

ADNI3 Procedures Manual
Version 3.0

**ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE 3:
DEFINING ALZHEIMER'S DISEASE**

Keck School of Medicine of **USC**
Alzheimer's Therapeutic Research Institute

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Chapter 1

Protocol Synopsis and Schedule of Events

Protocol Synopsis

As outlined in the protocol, below is a copy of the protocol synopsis.

PROTOCOL TITLE	Alzheimer's Disease Neuroimaging Initiative 3 (ADNI3)
PROJECT DIRECTOR	Michael W. Weiner, M.D.
STUDY SPONSOR	National Institute on Aging, National Institute of Health
COORDINATING CENTER	Alzheimer's Therapeutic Research Institute (ATRI)
STUDY DESIGN	A non-randomized natural history non-treatment study
DURATION OF STUDY PARTICIPATION	Screening period will be open for approximately two years followed by a 2-4 year longitudinal follow-up period based on cohort.
SAMPLE SIZE	1,070-2000 total participants will be enrolled across 3 cohorts: cognitively normal (CN), mild cognitive impairment (MCI), and mild AD dementia. Approximately, 700-800 will be Rollover participants from ADNI2, and 370-1200 will be newly enrolled.
SUMMARY OF KEY ELIGIBILITY CRITERIA	<p>Newly enrolled participants will be 55-90 (inclusive) years of age, willing and able to undergo test procedures that include neuroimaging and lumbar punctures to be carried out longitudinally.</p> <p>Rollover participants must have been enrolled in ADNI previously and willing to continue participation.</p> <p>MMSE, CDR, and Logical Memory meeting cut-off scores for each diagnostic category.</p>
PRIMARY OBJECTIVE	ADNI3 will continue to discover, optimize, standardize, and validate clinical trials measures and biomarkers used in AD research.
OTHER MEASURES/STUDY PROCEDURES	Rates of decline on cognitive, global and functional tests; rate of conversion to MCI or dementia due to AD; volumetric and structural MRI measures; rates of change on each specified biochemical biomarker; correlations and change among biomarkers; longitudinal extent and rate of amyloid deposition; longitudinal changes in tau; subgroup analyses among all the biochemical and imaging biomarkers.

Schedule of Events

As outlined in the protocol, below is a copy of the Schedule of Events.

ROLLOVER PARTICIPANTS: CN, MCI, AND AD

Clinic Visit Name	Initial ¹	Ongoing In-Clinic ^{2,3}	Phone Check ⁴
Explain Study and Obtain consent	X		
Neuropath discussion/ Provisional consent ⁵	X	X	X
Demographics	X		
Medical History	X		
Vital Signs	X	X	
Mini Mental State Examination (MMSE)	X	X	
Cogstate Brief Battery (CBB) ⁶	X	X	
Logical Memory I and II	X	X	
Everyday Cognition (ECog)	X	X	
Montreal Cognitive Assessment (MoCA)	X	X	
Category Fluency (Animals)	X	X	
Trails A & B	X	X	
Multi-Lingual Naming Test (MINT)	X	X	
Auditory Verbal Learning Test	X	X	
Geriatric Depression Scale	X	X	
Clock drawing	X	X	
Neuropsychiatric Inventory (NPI) / (NPI-Q for Phone Check)	X	X	X
ADAS-Cog 13 (w/ Delayed Recall and Number Cancellation)	X	X	
Clinical Dementia Rating Scale	X	X	
Activities of Daily Living (FAQ)	X	X	
Financial Capacity Instrument - Short Form (FCI-SF)	X	X	
Plasma and Serum Biomarker Collection	X	X	
DNA and RNA Sample Collection	X	X	
Concomitant Medications	X	X	X
Adverse Events	X	X	X
Diagnostic Summary	X	X	
3T MRI Imaging ⁷	X	X	
FDG-PET Imaging ⁸	X		
Florbetapir Imaging ⁹	X	X	
ECG ¹⁰	X	X	
AV-1451 PET Imaging ¹¹	X	X	
CSF Collection by Lumbar Puncture (LP) ⁹	X	X	

¹**Rollover participants** who are being followed from ADNI2 should be enrolled into ADNI3 in Year 1 for a complete In-clinic Visit.

²**CN** participants are seen in the clinic biennially (every other year) unless they are required to come in on an off year for AV-1451 PET imaging (see footnote 8). **MCI and AD** participants are seen in the clinic annually.

³**AD** participants are seen in-clinic for 24 months from Baseline (total of 3 in-clinic visits at Baseline, Year 2, and Year 3) and then ongoing phone follow-up will continue annually for those that have consented or are undecided about Neuropathology program.

⁴**Only applies to CN participants** when an ongoing In-clinic Visit is not called for or needed for AV-1451 PET imaging.

⁵**Neuropath discussion** to confirm consent/interest (see section 9.5). If a participant has refused to participate, no further inquiry should take place.

⁶**CBB** will be conducted at each In-Clinic Visit and up to quarterly interval remotely for the CN and MCI cohorts only.

⁷**Ongoing MRI** conducted at each In-clinic Visit.

⁸**FDG-PET** is only assessed at baseline for MCI and AD participants only; CN participants are not required to conduct FDG-PET.

⁹**Florbetapir and LP for CSF** starts at Initial Visit and is then repeated every two years.

¹⁰**ECG** will be recorded at baseline if a previous ECG within the last 12 months is not available for review. if a previous ECG within the last 12 months is not available for review.

¹¹**Tau-PET Imaging** is at the Initial Visit and last visit (2 scans) for all participant groups. Additionally, 20% amyloid negative, and 80% amyloid positive CN and MCI participants will have two more scans (for a total of four scans). AD participants will have an AV-1451 PET scan at each In-clinic Visit (for a total of three scans).

NEWLY ENROLLED PARTICIPANTS: CN, MCI, AND AD

Clinic Visit Name	Screen ¹	Baseline	Ongoing In-Clinic ^{2, 3}	Phone Check ⁴
Explain Study and Obtain consent	X			
Neuropath discussion/ Provisional consent ⁵	X	X	X	X
Demographics, Family History, Inclusion and Exclusion Criteria	X			
Medical History, Physical Exam, Neurological Exam, Modified Hachinski Ischemic Score	X			
Vital Signs	X	X	X	
Height	X			
Screening Labs (hematology, chemistry panel, urinalysis, B12, TSH)	X			
Genotyping and Cell Immortalization Sample Collection		X		
American National Adult Reading Test		X		
Cognitive Change Index (CCI)	X			
Mini Mental State Examination (MMSE)	X		X	
Cogstate Brief Battery (CBB) ⁶		X	X	
Logical Memory I and II	X		X	
Everyday Cognition (ECog)		X	X	
Montreal Cognitive Assessment (MoCA)		X	X	
Category Fluency (Animals)		X	X	
Trails A & B		X	X	
Multi-Lingual Naming Test (MINT)		X	X	
Auditory Verbal Learning Test		X	X	
Geriatric Depression Scale	X		X	
Clock drawing		X	X	
Neuropsychiatric Inventory (NPI) / (NPI-Q for Phone Check)		X	X	X
ADAS-Cog 13 (w/ Delayed Recall and Number Cancellation)		X	X	
Clinical Dementia Rating Scale	X		X	
Activities of Daily Living (FAQ)		X	X	
Financial Capacity Instrument – Short Form (FCI-SF)		X	X	
Plasma and Serum Biomarker Collection		X	X	
DNA and RNA Sample Collection		X	X	
Concomitant Medications	X	X	X	X
Adverse Events	X	X	X	X
Diagnostic Summary	X	X	X	
3T MRI Imaging ⁷	X		X	
FDG-PET Imaging ⁸		X		
Amyloid Imaging ⁹		X	X	
ECG ¹⁰		X	X	
AV-1451 PET Imaging ¹¹		X	X	
CSF Collection by Lumbar Puncture (LP) ⁹		X	X	

¹Screening is open through Year 2

²CN participants are seen in the clinic biennially (every other year) unless they are required to come in on an off year for AV-1451 PET imaging (see footnote 8). **MCI and AD** participants are seen in the clinic annually.

³AD participants are seen in-clinic for 24 months from Baseline (total of 3 in-clinic visits at Baseline, Year 1, and Year 2) and then ongoing phone follow-up will continue annually for those that have consented or are undecided about Neuropathology program.

⁴Only applies to CN participants when an ongoing In-clinic Visit is not called for or needed for AV-1451 PET imaging.

⁵Neuropath discussion to confirm consent/interest (see section 9.5). If a participant has refused to participate, no further inquiry should take place.

⁶CBB will be conducted at each In-Clinic Visit and up to quarterly interval remotely for the CN and MCI cohorts only.

⁷Ongoing MRI conducted at each In-clinic Visit.

⁸FDG-PET is only assessed at Baseline for MCI and AD participants only; CN participants are not required to conduct FDG-PET.

⁹Amyloid Imaging (florbetapir or florbetaben) and LP for CSF starts at Baseline and is then repeated every two years.

¹⁰ECG will be recorded if a previous ECG within the last 12 months is not available for review.

¹¹Tau-PET Imaging is at the Baseline and last visit (2 scans) for all participant groups. Additionally, 20% amyloid negative, and 80% amyloid positive CN and MCI participants will have two more scans (for a total of four scans). AD participants will have an AV-1451 PET scan at each in-clinic visit (for a total of three scans).

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 **ADNI3 Study Contact Sheet for contact information**.

- ➔ Regulatory Documents and IRB approval – ATRI Regulatory Affairs
- ➔ Personnel Requirements – ATRI Clinical Operations - ADNI3 Team
- ➔ MRI Scanner Certification – Mayo MRI Core
- ➔ PET Scanner Certification (new sites only) – ADNI PET Core

Requirements as presented by each group must be met in order to receive full approval to begin screening participants. Sites are encouraged to work on requirements in parallel, as they are not listed in any particular order.

Regulatory Documents

Below is a *sample* of regulatory documents that are required for this study.

