample Collection worksheet: Plasma, Serum, CSF to **ADNI@uphs.upenn.edu.**

NOTIFYING WUSTL:

The NPC must be notified of the death as soon as possible. The NPC must collect information about changes in health or cognition since the final in-person ADNI assessments to identify any safety concerns for personnel involved in conducting the port mortem examination. The ADNI NPC coordinator will help schedule the shipment of the brain tissue and provide materials for shipment. NPC Coordinator must be notified when material is shipped.

14.15 NCRAD SHIPPING

NCRAD Shipping Address: **NCRAD Helpdesk:**

Kelley Faber
National Centralized Repository for ADRD
351 W. 10th Street
TK-217

Indianapolis, IN 46202

alzstudy@iu.edu
Tel: (800) 526-2839

Fax: (317) 278-1100

AMBIENT SHIPPING: PBMC, BUFFY COAT AND RNA*

***unless Buffy Coat and RNA drawn on Friday – then ship frozen**

Ambient samples are shipped by Federal Express – Priority Overnight (Monday – Thursday) to **NCRAD**. Pre-Paid Federal Express Air-bills and ambient shippers will be provided by ATRI. If your site needs additional Air-bills or ambient shippers, complete the online ADNI4 Supply Order Form

Ambient shipping supplies include:

- 1 medium 95kPa canister
- Aqui-Pak segmented absorbent pouch
- Cushioning material (bubble bag)
- Biohazard symbol label
- Biological Substance Category B label
- Shipping box
- List of contents card

Instructions:

1. Insert all tubes into tube sleeves
2. NEVER INSERT DISCHARGE TUBE INTO TUBE SLEEVE. If used, the discharge tube should be discarded.
3. Carefully roll up sleeve, insert into canister and wrap OUTSIDE canister in bubble wrap.
4. Fill out the list of contents card.
5. Place card and canister into shipping box
6. Fill out NCRAD FedEx Air-bills and attach to shipping box.
7. Depending on the number of specimen tubes collected at a given visit, the buffy coats may not fit in the existing ambient shipper used for the PBMC and RNA (shipper holds up to 6 tubes). In such cases, a smaller ambient shipper is being provided by the ATRI to ship the buffy coat to **NCRAD**.

Buffy Coat sample shipping supplies include:

- 1 medium 95kPa canister
- Aqui-Pak segmented absorbent pouch
- Cushioning material (bubble bag)
- Biohazard symbol label
- Biological Substance Category B label
- Shipping box
- List of contents card
- Instructions

Instructions:

1. Insert the 2ml cryogenic vials into tube sleeve
2. Carefully roll up sleeve, insert into canister and wrap **OUTSIDE** canister in bubble wrap.
3. Fill out the list of contents card.
4. Place card and canister into shipping box.
5. Fill out NCRAD FedEx Air-bill and attach to box.

MAKE SURE A COPY OF THE SAMPLE COLLECTION –NCRAD WORKSHEET IS INCLUDED WITH THE SHIPMENT

FROZEN SHIPPING: WHOLE BLOOD FOR LONG READ SEQUENCING, BUFFY COAT AND RNA*

***If Buffy Coat and RNA drawn on Friday – then ship frozen**

Frozen samples are shipped by Federal Express – Priority Overnight (Monday – Wednesday) to **NCRAD**. Pre-Paid Federal Express Air-bills and frozen shippers will be provided by ATRI. If your site needs additional Air-bills or frozen shippers, complete the online ADNI4 Supply Order Form.

Frozen shipping supplies include:

- Styrofoam Shipper with Cardboard Box
- UN3373 Category B Sticker
- UN1845 Dry Ice Sticker
- 95kPa Biohazard bag
- Bubble Wrap Bag

Instructions:

1. Place all tubes into segmented absorbent sleeve.
2. Place segmented absorbent sleeve into 95kPa shipping bag. Place into bubble wrap bag.
3. Place bag directly onto dry ice in Styrofoam shipper and fill rest of box with dry ice.
4. Cover Styrofoam box and place into cardboard box.
5. Seal cardboard box firmly with packaging tape, affix preprinted FedEx label (included with supplies provided by ATRI), and call for pickup.