- ➔ Documentation of IRB Approval
- ➔ Protocol / Investigator Brochure Signature Sheet
- ➔ FDA Form 1572

Contracts

An executed Master Contract, NIH Clinical Trial Agreement (CTA) is **not** required by ATRI to start ADNI3 activities, but may be required by the site's institution. The Contracts & Budgets Team will work with each site to ensure a master contract and a study signed agreement is completed.

PET Scanner Certification

PET scanners certified for ADNI2 are considered certified for ADNI3 provided they have not undergone a software or hardware upgrade. If site is new to ADNI or PET machine has undergone changes, please contact the PET Core Team. For more information, refer to the PET Technologist Manual.

If you have a new scanner or have upgraded your scanner, please request a Hoffman phantom by contacting the PET Core.

MRI Scanner Certification

MRI qualification requires a phantom scan and a volunteer scan.

- Volunteer scanning may be done before IRB approval since imaging data will not be stored. However, please check with your IRB if this is allowed.

The MRI Core Team will be in contact with your site to confirm which scanner will be used and provide the necessary certification requirements. For more information, refer to the MRI Technologist Manual.

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 and which duties an individual will fill. The Personnel Sheet Completion 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 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:
<p>SITE PROTOCOL PRINCIPAL INVESTIGATOR (PI)</p> <p>The PI's education, training, and experience qualifies her/him to assume responsibility for the proper conduct of the trial.</p>	<ul style="list-style-type: none"> • 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 • The Site PI may also serve as the study physician/study clinician
<p>STUDY PHYSICIAN/SITE CLINICIAN</p> <p>This person <u>must</u> have credentials MD, DO, NP, APRN, MBBS, or PA-C.</p>	<ul style="list-style-type: none"> • 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 • Review ECG report

STUDY COORDINATOR	<ul style="list-style-type: none"> • 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 liaison with the Coordinating Center/Clinical Monitor • May serve as the interviewer/psychometrician as long as he/she is properly trained
REGULATORY	<ul style="list-style-type: none"> • Manage all regulatory related documents for the duration of the trial, including submitting all required regulatory documents to ATRI 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	<ul style="list-style-type: none"> • Accept and process payments from ATRI
BILLING – STATEMENT	<ul style="list-style-type: none"> • Review and verify payments from ATRI are in alignment with procedures completed
MRI CONTACT	<ul style="list-style-type: none"> • 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 EDC in a timely manner • Ensure that all MRI data is archived according to protocol
PET CONTACT	<ul style="list-style-type: none"> • 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 EDC in a timely manner • Ensure that all PET data is archived according to protocol
PROJECT INTERVIEWER / PSYCHOMETRIST/ RATER	<ul style="list-style-type: none"> • 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, CDR, FCI-SF, and/or Cogstate Brief Battery (CBB) and Neuropsychological battery
RECRUITMENT CONTACT	<ul style="list-style-type: none"> • Manage all recruitment for the duration of the trail • Serve as the liaison between the ATRI Recruitment Core • Is listed in all recruitment and government websites

Chapter 3

Certification, Training and Experience

It is the responsibility of the Principal Investigator 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. It is imperative that all such training records, certifications etc. are maintained in your site's regulatory binder or study binder. The Protocol-Specific Training Log template is available as a resource to document protocol required trainings (when no other documentation is provided to document such training). Such documentation may need to be submitted to the Coordinating Center during start-up and throughout the course of the study as personnel changes are made and new personnel are delegated.

Activities requiring certification:

- ➔ Protocol Training
- ➔ Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog)
- ➔ Clinical Dementia Rating Scale (CDR)
- ➔ Financial Capacity Instrument Short Form (FCI-SF)
- ➔ Cogstate Brief Battery (CBB)
- ➔ ATRI Electronic Data Capture (EDC): ADNI3 Data Portal

Protocol Training

It is the responsibility of the Principal Investigator to ensure that the staff involved in the study has the necessary protocol training.

- ➔ As you get closer to site approval, protocol training will be provided, either by live or recorded webinar or site initiation visit. Attendance letters for webinars will be provided after webinar. The letter serves as documentation for protocol training.
- ➔ When new staff comes in to the study, please contact your monitor to complete your protocol training.

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**.

ADAS NAÏVE:

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 to set up observations. Certification will be provided after rater provides documentation of the following in the ADAS worksheet/Rater Worksheet to ATRI.

1. Review of ADAS Manual (version dated October 10th, 2013)
2. Review of Site-Specific Scoring Rules approved by Coordinating Center
3. 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 ADNI2/DOD ADNI certified raters will complete the Expedited certification guidelines. Experienced Raters complete all steps (1-3) 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 (UNDER THIS SAME MODEL), THE ADAS CERTIFICATION LETTER WILL SPECIFY IF IT IS STILL VALID. PLEASE REFER YOUR QUESTIONS TO ATRI-CLINOPS@USC.EDU

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 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 NAÏVE:

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.

CDR Certification and Refresher Course can be found online at the following url:

<http://alzheimer.wustl.edu/cdr/application/step1.htm>

**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.**

Cogstate Brief Battery (CBB)

Cogstate certification is required for anyone who has been delegated on the personnel sheet to administer this assessment. Site staff currently certified for the ADNI2 study will not need to complete the training again. Instead, it is requested that certified raters review the CBB instructions manual. Please note the ADNI3 CBB has been updated specifically for ADNI3. A new version of the Cogstate platform technology and user interface functionality has been implemented.

If you have not been certified for CBB in ADNI2, training and certification is required. Training for another study (e.g. A4, FYN, or LEARN) does not meet ADNI3 requirements, as the interface is different. To schedule your CBB webinar, please email the Cogstate Project Manager at adni3-cbb-l@usc.edu.

Test Administrators/Raters will be trained by a Cogstate Project Manager via a webinar session. A desktop or laptop computer is required for training. The Cogstate training will cover the following:

- ➔ How to prepare the testing environment
- ➔ Hardware needed for testing
- ➔ How to launch the Cogstate tests
- ➔ How to administer the Cogstate test

A letter of certification will be emailed to you from your Cogstate Manager. Please keep this for your records. For more information, refer to the CBB Manual.

Financial Capacity Instrument - Short Form (FCI-SF)

The FCI-SF measures both performance and time to completion on financial tasks. The instrument takes 15 minutes to administer. Each site will receive an FCI-SF kit and document binder. The kit and binder contain administration, scoring guidelines, and test stimuli needed to administer and score the FCI-SF.

FCI-SF raters need to have 1-year of experience as a psychometrian/rater. All FCI-SF raters will need to attend a webinar or review the recorded webinar posted to the FCI-SF training portal. The webinar is approximately one hour long.

You can access the portal by clicking on this link: <https://www.brookwood-lms.com/clients/adni/>

The FCI Webinar will:

- Introduce measure and stimuli, administration instructions, scoring manual
- Show a mock video of FC-SF administration
- Show segmented version of same video with discussion of administration and scoring
- FAQ review

After the webinar (or review of recorded webinar on the FCI portal), the rater must complete 2 self-practice administrations of the FCI-SF at the site. Log completion of the practice assessment in the FCI-SF portal by checking the box that you have administered and scored 2 FCI-SF assessments at your local site in the “Confirmation Local Practice Assessment” page prior to seeking certification.

It is requested that you also observe and fully score a mock FCI-SF video. One hour of preparation is recommended. Rater can review the binder materials and FCI-SF portal training webinar and FAQs as a resource. The portal is an educational resource and will also support site certification for FCI-SF.

FCI-SF CERTIFICATION:

The rater is required to take a multiple-choice quiz on FCI-SF administration/scoring with a passing score of 80% or better. If the rater does not pass the first time, the rater has an immediate opportunity to take a second quiz.

Once the FCI rater has obtained certification, ATRI will automatically be notified and the site will receive approval for ADNI3 FCI-SF administrations. Raters will use the FCI-SF kits, forms and binder materials to collect FCI-SF data from study participants, and will enter FCI-SF data into the respective eCRF located in the ATRI ADNI3 web portal. For more information, please review the FCI-SF binder.

ADNI3 Study Data Portal - Electronic Data Capture (EDC)

ATRI EDC certification is required for anyone with access to edit study data or provide electronic signatures. View only access does not require certification. Account creation will be based on the access level selected on the ADNI3 Personnel Sheet.

ATRI EDC certification can be completed as a self-study by reviewing the training slides. Personnel must review the training presentation and sign the certificate (last page) of the presentation. Submit your signed certification to atri-clinops@usc.edu and keep a copy on file at site.

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

Accounts will be created within one week of the approval to enroll notification, which is sent by ATRI Regulatory Team. Email confirmation will be sent to delegation staff. Confirmation 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, please review the ADNI3 Data Entry Manual.

OTHER INSTRUMENTS ADMINISTERED FOR ADNI3 STUDY DO NOT REQUIRE FORMAL TRAINING CERTIFICATION. IT IS THE RESPONSIBILITY OF THE PI TO ENSURE EVERY RATER RECEIVES APPROPRIATE TRAINING.

Chapter 4

Recruitment and Retention

Recruitment & Retention Materials

The Recruitment and Retention group maintains a “library” of documents and other resources, including recruitment materials, educational tools, and templates for media activities. The recruitment materials are made available throughout the study.

Examples of the types of materials that are available for your use and handout needs include:

TRADITIONAL RECRUITMENT MATERIALS

- ➔ One-page Flyer
- ➔ Voicemail script
- ➔ Tri-fold Brochure/ Direct Mail Piece
- ➔ Brain donation brochure

WEBSITE AND PHONE NUMBER

- ➔ ADNI3.org with personalized site webpage
- ➔ 1-888-2-ADNI-95

BRAIN HEALTH REGISTRY (BHR)

- ➔ Referrals from BHR provided weekly
- ➔ Referrals can be adjusted throughout the study to fit site’s needs

RESOURCES

Please [follow this link](#) to access the folder: **ADNI3 Site Recruitment Materials for IRB Submission**. Password: adni32016.

What’s New in ADNI3?

- ➔ **Recruitment Material**
 - Re-branded recruitment material reflecting an updated logo.
- ➔ **Phone Number**
 - Centralized ADNI3 recruitment phone number: 1-888-2-ADNI-95 (1-888-223-6495). Once the sites are open for enrollment, this number will connect participants to their local site or provide them with further information, in the event that there is not a site in their local area.
- ➔ **Website**
 - Updated recruitment website (ADNI3.org) which includes a site finder and sign-up page.
- ➔ **Personalized Site Webpages**
 - In addition to the ADNI3.org page, we are excited to be offering personalized

site web pages, which will allow sites to incorporate their local branding and contact information with general information about the ADNI3 study.

➡ **Recruitment Plan**

- If a Site experiences challenges in study recruitment and/or retention they may be asked to create a recruitment and retention plan with the help of ATRI staff who provides problem solving and supportive assistance over the phone as needed.

Minority Recruitment

Efforts will be made to target at least 12% minority enrollment. Spanish speaking participants are encouraged to participate in ADNI3. Study recruitment materials and scales are available for use by Site Personnel with Spanish speaking participants and whose IRB has approved enrollment of Spanish speaking participants.

Targeted efforts will include the BHR registry that has successfully engaged and enrolled large numbers from the African Against AD and Latinos Against AD groups.

**FOR ANY QUESTIONS, REQUESTS, COMMENTS, OR SUGGESTIONS, PLEASE
CONTACT THE RECRUITMENT AND RETENTION TEAM AT**

ADNI3-PARTICIPATE@USC.EDU

Chapter 5

General Information

ATRI Coordinating Center

You will be working closely with several groups at the ATRI including: Monitors, Regulatory Affairs, Contracts, Recruitment, and Clinical Operations. A representative from each of these groups will be in touch to assist you through start-up phase of the study.

As you get closer to site approval, protocol training will be provided, either by live or recorded webinar or site initiation visit.

After startup, sites are encouraged to reach out to monitors for help. Monitors should always be the main point of contact for clarification on visit procedures, or for help on entering data.

Please reference the ADNI3 study contact sheet for email addresses and phone numbers to all ATRI groups other core groups involved in the ADNI study. If you have any questions regarding who your assigned monitor will be, please reach out to us at adni-study@usc.edu.

Study Supplies

ATRI PROVIDED SUPPLIES

ATRI will provide some supplies for the collection of research labs and conduct of the study.

- ➔ **Initial Supplies:** Regulatory staff will notify sites by email when they are approved to launch study activities. Supplies are shipped within two weeks of site activation and may be expedited if prior arrangements have been made. An email notification will also be sent out on the day that supplies are shipped. If you have space limitations, please make sure to inform us at adni-study@usc.edu.
- ➔ **Follow-up Supplies:** There are no automatic shipments of ATRI supplies. To order additional supplies, use the online ADNI3 **Supply Order Form**. Please be sure to order supplies far enough in advance of scheduled visits (**at least 8 to 10 business days in advance, excluding holidays and weekends**). Click on the link to open the form: <https://goo.gl/forms/ue3TqNMV2Wdanz1A13>

OTHER SUPPLIES PROVIDED BY ATRI:

- ➔ Research Lab and CSF collection kits – refer to the sample collection chapter and CSF collection chapter of the Procedures Manual for more details
- ➔ Regulatory document binders
- ➔ Participant binder inserts/tabs, spines and covers
 - The cost of the actual participant binders has been factored into the startup funds distributed at the beginning of the study; therefore, actual participant binders will NOT be provided by ATRI.
- ➔ 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 if they are worn out or in poor condition
- FCI kits if needed
- ➔ 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 document repository: Protocol, Procedures Manual, Worksheets, ADNI3 Data Entry Manual.

LABORATORY SUPPLIES PROVIDED BY URMC (FOR SAFETY LABS)

URMC will provide supplies for safety labs. Each site will receive the following supplies within two weeks of the Site Approval notification:

- ➔ 8 screening kits
- ➔ 1 homocysteine/methylmalonic acid kit
- ➔ 8 ambient shippers
- ➔ 1 cooler

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 per the provided instructions. Please refer to the URMC Lab Manual for more information about the lab reports and alerts, specimen collection, packaging, and shipping.

Overview of Systems

ATRI ADNI3 DATA PORTAL

ADNI3 Data Portal accounts will be created once ATRI sends site approval email to begin screening participants for the study. Accounts will be created for each team member based on completion of the Study Personnel Sheet, indicating the required level of access (*see Personnel*

Sheet Completion Instructions for details on how to complete and submit the form) and completion of the EDC training certification.

- New accounts following site initiation will be set up following completion of the Study Personnel Sheet. Please allow 5 - business days turnaround time for the set-up of new accounts.
- Every interaction in the Study data portal is time/date stamped and can be traced back to the user who completed the transaction

NEVER SHARE YOUR PASSWORD WITH ANOTHER PERSON

The study data portal consists of the following systems and activities (access to individual tools is dependent on Personnel Sheet 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)
- **Study document folder (under construction, temporary location is [BOX website link](#))** - Access to study documents including the Protocol, Procedures Manual, Imaging Guides, Study Memos, Safety Lab Manual, Supply Order Form, Source Doc Worksheets, Training Materials, and Safety SAE Reports. Recruitment and regulatory materials are also available.

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

PASSWORD RESET

To reset a data portal password, go to the login page and click on 'Forgot password'. Enter the user's email address, and click 'submit'. A temporary password will be sent to that email address.

DATA ENTRY

Timely data entry and query resolution is important for data quality and integrity. During Screening it is especially important to enter data and resolve queries in a timely fashion in order to prevent out of window visits and/or delays in central review.

All data collected should be entered into the EDC system within 48 hours of collection for screening visits, except for SAEs, which must be entered within 24 hours. All other visits require no more than 5 business day turnaround for data entry and study doc upload.

REFER TO THE ADNI3 DATA ENTRY MANUAL FOR COMPLETE DETAILS ON HOW TO ENTER DATA FOR THIS STUDY

STUDY DOCUMENT UPLOAD

Source documents, safety laboratory reports, and ECG reports are uploaded to the EDC via Study Document upload eCRF within 48 hours for screening visit and 5 business for all other visits.

LABORATORY OF NEURO IMAGING (LONI)

All imaging data is uploaded to LONI.

USER REGISTRATION

<https://ida.loni.usc.edu>

- To upload data, you will need to self-register for an IDA account (if you don't already have one). You can create an account by clicking the "Instant free signup" button in the top right hand corner of the page.
- After you have an account, you'll need to request upload access by sending an email to the person managing access for your study. The email should include the name of the study, the email address you used to set up your IDA account, your site name and the name of your site PI. If you do not know who is managing access for your study, please email the same information to ida@loni.usc.edu and we will help to get your information to the right person.
- Check to see that your computer has the required Java Plug-in installed and operational in your browser by following this link.
- Instructions for uploading data may be found here in the IDA registration document in the document repository.

DOCUMENT REPOSITORY

The document repository contains study documents including the Protocol, Procedures Manual, Imaging Guidelines, Study Memos, Safety Lab Manual, Source Doc Worksheets, Training Materials, and Safety SAE Reports. Recruitment and regulatory materials are available.

ELECTRONIC ASSESSMENTS

COGSTATE BATTERY

As part of the training and certification process available through Cogstate's DataPoint website (<https://nic.cogstate.com>), the test administrator will be guided through the process for activating the software. Refer to Chapter 3 Certifications for more information.

FCI PORTAL

As part of the training and certification process available through Brookwood portal (FCI LINK), the test administrator will be guided through the process for activating the software. Refer to Chapter 3 Certifications for more information.

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. MRI and 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 LOCATION TO CONDUCT THE STUDY
MUST BE APPROVED BY ATRI.**

Chapter 6

New Enrollees: Screening Procedure

Screening

The purpose of the ADNI3 Screening Visit is to determine eligibility and to collect measures that will be used as a reference to assess change. Only newly enrolled participants will have a screening visit. A standardized evaluation will be performed at each clinical site.

Consent will be obtained before any portion of the screening visit is initiated. Eligibility will be determined per the Inclusion/Exclusion criteria outlined in the protocol before the participant can be brought back for Baseline.

KEY REMINDERS:

- ➔ The window from Screening to Baseline is 28 days
- ➔ Participants must meet all inclusion/exclusion criteria
- ➔ Complete data entry within 1-2 business days of the screen, including laboratory reports
- ➔ Screening for New Participants will be open for the first two years of the ADNI3 study

PARTICIPANT IDENTIFIERS

The ADNI Participant ID (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 ADNI1 began at 0001, EMCI participants enrolled into ADNIGO began at 2001, and participants enrolled into ADNI2 began at 4001. ADNI3 participants enrolled into ADNI3 will begin at 6000.

**EXAMPLE: A PARTICIPANT FROM SITE 900 WHO IS THE THIRD SUBJECT
ASSIGNED FOR ADNI3 WOULD BE 900_S_6003**

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 technical manuals. For instructions on how to assign a new screening participant ID, please refer to the ADNI3 Data Entry Manual.

**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 ADNI3 DATA PORTAL**

Study Population

The study will enroll men and women aged 55-90 years across MCI and mild AD dementia participant groups.

Until notified by the coordinating center, the lower age limit that a CN participant can be screened/enrolled has been restricted to 65 years with exceptions granted for minority participants.

PLEASE CONTACT YOUR MONITOR IF YOU HAVE QUESTIONS ON INCLUSION CRITERIA FOR NEW PARTICIPANTS AND ROLLOVER PARTICIPANTS.