MAKE SURE A COPY OF THE SAMPLE COLLECTION –NCRAD WORKSHEET IS INCLUDED WITH THE SHIPMENT

14.16 UPENN SHIPPING

MAKE SURE TO NOTIFY THE UPENN BIOMARKER CORE THE DAY SAMPLES ARE SHIPPED BY EMAILING THE BIOMARKER SAMPLE COLLECTION WORKSHEET .

UPENN Shipping Address:

University of Pennsylvania Medical Center

ADNI Biomarker Core Laboratory

7 Maloney South

3400 Spruce Street

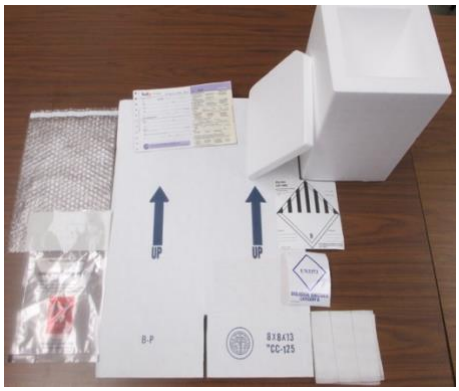
UPENN helpdesk:

Email: ADNI@uphs.upenn.edu

Phone: (215) 662-6266

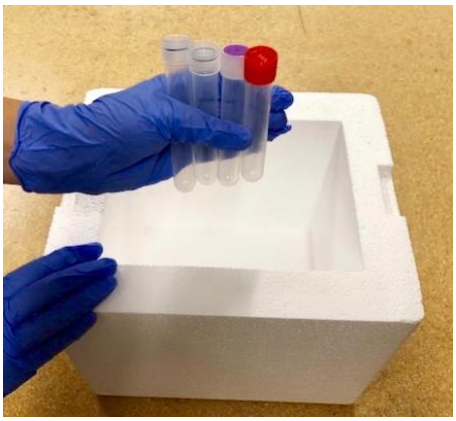
Philadelphia, PA 19104

FROZEN SHIPPING



1. Frozen Shipping Supplies – ATRI Provided

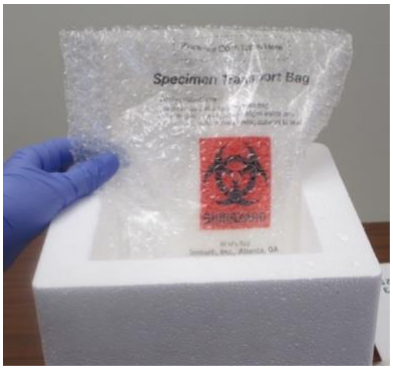
- Styrofoam Shipper with Cardboard Box
- UN3373 Category B Sticker
- UN1845 Dry Ice Sticker
- 95kPa Biohazard bag
- Bubble Wrap Bag



2. Place the four polypropylene tubes (1 serum, 1 plasma and 2 CSF) upright in dry ice and allow to completely freeze.

3. Place the polypropylene tubes into segmented absorbent sleeve.

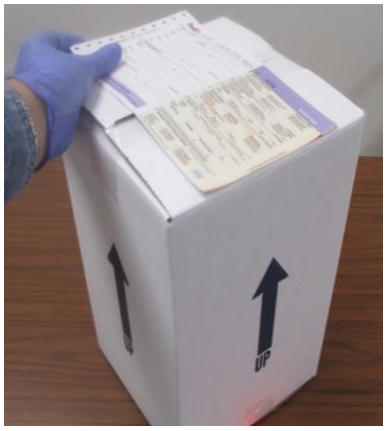
4. Place segmented sleeve and copy of collection worksheet into the 95kPA shipping bag. Place into bubble wrap bag.