Data Flow

PRESCREENING:

- ➔ Review participant's medical history, medications, and any past diagnoses for eligibility
- ➔ Complete MRI and PET Prescreening
- ➔ Pencil in a slot for the 3T MRI 7-10 days from Screening Visit

SCREENING VISIT

- ➔ Consent must be obtained prior to assigning a Participant ID.
- ➔ Explain Study and Obtain consent
- ➔ Demographics (Participant and Study Partner)
- ➔ Family History
- ➔ Inclusion and Exclusion Criteria
- ➔ Physical Exam
- ➔ Neurological Exam
- ➔ Cognitive Change Index (CCI)
- ➔ Mini Mental State Examination (MMSE)
- ➔ Logical Memory I and II
- ➔ Geriatric Depression Scale
- ➔ Clinical Dementia Rating Scale
- ➔ Modified Hachinski Ischemic Score
- ➔ Vital Signs
- ➔ Height (only taken during screening visit)
- ➔ Screening labs (hematology, chemistry panel urinalysis, B12, TSH)*
- ➔ Concomitant Medications & Key Background Medications
- ➔ 3T MRI Imaging (only to be conducted after confirmation from clinician that the subject has met all other inclusion/exclusion criteria). Enter all data and upload worksheets in the ADNI3 Data Portal within 1-2 business days of screen.
- ➔ Initial Health Assessment
- ➔ Adverse Events
- ➔ Publicity Tracking
- ➔ Diagnostic Summary
- ➔ Autopsy consent discussion

*New participants must have screening labs to aid in assessing eligibility. Screening lab kits are provided by URM; please refer to the clinical laboratory samples section in the Clinical

Laboratory Samples at Screening - URM Chapter of this Procedures Manual and the URM Laboratory Manual for details.

3T MRI SCAN:

- Confirm eligibility requirements are met BEFORE moving participant forward to the MRI step (including review of cognitive testing, lab results, etc.). Clinician review of local MRI read and approval is required before proceeding to MRI.
- Ensure Participants and Study Partner are provided appointment reminder and directions
- 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
- Email clinical monitor that scan has been conducted and entered in the EDC system

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

IF A SIGNIFICANT ABNORMALITY IS SEEN (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

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 and confirm eligibility and will alert sites if there is a safety concern. Sites do not need to review the central read report for eligibility. 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.

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; required before proceeding to baseline.

Important Reminders:

- 3T MRI may NOT be conducted until screen is approved by the site clinician
- Baseline may NOT be conducted until 3T MRI local 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 28 days of screening visit. There is an additional 2 weeks to complete other Baseline procedures (e.g. PET, LP, Neuropsych battery)

DO NOT CONTINUE TO BASELINE UNTIL MONITOR ELIGIBILITY IS CONFIRMED!



- Enter all data and upload worksheets and safety lab report in the ADNI3 Data Portal within 1-2 business days of screen

SCREEN FAILURES

All participants who sign consent must be assigned an ADNI3 PTID, even if a Screening Visit is not completed and all data 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 (For all participants, even those who screen fail).
- Study Visits Summary
- Participant Demographics
- Clinician Verification
- Publicity Tracking

REFER TO THE ADNI3 DATA ENTRY MANUAL FOR COMPLETE DETAILS ON HOW TO CAPTURE AND ENTER DATA FOR A SCREEN FAIL

RESCREENS

Per the protocol, unless otherwise approved by the Project Director, only one re-screen is allowed, should the original screen be a failure. The re-screen should typically occur at least 2 months after the original screen failure. Before scheduling a rescreen, contact your clinical monitor for approval. Rescreens must be assigned a new ADNI3 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

Eligibility Criteria

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

As a reminder: until notified by the coordinating center, the lower age limit that a CN participant can be screened/enrolled has been restricted to 65 years with exceptions granted for minority participants.

Excluded Medications

The **ADNI3 Prohibited & Cautionary medication list** is available in the study folder and provides a listing of common medications (both brand and generic names) and whether they are prohibited, allowable, or if use is conditional (prohibited in specific instances).

THIS IS NOT A COMPLETE LIST OF ALL EXCLUDED MEDICATIONS. FOR DRUGS NOT INCLUDED HERE AND/OR IF YOU ARE UNSURE ABOUT A SPECIFIC MEDICATION, PLEASE BRING TO THE ATTENTION OF YOUR CLINICAL MONITOR PRIOR TO SCREENING

- ➔ Current use of Coumarin (Warfarin), Pradaxa (Dabigatran) or Heparin (exclusionary for LP)
- ➔ Antidepressants with anticholinergic properties are excluded

- Regular use of narcotic analgesics (>2 doses per week) within 4 weeks of screening
- Use of neuroleptics with anticholinergic properties (e.g., chlorpromazine, thioridazine) within 4 weeks of screening
- Chronic use of other medications with significant central nervous system anticholinergic activity within 4 weeks of screening (e.g., diphenhydramine)
- Use of Anti-Parkinsonian medications (including Sinemet, amantadine, bromocriptine, pergolide, selegeline) within 4 weeks of screening
- Participation in any other investigational drug study within 4 weeks of screening (individuals may not participate in any drug study while participating in this protocol)
- Diuretic drugs should not be started or discontinued within 4 weeks prior to screening. Any change in diuretic medication during the study should be reported

REFER TO THE ADN13 PROHIBITED & CAUTIONARY MEDICATION LIST FOR AN EXPANDED LIST OF MEDICATIONS.

Permitted Medications

- This protocol allows concomitant treatment with cholinesterase inhibitors and memantine if on a stable dose for 12 weeks prior to screening.
- Use of estrogen and estrogen-like compounds is allowed if the dose has been stable for 4 weeks prior to screening.
- Use of vitamin E is allowed if the dose has been stable for 4 weeks prior to screening (no cap on amount allowed).

EXCEPTIONS TO THESE CRITERIA MAY BE CONSIDERED ON A CASE-BY-CASE BASIS AT THE DISCRETION OF THE PROTOCOL PI AND MEDICAL MONITOR

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.

Private MD Notification

CONSENT FROM THE PARTICIPANT IS REQUIRED BEFORE SENDING INFORMATION TO HIS/HER 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 ADNI3 trial and outline the study procedures. In the letter, include the name and telephone number of a clinician at the site who will be available to answer any questions about the study. A template letter is posted to the study documents folder.

Chapter 7

New Enrollee Baseline and Longitudinal Follow Up

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

Baseline Overview

The Baseline visit may only be initiated following completion of all screening assessments and required clinical monitor and clinical eligibility approvals, and must start within 28 days of Screening. Once the Baseline visit has started, there are 2 weeks to complete all Baseline procedures. The Baseline visit procedures may be completed over multiple days and will typically require at least three visits. Once the visit begins, all imaging, biofluid collection, and clinical/cognitive assessments must take place within the next 2 weeks; if not already conducted at screening.

BASELINE ASSESSMENTS / PROCEDURES

Cognitive testing will be done prior to, or at least 24 hours after any procedures that require fasting. In **no** instance, should cognitive assessments be performed while the subject is in a fasted state.

- Discuss Neuropathology program until a definitive decision is made
- ADAS-Cog
- Neuropsychological Battery
- MoCA
- American National Adult Reading Test (ANART); only at Baseline Visit
- Everyday Cognition – Participant and Study Partner Self-Report
- Financial Capacity Instrument Short Form (FCI-SF)
- Neuropsychiatric Inventory
- Activities of Daily Living (FAQ)
- Computerized testing - Cogstate Brief Battery (CBB) and Brain Health Registry (BHR) (CBB and BHR is offered to CN and MCI participants only)
- Diagnostic Summary
- Vital Signs
- Safety assessments (review of concurrent medications and adverse events)
- Genetics and Cell Immortalization Sample collection
- Biomarker – Plasma, Serum and buffy coat will be collected. All samples will be collected in the morning before breakfast*
- Whole blood samples will be collected for peripheral blood mononuclear cell (PBMC) banking for genetic analysis. Red Blood Cell (RBC) pellet will be extracted from buffy coat); only at Baseline Visit
- Amyloid PET imaging (florbetapir or florbetaben), AV-1451, and LP for CSF* starts at Baseline
- ^{18}F -FDG PET, if done on the same day, Baseline cognitive assessments must be done prior to the ^{18}F -FDG PET scan* (Only at Baseline for MCI and AD participants)
- Global Unique Identifier (GUID) assignment requires the participant's full name, and date, city, and sex at birth. (Generated in the GUID eCRF located in the ADNI3 study portal)

*Keep in mind that CSF, plasma, and serum collected for biomarker analysis is after a minimum 6-hour fast; FDG-PET is a minimum of 4-hour fast or overnight.

Special scheduling highlights

- CN participants are not required to have an FDG-PET scan
- MCI and AD participants are required to have FDG-PET scan at Baseline Visit only
- There are no longitudinal FDG-PET scans
- Each PET scan must be done on a separate day or at least 12 hours after a prior scan
- AD participants do not undergo any computerized testing

FOR NEW PARTICIPANTS ALL THESE PROCEDURES ARE REQUIRED AT BASELINE. IF YOU HAVE ANY QUESTIONS, PLEASE EMAIL YOUR MONITOR. REFER TO WORKSHEET VISIT COMPLETION CHECKLIST FOR RECOMMENDED TESTING AND PROCEDURE ORDER.

Longitudinal Follow-Up Assessments / Procedures

In general, the ongoing In-clinic Visits (follow-up visits) will be timed every 12 months from Baseline Visit day 1; exceptions to this are CN participants who are seen in the clinic every other year (see guidance on CN participant scheduling in next section). Ongoing In-Clinic visits include:

- Discuss Neuropathology program until a definitive decision is made
- Safety assessments (review of concurrent medications and adverse events)
- MMSE
- ADAS-Cog
- Neuropsychological Battery
- CDR
- MoCA
- Everyday Cognition – Participant and Study Partner Self-Report
- Financial Capacity Instrument Short Form (FCI-SF)
- Computerized testing - Cogstate Brief Battery (CBB) and Brain Health Registry (BHR)
- (CBB testing and Brain Health Registry (BHR) brochure is offered to CN and MCI participants only)
- GDS
- Neuropsychiatric Inventory
- Activities of Daily Living (FAQ)
- Diagnostic Summary
- Vital Signs
- 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*
- 3T MRI is conducted at each ongoing In-clinic Visit
- Amyloid PET (florbetapir or florbetaben) and LPs are conducted every two years.
- Tau-PET (AV-1451) at Baseline and then again at the end of the study (Year 5) for a total of two tau-PET scans. Additionally, 80% of amyloid-positive and 20% of amyloid-negative CN and MCI participants will be randomly selected to have two additional tau-PET scans. AD participants will have three tau PET scans, one at each visit.

*Keep in mind that CSF, plasma, and serum collected for biomarker analysis is after a minimum 6-hour fast.

Please email your clinical monitor for approval of out of window procedures / visits.

CN Follow-up Procedures (New Participants)

- CN participants are seen in-clinic (CV) every other year
- Longitudinal tau PET scan will be conducted at the end of the study at Year 5
- Phone Check Visit will be conducted on years not seen in the clinic (“off-years” = Year 2 & Year 4) a

Baseline	On-going Year 1	On-going Year 2	On-going Year 3	On-going Year 4
CV	Phone Check	CV	Phone Check	CV
MRI		MRI		MRI
Tau				Tau
Amyloid		Amyloid		Amyloid
LP		LP		LP

CN SELECTED TO HAVE ADDITIONAL TAU PET SCANS

- 80% of amyloid positive and 20% of amyloid negative CN participant will be randomized to receive two additional tau-PET scans for a total of four tau PET scans
- Amyloid status will be assessed within the first year of participation, those randomized to receive two additional tau-PET scans will be identified by the Coordinating Center and communicated to the site
- Participants selected for the two additional tau PET scans will conduct the scans in their Ongoing Year 1 and Ongoing Year 2 along with a full In-clinic Visit (CV) (added assessments/procedures due to tau PET are highlighted in red in table below)

Baseline	On-going Year 1	On-going Year 2	On-going Year 3	On-going Year 4
CV	CV	CV	Phone Check	CV
MRI	MRI	MRI		MRI
Tau	Tau (+/-)	Tau (+/-)		Tau
Amyloid		Amyloid		Amyloid
LP		LP		LP

SUMMARY OF VISIT ACTIVITIES: NEW CN PARTICIPANTS

	Screening Visit	Baseline Visit	Year 1 Clinic Visit	Year 2 Clinic Visit	Year 3 Clinic Visit	Year 4 Clinic Visit
Informed Consent	X					
Personal Information and Medical History	X					
Weight & Vital Signs	X	X	X*	X		X
Height	X					
Physical & Neurological Exam	X					
Adverse Events	X	X	X*	X		X
List of Medications Collected	X	X	X*	X		X
Blood draw and urine collection for screening labs	X					
Fasting blood draw for biomarker and genetic testing		X	X*	X		X
Memory & Thinking Skills Tests	X	X	X*	X		X
Computer Based Memory Testing		X	X*	X		X
Behavior and Functional Tests	X	X	X*	X		X
Depression Test	X		X*	X		X
MRI Scan	X		X*	X		X
Fasting Lumbar Puncture		X		X		X
Amyloid PET scan		X		X		X
Tau PET Scan		X	X*	X*		X
ECG		X	X*	X*		X
Telephone Check			X**		X	

* Participants selected for the additional Tau PET scans will have a full Clinic Visit

** Participants NOT selected for the additional Tau PET scans will have a Phone Check at Year 1.

MCI Follow-up Procedures (New Participants)

- MCI participants are seen in-clinic (CV) annually.
- Longitudinal tau PET scan will be conducted at the end of the study at Year 5]

Baseline	On-going Year 1	On-going Year 2	On-going Year 3	On-going Year 4
CV	CV	CV	CV	CV
MRI	MRI	MRI	MRI	MRI
Tau				Tau
Amyloid		Amyloid		Amyloid
LP		LP		LP
FDG				

MCI RANDOMIZED TO HAVE ADDITIONAL TAU PET SCANS

- 80% of amyloid positive and 20% of amyloid negative MCI participant will be randomized to receive two additional tau-PET scans for a total of four tau PET scans
- Amyloid status will be assessed within the first year of participation, those randomized to receive two additional tau-PET scans will be identified by the Coordinating Center and communicated to the site
- Participants selected for the two additional tau PET scans will conduct the scans in Year 2 and Year 3 along with a full In-clinic Visit (CV) (added tau PET scans are highlighted in red in the below scheduling table)

Baseline	On-going Year 1	On-going Year 2	On-going Year 3	On-going Year 4
CV	CV	CV	CV	CV
MRI	MRI	MRI	MRI	MRI
Tau	Tau (+/-)	Tau (+/-)		Tau
Amyloid		Amyloid		Amyloid
LP		LP		LP
FDG				

SUMMARY OF VISIT ACTIVITIES: NEW MCI PARTICIPANTS

	Screening Visit	Baseline Visit	Year 1 Clinic Visit	Year 2 Clinic Visit	Year 3 Clinic Visit	Year 4 Clinic Visit
Informed Consent	X					
Personal Information and Medical History	X					
Weight & Vital Signs	X	X	X	X	X	X
Height	X					
Physical & Neurological Exam	X					
Adverse Events	X	X	X	X	X	X
List of Medications Collected	X	X	X	X	X	X
Blood draw and urine collection for screening labs	X					
Fasting blood draw for biomarker and genetic testing		X	X	X	X	X
Memory & Thinking Skills Tests	X	X	X	X	X	X
Computer Based Memory Testing		X	X	X	X	X
Behavior and Functional Tests	X	X	X	X	X	X
Depression Test	X		X	X	X	X
MRI Scan	X		X	X	X	X
Fasting FDG-PET Scan		X				
Fasting Lumbar Puncture		X		X		X
Amyloid PET scan		X		X		X
Tau PET Scan		X	X*	X*		X
ECG		X	X*	X*		X

* Participants selected for additional PET scans.

AD Follow-up Procedures (New Participants)

- AD participants are seen in-clinic (CV) annually for 24 months from Baseline (total of three in-clinic visits at Baseline/Year 1, Year 2, and Year 3) and then ongoing phone follow-up will continue annually for those that have consented or are undecided about the Neuropathology program
- AD participants will have a tau PET scan at each in-clinic visit (for a total of three scans tau PET scans)

Baseline	On-going Year 1	On-going Year 2	On-going Year 3	On-going Year 4
CV	CV	CV		
MRI	MRI	MRI	Neurpath Phon	Neurpath Phon
Tau	Tau	Tau	Check	Check
Amyloid		Amyloid		
LP		LP		
FDG				

SUMMARY OF VISIT ACTIVITIES: NEW AD PARTICIPANTS

	Screening Visit	Baseline Visit	Year 1 Clinic Visit	Year 2 Clinic Visit	On-Going Annual Phone Check
Informed Consent	X				
Personal Information and Medical History	X				
Weight & Vital Signs	X	X	X	X	
Height	X				
Physical & Neurological Exam	X				
Adverse Events	X	X	X	X	
List of Medications Collected	X	X	X	X	
Blood draw and urine collection for screening labs	X				
Fasting blood draw for biomarker and genetic testing		X	X	X	
Memory & Thinking Skills Tests	X	X	X	X	
Behavior and Functional Tests	X	X	X	X	
Depression Test	X		X	X	
MRI Scan	X		X	X	
Fasting Lumbar Puncture		X		X	
Fasting FDG PET Scan		X			
Amyloid PET scan		X		X	
Tau PET Scan		X	X	X	
ECG		X	X	X	
Telephone Check					X

Chapter 8

Initial Rollover Visit & Longitudinal Follow Up

Summary

Consent will be obtained before any portion of the initial ADNI3 visit begins. There is no screening visit for continuing participants and no prior approval necessary before the MRI scan is conducted.

ALL ROLLOVER PARTICIPANTS ARE EXPECTED TO BE SEEN FOR THEIR INITIAL VISIT IN THE FIRST YEAR OF ADNI3; PLEASE TRY YOUR BEST TO SEE THEM BY SEPTEMBER 2017

When possible, each Rollover participant should enroll in the ADNI3 study on the projected month time point based from the **initial baseline month date (from ADNI1, ADNIGO, or ADNI2)**. The initial visit assessments can occur +/-2 weeks from the target time point. The Initial Visit will include clinical, cognitive, behavioral, and functional testing, MRI, tau-PET scan, Lumbar Puncture, Florbetapir F18 PET and FDG-PET scans (FDG-PET for MCI and AD only).

For sites that are not able to schedule the Initial ADNI3 visit on the anniversary month because they did not have approval to commence study activity, will need to schedule visits as soon as possible upon site approval. This “late” visit will reset the anniversary month; all subsequent ADNI3 visits will be anchored to the Initial ADNI3 Visit.

The only ADNI2 visits that should be occurring in 2017 are those that do not plan on rolling over into ADNI3. Sites that conducted ADNI2 visits in October 2016 through the end of December 2016, will schedule the first ADNI3 visit in September 2017. This ensures Initial ADNI3 Visit occurs within the first year of the study.