5. Place bag directly on to dry ice in Styrofoam shipper and fill rest of box with dry ice.

6. Cover Styrofoam box and place into cardboard box.

7. Seal cardboard box firmly with packing tape.



8. Affix preprinted, included FedEx label and call for pickup.

SHIPPING TO UPENN:

1. FedEx all biomarker biofluid samples the **SAME DAY on DRY ICE** by FedEx.
2. For those instances in which a Friday study visit is necessary, CSF, plasma and serum samples should be placed in a -80ºC freezer until Monday and shipped on dry ice to UPENN. If a -80ºC freezer is not available, a -20ºC freezer is acceptable.
3. Pre-Paid Federal Express Air-bills and frozen shippers will be provided by the ATRI. If your site needs additional UPENN Air-bills or frozen shippers, please complete the ADNI4 online Supply Order Form.
4. Enter the sample collection data on the Biomarker Samples_Plasma_Serum CSF eCRF in the ADNI4 EDC immediately after sample collection. Make sure to enter the Bar Code License Plate (one per visit) and FedEx tracking number.
5. Print a pdf of the completed form and include a copy with the shipment.

1. **PRIORITY OVERNIGHT SHIPPING (MONDAY – THURSDAY)**

2. **UPENN WILL NOT BE ABLE TO RECEIVE ANY SHIPMENT ON SATURDAY OR SUNDAY**

14.17 WUSTL SHIPPING

MAKE SURE TO NOTIFY THE WUSTL NEUROPATHOLOGY CORE PRIOR TO SHIPPING BRAIN TISSUE

WUSTLSHIPPING ADDRESS:

ADNI4 Neuropathology Core
c/o Haley Bernhardt
Washington University School of Medicine
Dept. of Path West Bldg Rm. 4713
425 S. Euclid Ave.
Saint Louis, Missouri 63110

WUSTL NPC CONTACT:

Email: ADNI-NPC@email.wustl.edu

Phone: 314-273-1269

After Office Hours Pager: 314-841-4738

Shipping supplies for formalin fixed and frozen/fresh tissue are provided by the NPC. The following components will be provided:

An Insulated Category B Shipping System:

- Outer Box pre-printed with Biological Substance, Category B, UN3373 and Exempt Human Specimen Markings
- Inner Box
- Insulated Chest
- Class 9 Hazard Label
- Dry Ice UN1845 Label
- Disposable plastic and paper biohazard bags

Pre-paid FEDEX airway bills to return shipping materials and brain tissue to St. Louis

SHIPPING TO WUSTL:

1. **Provide mailing address for supplies for shipment.**
2. Once materials are received, schedule the shipment of the brain tissue with the NPC Coordinator.

3. Ship via FEDEX Priority Overnight (Monday-Wednesday)
4. The Formalin Fixed tissue must sit in 10% neutral buffered Formalin at room temperature for at least two weeks prior to shipping to St. Louis. To ship, place the bag with the wrapped fixed hemisphere in the cardboard box inside the insulated cooler box (both provided). Place extra packing material inside the box to secure the brain tissue within the box. Place the frozen hemisphere in the insulated box packed full of dry ice.
5. The Frozen/Fresh tissue must be kept frozen (-80°C freezer is preferred). To ship, place the frozen hemisphere in the insulated box packed full of dry ice.
6. Do not place frozen tissue and fixed tissue in the same box.
7. Please reference the ADNI Neuropathology Procedures Manual for more details on the shipping protocol.

CHAPTER 15: ADVERSE EVENTS

The U.S. Code of Federal Regulations (CFR) defines procedures and requirements governing the use of investigational new drugs regulated by the U.S. Food and Drug Administration (FDA), including the monitoring and reporting of adverse events (21 CFR 312). The ATRI is responsible for ensuring that ATRI studies are conducted in accordance with the above referenced regulation as well as other applicable CFRs, FDA guidelines, and International Conference on Harmonization (ICH) guidelines.

15.1 AE AND SAE DEFINITIONS

ADVERSE EVENTS (AE)

An **Adverse Event (AE)** is any adverse change from the participants baseline (Screening Visit or Initial Visit) condition including clinical or laboratory test, or abnormalities that occur during the course of the study after consent. **All AEs should be reported.**

The event can include any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease temporally associated with the participants' involvement in the research.