ROLLOVER PARTICIPANTS SCHEDULING SCENARIOS – ADNI3 INITIAL VISIT

Scenario		ATRI Approval to screen	Initial ADNI3 Visit*
1	Last ADNI2 visit was in 2015 (e.g. December 2015)	Yes	December 2016
		No, site does not have ATRI approval yet	ASAP upon approval
2	Last ADNI2 visit was in 2016 (e.g. July 2016)	N/A (all sites expected to have approval by projected entry into ADNI3)	July 2017
3	Last ADNI2 visit was conducted or expected October - December 2016	N/A (all sites expected to have approval by projected entry into ADNI3)	No later than September 2017

*Subsequent ADNI3 visits are anchored to Initial ADNI3 Visit (resets clock/anniversary month)

KEY REMINDERS

- Rollover participants must have been enrolled and followed in ADNI2 for at least one year
- 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 as possible
- Rollover participants who are being followed from ADNI2 should be enrolled into ADNI3 for a complete “Initial In-Clinic Visit” in the first year of the study (by September 2017)
- Exceptions can be made to extend the time allowed for the Rollover’s Initial Visit (please email cc for any issues or questions that come up)
- Longitudinal follow-up period for both Rollover and New participants is approximately 4-6 years
- Please note that even for Rollovers that are seen biennially, and participants that received a complete clinic visit (CV, LP, PET, MRI) will be brought back in for a full visit in the first year

Initial ADNI3 Visit and Longitudinal Follow-Up Assessments / Procedures

ONLY COMPLETED AT THE INITIAL VISIT

- Explain Study
- Obtain Consent
- Study Partner Information
- Initial Health Assessment
- Genetic Sample Collection (10 mL Purple EDTA tube)
- Whole blood samples will be collected for peripheral blood mononuclear cell (PBMC) banking for genetic analyses, as well as RBC pellet sample collection
- FDG PET; if done on the same day, cognitive assessments must be done prior to the ¹⁸F-FDG PET scan. Participants must be fasting for 4 hours or overnight
- CN participants do not conduct FDG PET scan; only at Baseline for MCI and AD participants
- Global Unique Identifier (GUID) assignment (is generated in the GUID eCRF located in the ADNI3 study portal and requires the participant’s full name, and date, city, and sex at birth)

AT EACH IN-CLINIC VISIT (INITIAL AND FOLLOW-UP VISITS):

- Safety assessments (review of concurrent medications and adverse events)
- Vital Signs
- Discuss Neuropathology program until a definitive decision is made
- MMSE
- ADAS-Cog
- Neuropsychological Battery
- MoCA
- CDR

- ➔ Everyday Cognition – Participant and Study Partner Self-Report
- ➔ Financial Capacity Instrument (FCI-SF)
- ➔ Computerized testing - Cogstate Brief Battery (CBB) and Brain Health Registry (BHR)
- ➔ AD participants do not undergo computerized testing. CBB testing and Brain Health Registry (BHR) brochure is offered to CN and MCI participants only.
- ➔ Geriatric Depression Scale (GDS)
- ➔ Neuropsychiatric Inventory
- ➔ Activities of Daily Living (Functional Assessment Questionnaire)
- ➔ Diagnostic Summary
- ➔ Blood collection for longitudinal DNA and RNA genetic analyses
- ➔ Biomarker – Plasma, Serum and buffy

coat. All samples will be collected in the morning before breakfast and after a 6-hour or overnight fast

- ➔ LPs for CSF collection at Initial Visit and then every two years thereafter (minimum 6-hour or overnight fast)
- ➔ Amyloid PET scan with florbetapir only (florbetaben will not be administered to Rollover participants) at Initial Visit and then every two years thereafter
- ➔ Tau-PET (AV-1451) will be conducted at the Initial Visit and then again at the end of the study (Year 5) for a total of two tau-PET scans. Additional, 80% of amyloid-positive and 20% of amyloid-negative CN and MCI participants will be randomly selected to have two additional tau-PET scans. AD participants will have three tau PET scans, one at each visit. (See guidance by cohort below for more information).
- ➔ Clinician Review

COGNITIVE ASSESSMENTS SHOULD NOT BE SCHEDULED WHILE THE PARTICIPANT IS FASTING, OR IMMEDIATELY AFTER AN LP OR IMAGING SESSION

CN Follow-up Procedures (Rollover)

- ➔ CN participants that are not paired with an AV-1451 PET scan, are seen in-clinic (CV) every other year
- ➔ One longitudinal tau PET scan will be conducted at the end of the study at Year 5
- ➔ On years not seen in the clinic (“off-years” = Year 1 & Year 3) a Phone Check Visit will be conducted

Initial Visit	On-going Year 1	On-going Year 2	On-going Year 3	On-going Year 4
CV	Phone Check	CV	Phone Check	CV
MRI		MRI		MRI
Tau				Tau
Amyloid		Amyloid		Amyloid
LP		LP		LP

CN SELECTED TO HAVE ADDITIONAL TAU PET SCANS

- 80% of amyloid positive and 20% of amyloid negative (AMY) CN participant will be randomized to receive two additional tau-PET scans for a total of four tau PET scans
- Amyloid status will be assessed within the first year of participation, those randomized to receive two additional tau-PET scans will be identified by the Coordinating Center and communicated to the site
- Participants selected for the two additional tau PET scans will conduct the scans in On-going Year 1 and On-going Year 2 along with a full In-clinic Visit (CV) (added assessments/procedures due to tau PET are highlighted in red in the below scheduling table)

Initial Visit	On-going Year 1	On-going Year 2	On-going Year 3	On-going Year 4
CV	CV	CV	Phone Check	CV
MRI	MRI	MRI		MRI
Tau	Tau (+/-)	Tau (+/-)		Tau
Amyloid		Amyloid		Amyloid
LP		LP		LP

SUMMARY OF VISIT ACTIVITIES: CN PARTICIPANTS (ROLLOVER)

	Initial Clinic Visit	Year 1 Phone Check or Clinic Visit	Year 2 Clinic Visit	Year 3 Phone Check
Informed Consent	X			
Medical History	X			
Weight & Vital Signs	X	X*	X	
Adverse Events	X	X*	X	
List of Medications Collected	X	X*	X	
Fasting blood draw for biomarker and genetic testing	X	X*	X	
Memory & Thinking Skills Tests	X	X*	X	
Computer Based Memory Testing	X	X*	X	
Behavior and Functional Tests	X	X*	X	
Depression Test	X	X*	X	
MRI Scan	X	X*	X	
Fasting Lumbar Puncture	X		X	
Amyloid PET scan	X		X	
Tau PET Scan	X	X*	X*	
ECG	X	X*	X*	
Telephone Check		X**		X

* Participants selected for the additional PET scans.

MCI Follow-up Procedures (Rollover)

- MCI participants are seen in-clinic (CV) annually.
- One longitudinal tau PET scan will be conducted at the end of the study at Year 5

Initial Visit	On-going Year 1	On-going Year 2	On-going Year 3	On-going Year 4
CV	CV	CV	CV	CV
MRI	MRI	MRI	MRI	MRI
Tau				Tau
Amyloid		Amyloid		Amyloid
LP		LP		LP
FDG				

MCI randomized to have additional tau PET scans

- 80% of amyloid positive and 20% of amyloid (AMY) negative MCI participant will be randomized to receive two additional tau-PET scans for a total of four tau PET scans
- Amyloid status will be assessed within the first year of participation, those randomized to receive two additional tau-PET scans will be identified by the Coordinating Center and communicated to the site
- Participants selected for the two additional tau PET scans will conduct the scans in the Ongoing Year 1 and Ongoing Year 2 along with a full In-clinic Visit (CV) (added tau PET scans are highlighted in red in the below scheduling table)

Initial Visit	On-going Year 1	On-going Year 2	On-going Year 3	On-going Year 4
CV	CV	CV	CV	CV
MRI	MRI	MRI	MRI	MRI
Tau	Tau (+/-)	Tau (+/-)		Tau
Amyloid		Amyloid		Amyloid
LP		LP		LP
FDG				

SUMMARY OF VISIT ACTIVITIES: MCI PARTICIPANTS (ROLLOVER)

	Initial Clinic Visit	Year 1 Clinic Visit	Year 2 Clinic Visit	Year 3 Clinic Visit	Year 4 Clinic Visit
Informed Consent	X				
Medical History	X				
Weight & Vital Signs	X	X	X	X	X
Adverse Events	X	X	X	X	X
List of Medications Collected	X	X	X	X	X
Fasting blood draw for biomarker and genetic testing	X	X	X	X	X
Memory & Thinking Skills Tests	X	X	X	X	X
Computer Based Memory Testing	X	X	X	X	X
Behavior and Functional Tests	X	X	X	X	X
Depression Test	X	X	X	X	X
MRI Scan	X	X	X	X	X
Fasting FDG-PET Scan	X				
Fasting Lumbar Puncture	X		X		X
Amyloid PET scan	X		X		X
Tau PET Scan	X	X*	X*		X
ECG	X	X*	X*		X

* Participants selected for the additional PET scans.

AD Follow-up Procedures (Rollovers)

- AD participants are seen in-clinic (CV) annually for 24 months from Initial Visit (total of 3 in-clinic visits at Initial, then Ongoing Year 1, and Ongoing- Year 2) and then ongoing phone follow-up will continue annually for those that have consented or are undecided about the Neuropathology program
- AD participants will have a tau PET scan at each in-clinic visit (for a total of 3 scans tau PET scans)

SCHEDULING OVERVIEW: AD PARTICIPANTS (ROLLOVER)

Initial Visit	On-going Year 1	On-going Year 2	On-going Year 3	On-going Year 4
CV	CV	CV	Neurpath Phone Check	Neurpath Phone Check
MRI	MRI	MRI		
Tau	Tau	Tau		
Amyloid		Amyloid		
LP		LP		
FDG				

SUMMARY OF VISIT ACTIVITIES: AD PARTICIPANTS (ROLLOVER)

	Initial Clinic Visit	Year 1 Clinic Visit	Year 2 Clinic Visit	On-Going Annual Phone Checks*
Informed Consent	X			
Medical History	X			
Weight & Vital Signs	X	X	X	
Adverse Events	X	X	X	
List of Medications Collected	X	X	X	
Fasting blood draw for biomarker and genetic testing	X	X	X	
Memory & Thinking Skills Tests	X	X	X	
Behavior and Functional Tests	X	X	X	
Depression Test	X	X	X	
MRI Scan	X	X	X	
Fasting Lumbar Puncture	X		X	
Fasting FDG PET Scan	X			
Amyloid PET Scan	X		X	
Tau PET Scan	X	X	X	
ECG	X	X	X	
Telephone Check				X

Chapter 9

Diagnostic Converters

Overview

Diagnostic Category is determined upon entry into ADNI3 using the Diagnostics Summary Forms. A converter is a participant that changes diagnostic category (e.g. CN to MCI, MCI to AD) based on the cognitive criteria of this study and includes conversion back to MCI or CN. Conversion can happen at any point of the study. Specifically, for Rollover participants, conversion into a different diagnostic category can occur upon entry (rolling over) into ADNI3.

Scheduling

- ➔ Annual In-Clinic Visits will assume at their next visit

DIAGNOSTIC CATEGORY CONVERTERS ARE SEEN IN THE CLINIC ANNUALLY. IF THERE ARE ANY QUESTIONS ABOUT VISIT SCHEDULE PLEASE WORK YOUR MONITOR.

- ➔ Converters, even if converted back to CN are seen annually

Special scheduling highlights

- ➔ FDG scan will be conducted based on diagnosis upon entry into ADNI3. CN participants at Baseline/Initial are not required to have an FDG-PET scan
- ➔ Participant that are diagnosed with MCI and AD at baseline are required to have FDG-PET scan at Baseline Visit only
- ➔ If converted to AD, the participant will no longer have to undergo any computerized testing (Cogstate or BHR)
- ➔ If a participant converts to AD, he/she will be seen in-clinic annually for the remainder of the study (Year 5 plus any no cost extensions)

Chapter 10

Post-Visit Follow Up Assessments

Lumbar Puncture (LP)

Each study participant or a person designated to speak for them will be contacted by phone one day after the LP to confirm participant well-being and to query about any adverse events. The follow-up phone call will be documented in the corresponding worksheet; there is no eCRF for follow-up LP phone call.

Tau-PET (AV-1451)

Each study participant or a person designated to speak for them will be contacted by phone two to three days (no sooner than two days) after the tau-PET scan to confirm participant well-being and to query about any adverse events. The follow-up phone call will be documented in the corresponding follow-up phone call worksheet; there is no eCRF for follow-up tau PET phone call.

Chapter 11

Types of Telephone Visits

Telephone Check for CN Participants

CN participants are seen in the clinic every other year (biennially) unless they are randomized to receive more frequent tau PET scans or they are considered Converters. A Phone Check Visit is conducted on the “off-years” where no In-clinic Visit is called for by protocol.

SCHEDULING REMINDERS

- For those CN participants that are not randomized to receive additional tau PET scans, the annual Phone Check Visits are at Year 2 and Year 4 from the Baseline/ Initial ADNI3 visit
- For those CN participants that are randomized to receive additional tau PET scans, only one Phone Check Visit will be needed at YEAR 4 (see CN scheduling overview diagrams above)

DATA FLOW



Complete Data entry within 5 business days of the visit. Scan and Upload worksheets to the ADNI3 Data Portal:

ANNUAL CN TELEPHONE CHECK ASSESSMENTS

- Concurrent Medication Review
- Adverse Event Review
- Neuropsychiatric Inventory Q
- Neuropathology Discussion
- Clinician Review

Neuropathology Phone Check

An ADNI site clinician will discuss autopsy brain donation with each participant (CN, MCI, and AD) during the consent process, at Initial/Baseline visit and at every In-clinic Visit thereafter until permission is granted or the participant indicated refusal. Additionally, annual follow-up Phone Check Visits for the AD cohort who have provisionally consented to neuropathology or are undecided will continue through the end of the study. These phone calls are crucial for a successful brain autopsy.

- No data is collected during these phone calls and serves to assess the participants' wishes regarding brain donation, the value of brain donation, and to answer any questions they may have regarding brain autopsy and the process.
- If participant is not interested in the brain donation program, these annual phone checks should not be conducted.

CONFIRM THE PARTICIPANT'S CONTACT INFORMATION DURING THE CALL

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. ADNI3 new enrollees, who have completed all ADNI3 baseline assessments, then after this visit, are only available by phone

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. You should offer the phone visit option to any eligible participant who is no longer able to come to the clinic for annual visits.

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

For these visits please select “non-standard’ visit on the registry form online.

REPLACEMENT OF IN-CLINIC VISIT TELEPHONE ASSESSMENTS

- | | |
|--|--|
| ➤ Clinician Dementia Rating Version 2* | ➤ Everyday Cognition – Participant and Study Partner Self Report** |
| ➤ Geriatric Depression Scale | ➤ Concurrent Medication Review |
| ➤ Neuropsychiatric Inventory | ➤ Adverse Event Review |
| ➤ Activities of Daily Living | ➤ Clinician Review |

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

**Everyday Cognition Assessment (when not done in clinic) should be mailed to participant and study partner to be done at home and returned by mail. If participant and partner are not able to return by mail, the interview may be done on the phone, but the participant and study partner must be looking at the worksheet during the phone visit.

If a change in cognitive status is apparent during the phone visit, this should be documented in the visit comment form. The diagnosis summary and diagnosis summary clinical status forms cannot be completed with a telephone visit

Chapter 12

Participant Transfers

DEFINITIONS:

Permanent Transfer	A participant moves from one site to another without the expectation of return to the originating site.
Temporary Transfer	A participant is seen for one or more visits by an alternate site with the expectation of return to the originating site.
Home Site	The site where the participant is being seen at the time the transfer process is initiated, even if it was under the ADNI2 study. Usually this is the site that generated the Participant ID and enrolled the subject.
Transfer Site	The alternate site where the participant will be seen going forward, for a permanent transfer, or for certain visit(s), for a temporary transfer.
Certified Copy	A paper or electronic copy of the original record that has been verified (e.g. by a dated signature) or has been generated through a validated process to produce an exact copy having all of the same attributes and information as the original.

All new ADNI3 participants are allowed to transfer to another site after their baseline visit. ADNI2 Rollover participants are allowed to begin their ADNI3 initial visit at a transfer site. Both sites will need to provide information below. The assigned monitor will confirm that all data has been entered in the EDC. Once all steps have been completed, ATRI Data Management group will work on completing the transfer in the EDC.

NOTIFICATION TO ATRI

Study coordinators should immediately notify their assigned Site Monitor when a potential transfer situation has been identified, including the following information. Please send this information by email to your assigned monitor:

- ➔ Participant ID
- ➔ Reason for transfer
- ➔ Date/timing of transfer
- ➔ Last visit completed at home site and for temporary transfers which visit(s) are involved
- ➔ Type of Transfer: Permanent or Temporary
- ➔ Whether an alternate site has been identified and/or contacted
- ➔ Any additional information available regarding the situation

NOTIFICATION TO TRANSFER SITE

- ➔ The transfer site must have a current ADNI3 approval to enroll

- The study coordinator should communicate with the proposed transfer site regarding the potential transfer to confirm that the transfer site is willing and able to accept the participant transfer.
- If not, consult with ATRI regarding other possible transfer sites or alternative strategies for managing the participant.

NOTIFICATION TO INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE NOTIFICATION (IRB/EC)

Study Coordinators and/or Regulatory Coordinators from both sites are responsible for notifying their IRB/EC according to each site's local requirements that a participant originally consented at one site will be transferred to the other.

PARTICIPANT AUTHORIZATION

The Home Site must ensure that the participant is agreeable to the transfer arrangements, e.g. the transfer site is accessible to them and they would like to continue in the study at that site, and must obtain authorization from the participant to send his/her information to the new institution.

DOCUMENTATION AND CONSENT

The participant should sign a medical release allowing the home site to share medical records with the transfer site. For temporary transfers, another medical release should be signed allowing the transfer site to share medical records back to the original home site.

- **Source Documents:** Original source documents are retained at the site where the source was created.
- **Consent:** Each site will retain ICFs signed at that site. The transfer site must consent the participant using their site-specific, IRB approved consent form (and HIPAA authorization) prior to conducting any protocol specific procedures.
- **Temporary transfers:** once the participant returns to the home site, there is no need for the participant to sign another copy of the home site's IRB approved consent unless there has been a change in the home site's IRB approved consent form since the participant last signed at the home site.

Sharing of Research Records

- Certified copies of source documentation should be provided to the transfer site as needed depending on the type of transfer.
- IRB approval documents and consent will be provided as needed (if required by either the transfer or home site).

TEMPORARY TRANSFER:

- The home site should share a copy of any regulatory documentation (if required by the transfer site), source documents, research records, or medical records that are needed by the transfer site to provide adequate medical oversight of the participant while under their supervision.

- Upon return to the home site, the transfer site will provide copies of any regulatory documentation (if required by the home site), source documents, research records, or medical records to the home site.
- If the temporary transfer will cover more than one visit, the sharing of documents back to the home site should occur on an ongoing basis to facilitate data entry and to allow the home site to remain up to speed on the participant's study and health status.

PERMANENT TRANSFER:

- The home site should share a copy of any regulatory documentation (if required by transfer site), source documents, research records, and medical records that are needed by the transfer site to provide adequate medical oversight of the participant.

NOTE TO FILE (NTF)

- A NTF or formal documentation (if required by your site's institution) will be completed at both the home and transfer site to cover the sharing of research records between the sites.

Data Entry and Queries

TEMPORARY TRANSFERS

Data and queries remain under the home site and are not accessible to the transfer site.

- Only the home site will be able to enter data and respond to queries.
- The Study Coordinators (SCs) at the home site and the transfer site need to work together to manage data entry and query resolution.
- Use the Participant Transfer eCRF to capture any visit conducted at the transfer site. This eCRF serves as a record of the transfer and includes the PTID, home and transfer site, visit impacted, reason for transfer etc.
- Data entry timelines remain the same.
- If the participant will be at a transfer site for multiple consecutive visits, then we recommend the home site enters data in the Participant Transfer eCRF under the first visit conducted at the transfer site and selects all visits to be conducted as part of the temporary transfer.
- If the participant continues to transfer between the home site and the transfer site, each time the participant transfers, the home site enters data into a New Participant Transfer eCRF indicating the visits that will be conducted at the transfer site.

PERMANENT TRANSFERS

Data and queries will be "moved" to be accessible under the transfer site at which time they will not be accessible to the home site.

In order to reduce burden on the transfer site, every effort should be made to complete data entry and query resolution on existing data in advance of “moving” the data.

- The transfer site assumes responsibility for all data, including data entry and query resolution (including past data), and may need to consult with the home site on data clarifications.
- The SCs from the home site and the transfer site still work together to ensure the transfer site receives copies of source documents, research records, and medical records as needed (see section 2.3).
- The transfer site completes the Participant Transfer eCRF at the first visit conducted at the transfer site and indicates all visits conducted at the home site.

Medical/Safety Oversight

ASSESSING ADVERSE EVENTS

The home site will provide documentation to the transfer site, including, up-to-date information on concurrent medications, medical history, initial health status at study entry, and adverse events experienced in the study in order for the transfer to be able to properly assess AEs.