Examples:

- New symptoms and pre-existing symptoms that have worsened in frequency or severity, even if the event was not caused by a study procedure.
- Recurrence of a previously resolved condition.
- Intercurrent illness
- Drug interaction
- Any clinically significant findings from vital sign measurements, physical exams and other procedures must be reported as AEs.
    - An abnormal test finding should be reported as an AE if any of the following criteria are met: Test result is associated with accompanying symptoms
    - Test result requires additional diagnostic testing or medical/surgical intervention
    - Test result is considered to be clinically significant by the PI

    NOTE: If an abnormal test finding is the result of a condition, then the condition should be documented as an AE. If not, then the test finding itself should be reported as an AE (as with other signs/symptoms existing in the absence of a diagnosis). If/when a diagnosis is

subsequently made, it should be documented as a **new/separate** AE and the initial signs/symptoms should be referenced in the Comments/ Narrative section. The initial AE (which reported the signs/symptoms) should be updated **to include a cease date (based on the date that the condition was diagnosed)** and to include details in the Comments/Narrative section regarding the diagnosis.

- An abnormal test finding should **NOT** be reported as an AE if any of the following criteria are met:
  - Abnormal test is repeated in the absence of any of the above criteria
  - Test result is determined to be an error

SERIOUS ADVERSE EVENTS (SAE)

A **Serious Adverse Event (SAE)** is any untoward or unfavorable medical event that occurs in a study participant and results in any of the following outcomes:

- Death
- Life-threatening
- Hospitalization or prolongation of existing hospitalization
- Disability or permanent damage
- Congenital anomaly/birth defect
- Important medical events

The event does **not** need to have a causal relationship study procedures to be considered a serious adverse event.

DEATH/FATAL

Death is an OUTCOME of an event, not an event term or diagnosis. It is necessary to find out the cause of death. If the cause of death is unknown at first reporting, then provide an update in a follow-up report once the cause of death is known. Death can only be documented as the event if "death" is the only information available at the time the SAE is reported. In this case, be sure to explain that no qualifying information was available in the Comments/Narrative section. There should only be one SAE with an outcome of death for each participant.

Example: "Death due to myocardial infarction" is reported
Event: Myocardial Infarction
Outcome: Fatal

LIFE-THREATENING

An event is considered life-threatening if, in the opinion of the Investigator or ATRI, the participant was at risk of death at the time of the event; it does not refer to an event which might have caused death had the event been more severe.

Examples:

- Pacemaker failure
- Hepatitis resolved without hepatic failure
- Bone marrow suppression

HOSPITALIZATION OR PROLONGATION OF HOSPITALIZATION

Hospitalization is any event resulting in admission to a healthcare facility that requires an overnight stay.

Prolongation of existing hospitalization is any event that extends a hospital stay beyond the originally anticipated time.

Hospitalization does NOT include:

- Rehabilitation facilities
- Hospice
- Respite care
- Skilled nursing facilities
- Nursing homes
- Same day surgeries (i.e., outpatient and ambulatory procedures)

Any hospitalization or prolongation of hospitalization is considered serious in the presence of an AE; however, in the absence of a medical AE, hospitalization or prolongation of hospitalization is **not** considered an AE. Record events that occur during a hospitalization and are considered an AE or SAE. **Hospitalization or Prolongation of Hospitalization is NOT an event term.**

The following types of hospitalizations are **NOT** considered serious:

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

DISABILITY OR PERMANENT DAMAGE

An event that causes disability or permanent damage is any event that results in substantial or permanent disruption of a person's ability to conduct normal life functions (i.e., AE resulted in significant, persistent, or permanent change, impairment, or disruption in the person's body function/structure, physical activities, and/or quality of life).

CONGENITAL ANOMALY / BIRTH DEFECT

A congenital anomaly/birth defect is considered an SAE if it is suspected that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

IMPORTANT MEDICAL EVENTS

A medically important event is any event that does not fit neatly into any of the other categories but may jeopardize the participant and may require medical or surgical intervention/treatment in order to prevent one of the other outcomes.

Examples:

- Allergic bronchospasm that required treatment in an emergency room
- Seizures/convulsions that do not result in hospitalization

15.2 COLLECTION AND REPORTING OF AES AND SAES

Collect and document all AEs/SAEs that occur after CONSENT and up to 30 days after the last study visit or the last dose of study drug, whichever is longer, regardless of the investigator's opinion of causation.

An investigator must report to the ATRI any serious adverse event, including those listed in the protocol or investigator brochure and must include an assessment of whether there is reasonable possibility that the drug caused the event (21 CFR 312.64). **A serious adverse event must be reported within 24 hours of becoming aware of the event.**

Screen for new AEs/SAEs and review any unresolved AEs/SAEs at each study visit. Record any new condition, recurrence of a previously resolved condition, or worsening of a pre-existing condition initially reported in the Initial Health Assessment, as an AE.

NOTE: Upon entry into the study, enter any clinically significant medical history event and any current medical condition/symptom and provide details in Initial Health Assessment form. The initial health conditions are reviewed/updated at each visit. AE are unique to condition/symptom; any change in chronicity or severity is captured within a single record. If the AE is a worsening initial health condition, the Initial Health # is provided so the information can be linked.

The following questions may help identify an AE:

- Has your previous AE (if any) continued unchanged, worsened, or resolved since the last visit?
- Have you taken any new medication since the last study visit? If so, determine if a corresponding adverse event or condition needs to be entered in the eCRF.
- Have you stopped or changed the dosage or frequency of any medications you were taking at the last study visit?
- Has your health changed in any way through illness or injury since the last study visit?
- Question any missed study visits

REPORTING PROCESS:

1. Document the event (be it deemed serious or non-serious) as soon as possible after becoming aware of the event. **All SAEs must be documented within 24 hours of becoming aware of the event.**
2. Confirm if the event should be considered serious based on the event outcome and assessment by qualified staff personnel
3. Both the Adverse Event/Hospitalization Worksheet and the Adverse Event/Hospitalization Log eCRF must be completed (with as much information you have at the time of becoming aware of the event)
4. The event must be described in appropriate medical terminology with sufficient information to ensure the event is accurately recorded so it can be matched against a coding dictionary such as MedDRA (Medical Dictionary for Regulatory Activities).
5. Fulfill local IRB requirements, if applicable.

The Investigator MUST follow all SAEs to resolution. Resolution occurs when one of the following criteria are met:

- Health has returned to baseline status or applicable variables have returned to normal.

- The event has stabilized and the Investigator expects no further improvement or worsening of the event.

Some events do not resolve (e.g. metastasis). Once it has been determined that the event is stable or chronic, then the event can be considered 'resolved with sequelae'.

FOLLOW-UP AE/SAE REPORTS

The site is responsible for following up on events that were initially incomplete or unresolved. Whenever new information is obtained the site is also responsible for reporting the follow-up information as soon as it becomes available. Examples of reports that may require follow up:

- An event for which complete information was not available at the time of reporting to ATRI.
- Update or new information related to an event that was previously reported (e.g. receipt of hospitalization records, clarity from study participant on event details).

REMEMBER: document new/modified information in the participant's research chart, AE/Hospitalization Worksheet and eCRF.

For Follow-Up Reports do NOT delete entries in the narrative/comment section previously entered, rather append new information to the narrative with date and initials of entry.

IF AN ONGOING AE BECOMES SERIOUS, update the existing AE record to indicate that the event is serious and provide the date the event became serious.

AE/SAE REPORTING GENERAL NOTES

1. ADVERSE EVENT NUMBER

The Adverse Event Number is a unique identifier assigned by the site. Typically, each AE would be assigned a number in chronological order assigned by the site (e.g. 1, 2, 3 and so on).

2. EVENT DIAGNOSIS

If a diagnosis or syndrome is known, record the diagnosis in the Event Diagnosis field.

If a diagnosis or syndrome is not known, record the medical term for the event in the Event Diagnosis field.

Example: "Nausea and Vomiting" (with no apparent unifying diagnosis) should be documented as separate events:

- AE1: Nausea
- AE2: Vomiting

If signs/symptoms are reported as AE(s) in the absence of a diagnosis, but are later determined to be the result of a condition (diagnosis), document the condition (diagnosis) as a **new/separate** AE; the initial signs/symptoms should be referenced in the Comments/ Narrative section. The first AE report(s) about the initial signs/symptoms should be updated to include a cease date (which is the date of diagnosis); update the Comments/Narrative section to indicate a diagnosis/condition has been provided and reported as a new AE.

Make every attempt to establish a diagnosis based on signs/symptoms and/or other clinical information. If a diagnosis is suspected, state this in the Comments/Narrative section and indicate whether a workup is underway.

Example: "Headache, dizziness, and weakness in arm" should be documented as a single event once a diagnosis has been made:

- AE1: Intracranial Hemorrhage

Do NOT report procedures in place of a diagnosis or symptom. For example, if a participant breaks a tooth and visits the dentist, 'broken tooth' would be considered an AE but a 'visit to the dentist' would not qualify.

Review injuries and accidents for possible causes (i.e., dizziness or somnolence). If a cause is determined for the injury/accident, then list the cause as the event term.

3. PRE-EXISTING SYMPTOMS / CONDITION

Use the Initial Health Assessment worksheet / eCRF to record any pre-existing symptom(s) present at Screening. If any of the pre-existing symptoms worsen in frequency or severity after Screening, report as an AE. In the AE report for the worsened pre-existing symptom, select 'Change to a condition or symptom present at screening'.

Even if the subject is not experiencing them at the time of entry into the study, it is important to include conditions that are:

- Seasonal (e.g., seasonal allergies)
- Cyclical
- Intermittent (e.g., intermittent headaches)

4. COMPOUND EVENTS

Compound events generally cannot be coded together and should be reported as separate AEs. The report for each separate event should indicate that the event is part of a compound event and the related AE numbers should be provided. The following would be recorded as three separate events:

- **Dizziness** (AE1) which causes a
- **Subsequent fall** (AE2) resulting in a
- **Wrist fracture** (AE3)

5. DATES

Provide a start date for every adverse event when possible. If the study staff know the Event Cease Date and the approximate duration of the AE, the Event Onset Date can be calculated based upon the duration (number of days) from the calendar Event Cease Date. If a start date is unknown and cannot be calculated based on duration of event and cease date, the AE/Hospitalization Log eCRF does allow entry of month and year without a day. Please refer to the eCRF completion guidelines for guidance. .

Provide an Event Cease Date if the Event Outcome is:

- Recovered/Resolved
- Recovered/Resolved with sequelae
- Fatal

Events that are ongoing (Recovering/Resolving, Not Recovered/Not Resolved, or Unknown) at the time of death or at the end of study participation may remain as ongoing in the EDC system.

6. EVENT OUTCOME

Event outcome is captured in order to provide a complete picture of each event that occurred during the trial. Outcome must be answered for each individual event.

EVENT OUTCOME	DESCRIPTION
Recovered	An event has disappeared/resolved. *An Event Cease Date has been given.*
Recovering/Resolving	An event has not disappeared and the severity at the final observation is less than the maximum severity reported earlier in the trial.
Not Recovered/Not Resolved	The event has not disappeared and the severity at the final observation is equal to the maximum severity reported earlier in the trial.
Recovered/Resolved with sequelae	The event has disappeared yet there are sequelae present. *An Event Cease Date has been given.*
Fatal	Death has occurred and is possibly related to the event. *An Event Cease Date has been given.*
Unknown	The outcome was could not be determined.

If an event is ongoing at the time of the report, select either:

- Recovering / Resolving
- Not Recovered / Not Resolved
- Unknown

For ongoing events, the EDC requires completion of all fields except Cease Date. All fields may be updated over the course of the study. For more information, refer to the eCRF Completion Guidelines.

Example: If there is a compound event (stroke, hip fracture, pneumonia) in which death occurred as a direct result of one of those events (pneumonia), only that event (pneumonia) should have an outcome of Fatal. The other related events (stroke, hip fracture) cannot have Fatal as an event outcome nor can they have Recovering/Resolving as an outcome. If death occurs during the study, the participant should only have one SAE with an outcome of fatal.

7. CHRONICITY

If a participant describes multiple occurrences of the same event (e.g., "I've been having recurring headaches."), record the event as a single AE (e.g., 'intermittent headaches'). Clinical judgment should be used when determining if single events previously reported transition to an intermittent or chronic condition.

8. SEVERITY

Severity is not the same as seriousness. **Severity** is used to describe the intensity of an event (e.g., mild, moderate, or severe myocardial infarction). The event itself may be of relatively minor medical significance (e.g., severe headache) but it would not be *serious* unless it resulted in one of the SAE outcomes.

Seriousness is based on patient and/or event outcome, and is used to define regulatory reporting requirements.

SEVERITY	DESCRIPTION
Mild	Awareness of signs or symptoms but no disruption of normal daily activity. Signs and symptoms are transient. Event resolved without intervention.

Moderate	Discomfort sufficient to reduce or affect normal daily activity.
Severe	Incapacitating with inability to perform normal daily activity.

9. SERIOUSNESS

Seriousness is based on patient and/or event outcome (see definition above), and is used to define regulatory reporting requirements. All adverse events marked as serious will trigger an alert to the appropriate ATRI personnel and Protocol Project Director. The Protocol Project Director will review the event and initiate the creation of the SAE report. A notification will be sent to all participating sites and the DSMB once the report is available.

10. COMMENTS / NARRATIVE

USE THE COMMENTS/NARRATIVE SECTION ON THE LAST PAGE OF THE ADVERSE EVENTS WORKSHEET TO PROVIDE CONTEXT THAT INCLUDES A CLEAR, CONCISE, CHRONOLOGICAL, AND COMPREHENSIVE DESCRIPTION OF THE EVENT.

Be sure the information provided is **detailed** and **descriptive** enough to assess the event remotely. Do not repeat any information in the Comments/Narrative section that was previously reported on the AE/Hospitalization worksheet.

A detailed, descriptive and relevant history may include the following:

- Underlying medical conditions
- Significant medical history
- Precipitating events that may be a factor in the current event
- Concomitant medications
- Laboratory, radiological, or other diagnostic result

Begin all entries with the date and the initials of the person writing the narrative. For example, if the AE/Hospitalization worksheet was being completed on June 15, 2015 by Study Coordinator then the Comments/Narrative section might begin with something like, “(06-15-2015) SC initials”.

11. OTHER RELEVANT HISTORY

Provide a description of relevant medical history or pre-existing symptoms in the Other Relevant History section. If applicable, also comment on how the event might be related to other AEs / SAEs.

12. CONCURRENT MEDICATIONS

It is important that the Project Director and the ATRI Medical Operations are provided with the most up-to-date information about concurrent medications when reviewing AEs/SAEs. The Project Director will be provided with a summary of the medications present in the Concurrent Medications eCRF at the time the AE/SAE report is submitted, so **review and update the Concurrent Medications eCRF immediately prior to submitting the AE/SAE report.**

REPORTING RESPONSIBILITIES

ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS MUST BE REVIEWED AND SIGNED OFF BY A QUALIFIED CLINICIAN.

PROTOCOL PRINCIPAL INVESTIGATOR (PI)

- Primary responsibilities include: AE identification, documentation and assessment of

severity

- Ensure procedures are followed including accurate and timely reporting of all AEs and SAEs
- Clinically manage event to resolution or delegate event management to a site clinician
- Evaluate whether new information may affect participants' willingness to continue participation

STUDY COORDINATOR (OR DELEGATE AS APPROPRIATED BY THE PI)

- Screen for AEs on an ongoing basis using:
    - Reports of AEs by participants, family members or health care providers
    - Observations of reports by research staff
    - Events documented in medical records
- Accurate and timely documentation and reporting
- Prompt response to requests for additional information from the ATRI

CHAPTER 16: REVISION HISTORY

Version	Date	Description of Change	Location
1.0	13Apr2023	Initial	N/A
1.1	30May2023	More specific descriptions of what is sent to sites and from whom	Section 5.1: Study Supplies
		Update on the process and sites view of referrals in investigator portal	Section 4.5 Referrals from Ebisu
2.0	14Aug2023	Study coordinator expectations updated to serve as communication liaison for other personnel at their site.	Section 2.5 Personnel Requirements
		Updated to include requirements for Amyloid PET disclosure training and outline of Amyloid PET disclosure process under v2.0 of the ADNI4 protocol	Chapter 3: Certification, Training, and Experience Section 3.5 ADNI4 – Amyloid PET Disclosure Section 9.2 Amyloid PET Disclosure
		Updated images with correct tubes and labels	Chapter 14: Sample Collections, processing and shipment
		"Cheat sheet" for sites to use to minimize duplicative work while in this transition between v1.0 of the protocol/EDC and v2.0 of the protocol/EDC	Appendix 1 ADNI4 Procedures (v1.0 versus v2.0)

APPENDIX 1

ADNI4 Procedures (v1.0 versus v2.0)

The table below outlines the differences between v1.0 protocol/EDC and v2.0 protocol/EDC.

v1.0 (approval for v1.0 protocol and what you'll do in v1.0 EDC)	**v2.0 (approval for v2.0 protocol and what you'll do in v2.0 EDC)** ***reminder that sites will have to re-consent participants to v2.0****	**Comments**
Ebisu ID is not required in protocol. Site can fill out the Ebisu ID CRF on paper. However, site will need to fill out form as is in the v1.0 EDC to ensure that the right Ebisu ID is used.	Ebisu ID is required in the protocol. Site will delete eCRF in the EDC and re-enter the form under v2.0 EDC	Information about how to delete an eCRF can be found in the data entry manual
Consent tracking in v1.0 EDC only tracks whether or not a participant has agreed to participate in ADNI4. Site will complete form as is.	In v2.0 EDC, site will delete eCRF and re-do form to select activities the participate has agreed to.	CM may review consent remotely with site
Publicity form is available in the v1.0 EDC. *Site should **not** fill out this form in v1.0 EDC.* Site can fill out Recruitment CRF on paper but will not enter into EDC.	Publicity form will be updated to the Recruitment form and should be completed as soon as v2.0 EDC is implemented.	
In v1.0 EDC, site will maintain the same process of emailing the Biomarker Core (UPENN) to notify them when samples are shipping.	In v2.0 EDC, site will not need to email UPENN anymore. Instead, site will only need to complete the Biomarker form in the EDC the same day as samples are collected to notify them of shipment.	Biomarker/UPENN samples are collected at Initial visit for some rollovers and at baseline for new participants. Email for the Biomarker/UPENN team are available on the study contact sheet and the biomarker/genetics manual in the Doc Repository.
In v1.0 EDC, site will complete the Area Deprivation Index (ADI) form as is.	In v2.0 EDC, site will go back to the ADI form and complete the first question.	
In v1.0 EDC, site can ignore the Abbreviated Multidimensional Acculturation Scale (AMAS) if the participant is **not** Latinx.	In v2.0 EDC, the AMAS will have a question that site will fill out if participant is not Latinx	
In v1.0 EDC, site should collect 12-item ECog on paper but should not complete the eCRF in the EDC.	In v2.0 EDC, site can complete the ECog eCRF using the paper form that was collected under v1.0	

Longitudinal **clinical** labs: Rollovers (no PET scan in last year of ADNI3): Cystatin C **not** collected at initial visit. Rollovers (PET scan in last year of ADNI3) - CN: **no blood collected** at initial visit - MCI/DEM: Cystatin C **not** collected at initial visit.	Rollovers (no PET scan in their last year of ADNI3): Cystatin C collected at initial visit. Rollovers (PET scan in last year of ADNI3) - CN: blood collected at initial visit MCI/DEM: Cystatin C collected at initial visit.	Per leadership, you do **not** need to bring the participants back in to collect missing labs. Moving forward, any participants who come in under v2.0 will follow ADNI4 v2.0 SOE.
The **amyloid PET disclosure** process in v1.0 follows the same model as in ADNI3. Requests go through Gil's team – no assessments are collected. The amyloid PET disclosure process is not outlined in v2.0.	Once the participant is re-consented under v2.0. Sites will begin to collect amyloid disclosure assessments proceeding, during, and succeeding the amyloid disclosure visit if the participant has agreed to receive their amyloid PET results. Site will need to bring the participants back into clinic to complete these forms *or* complete these assessments remotely after re-consent.	Under v2.0, review the amyloid disclosure packets to ensure the right assessments are collected correctly. **We need a psheet and training cert for any clinicians/PI who discloses amyloid PET results to participants.**
RUCA & RUCC is not collected under v1.0 protocol. Do **not** collect this measure from participants under v1.0.	RUCA & RUCC is collected under v2.0 protocol. Site may be able to collect this measure without bringing the participant back in using local EMR.	