- The transfer sites should follow the normal SAE reporting process – the 24-hour rule still applies (SAEs must be reported within 24 hours of becoming aware of the event).

TEMPORARY TRANSFER:

- The home site should be kept informed of AEs identified by the transfer site so that they are prepared to resume management of those events upon the participant’s return to their site.
- When the participant is at the transfer site, the home site will be responsible for reporting SAEs.
- The transfer site will need to provide the home site with all required and supporting documentation for SAEs including the source document worksheet (DSW) as well as any medical records (may require a medical release if one is not already in place).
- If the transfer site cannot reach the home site to inform the home site about an SAE within 24 hours of becoming aware of the event, then the transfer site should follow the back-up SAE reporting process.

LAB AND ECG REPORTS AND ALERTS

Reports including ECG and safety lab reports are uploaded to the EDC and will be visible to transfer site. Consult with the ADNI team for any central lab/ECG reporting issues.

SPECIAL CIRCUMSTANCES

- Lost to Follow-up: Ideally the home site and the transfer site will work together to follow-up with a participant considered lost to follow-up during a temporary transfer; however, the home site will remain primarily responsible for due diligence in following-up.

Chapter 13

Early Termination

Per 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 ADNI3 DATA ENTRY MANUAL**

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

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) to allow the inadvertently enrolled participant to continue in the study. Considerations will be made on a case-by-case basis.

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.”

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 14

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.

Monitoring Frequency

The first onsite-monitoring visit will be conducted within 2 months of the first successful Baseline/Initial 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 yearly after the first baseline/initial 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 PROJECT MANAGER

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

Close-Out

The closing out of a site is a process involving a final and/or routine monitoring visit. A site's participation may conclude months before the last visit is conducted at other sites, and your clinical monitor may conduct a final monitoring visit some time before the entire trial is over; however, **do not close out any study with your IRB until you are officially notified by the ATRI that the trial has been completed and it is appropriate to do so.**

Until such time, it is essential that all study documents and information are easily retrievable and continue to be stored in a secure location.

The CM will conduct a site close-out visit after all participants at the site have completed all study visits and data queries have been resolved. Generally, the close-out visit should occur within 30 days of the last study visit, or sooner, as needed to meet the timeline for study close-out.

Close-Out activities may include but are not limited to:

- Ensure all eCRFs have been completed; Ensure data queries have been addressed
- Collect any follow-up data for AEs (or SAEs) and ensure all AEs (or SAEs) have been reported to ATRI, and their IRB (if appropriate)
- Perform a complete review of the regulatory document files and ensure that all study documents are present and appropriately filed
- Verify that the Regulatory binder is complete
- Remind the Principal Investigator of his/her responsibility to follow subjects, if required
- Inform the investigator that if he/she becomes unable to maintain the study records that he/she should notify ATRI of the location of the records and the person responsible for retention
- Ensure that all activities outlined in the close-out visit report checklist are performed at the visit
- Remind the Principal Investigator of the publication policy

Chapter 15

Cognitive / Clinical Assessments

All assessments and procedures are administered at the times shown in the Study Schedule of Events. Please also reference the Visit Completion Checklist for recommended order of assessments.

General Cognitive / Clinical Testing Guidelines

CREATING A PRODUCTIVE TESTING ENVIRONMENT

- Due to the many ways in which the examiner can influence testing, the same rater should administer the instrument for a study participant throughout the course of this protocol.
- 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.

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 before beginning any testing.
- 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.
- 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 AND KEEPING PARTICIPANTS FOCUSED

- The tests should be given in the same order indicated in the worksheet packets, with adherence to time limits and standardized instructions.
- If Participant digresses into excessive conversation or otherwise interrupts the testing process when focus on the task at hand, it is important the examiner should regain control of the testing session by reorienting Participant's focus to the task
- If the Participant is exhibiting signs of frustration or requests stopping 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. Differentiating between a Participant who *refuses* to continue a task and

one who *cannot* continue a task due to severe impairment is important. This is sometimes made difficult because a Participant may refuse testing because of frustration with 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 per the instructions for each task during the test session, taking care not to provide any new information, hints or answers.

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 **ADNI3 Data Entry Manual** for guidance on how to complete eCRFs and to learn which tests are auto-scored.

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

Alzheimer's Disease Assessment Scale-Cognition (ADAS-Cog12)

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 10/10/2013) available in the document repository.

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 conducted annually there is little concern about a learning effect; therefore, ADAS Word List 1 will be used at each annual In-Clinic Visit. If there is a concern for a learning effect; contact the coordinating center (adni-study@usc.edu) for guidance on alternate word lists.

American National Adult Reading Test (AMNART)

ADMINISTRATION INSTRUCTIONS

- Present the participant with the word list and say, **“I’m going to ask you to read a list of words aloud. Some of the words may be unfamiliar and difficult to pronounce, but do the best you can to pronounce them.”**
- The participant may self-correct; however, do not prompt them to repeat a word unless it was difficult to hear what was said and necessary to determine whether the pronunciation was correct or incorrect.
- If the participant reads a word with two different pronunciations, one correct and the other incorrect, ask which one they think is best.
- Administer all words, even when the participant begins having difficulty pronouncing them.

SCORING

- Total score = # of errors made.

NOTE: SOME WORDS HAVE MULTIPLE CORRECT PRONUNCIATIONS. BE FAMILIAR WITH THESE, SO AS TO SCORE ACCURATELY!

- This test is not available in Spanish. For Spanish speaking participants, indicate, “not done” on the eCRF.

Category Fluency Test

This is a widely used measure of semantic memory (verbal fluency, language). The participant is asked to name different exemplars from a given semantic category. The number of correct unique exemplars named is scored.

ADMINISTRATION

Read the initial instruction: **“I am going to give you a category and I want you to name, as fast as you can, all of the things that belong in that category. For example, if I say ‘articles of clothing,’ you could say ‘shirt,’ ‘tie,’ or ‘hat.’ Can you think of other articles of clothing?”**

Allow up to 20 seconds for the subject to produce two responses. Circle the number corresponding to the participant's responses, and read the associated instruction.

RESPONSE CODE & INSTRUCTION

- 0 (No response) - "You could have said 'shoes' or 'coat' since they are articles of clothing."
- 1 (One or more incorrect responses, no correct response) - "No, is (are) not an article(s) of clothing. You could have said 'shoes' or 'coat' since they are articles of clothing."
- 2 (One or more correct responses, no incorrect responses) - "That's right. You also could have said 'shoes' or 'coat.' "
- 3 (One or more correct responses, one or more incorrect responses) - "_____ is (are) correct, but _____ is (are) not an article of clothing. You also could have said 'shoes' or coat.' "
- 4 (Two or more correct responses) - "That's right."

Next, read the instructions for the Animal category: **"Now I want you to name things that belong to another category: Animals. You will have one minute. I want you to tell me all the animals you can think of in one minute. Ready? Begin."**

Start timer as you say **"Begin"**. Write actual responses as legibly as possible on the Worksheet or Category Fluency–Animals. Stop the procedure at 60 seconds. One prompt (**"Tell me all the animals you can think of."**) is permitted if the participant makes no response for 15 seconds or expresses incapacity (e.g., "I can't think of anymore"). It is also permissible to repeat the instruction or category if the participant specifically requests it.

SCORING

Defer scoring until after test administration is finished.

The total score on the Worksheet for Category Fluency–Animals is the number of correct unique animal names produced within the one-minute time limit. Intrusions are defined as any word that does not fit the category of animals spoken by the participant during the one-minute fluency test. Any word repeated, even if an intrusion, is counted as a perseveration. The non-categorical word is counted as an intrusion the first time, then a perseveration the second time, not as a second intrusion.

Example: Carrot, cat, carrot would be scored as one correct response (cat), one intrusion (carrot), and one perseveration (carrot #2).

CREDIT: breeds (e.g., terriers); male, female, and infant names of a species (e.g., bull, cow, calf); both superordinate and subordinate examples of a species (e.g., both dog and terrier are credited); birds; fish; reptiles, insects.

DO NOT CREDIT: Repetitions, mythical animals.

Clinical Dementia Rating Scale (CDR)

ADMINISTRATION

The interview is to be conducted by a **certified CDR rater** with the informant and study participant. For information about CDR certification and training, refer to the Site Approval and Start-Up chapter of this procedures manual. 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 | 4. Community Affairs |
| 2. Orientation | 5. Home and Hobbies |
| 3. Judgment and Problem Solving | 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:

- 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).
- 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.
- 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 considered 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 per 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:

[HTTP://WWW.BIOSTAT.WUSTL.EDU/~ADRC/CDRPGM/INDEX.HTML](http://www.biostat.wustl.edu/~adrc/cdrpgm/index.html)

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.

Clock Drawing

This is a test of constructional ability that has two components: a command condition in which the participant draws a clock to verbal instructions, and a copy condition in which the participant copies a model clock drawn at the top of response form.

CLOCK DRAWING ADMINISTRATION

Before beginning the task, make sure there are no clocks visible to the Participant.

- ➔ To begin, present the Participant with a felt-tipped pen (or a pencil without an eraser) and an 8 1/2" x 11" blank sheet of white paper and say, **"Draw the face of a clock showing the numbers and two hands set to ten after eleven."**
- ➔ Allow the Participant to work without feedback; interrupt only if the patient starts to scratch out or destroy any of their drawing.
- ➔ If the Participant tries to erase or scratch out an error, immediately intervene and gently instruct them to try again by saying, **"Don't take the time to make corrections."** While pointing to a clean area of the paper, say, **"You may start over here and draw the clock again. Remember you are to draw the face of a clock showing the numbers and two hands set to ten after eleven."**

Allow only two attempts on the clock-drawing task. If a Participant needs an additional reminder about the specific time that is to be indicated on the clock, the examiner may repeat the time again, e.g., **"set the clock to ten after eleven."** Although this task is not timed, keep the Participant actively engaged in the task; the examiner may use their clinical judgment as to when the task should be abandoned in order to spare the Participant undue anxiety or frustration when they are unable to perform the clock drawing task.

CLOCK COPYING ADMINISTRATION

Immediately after the Clock drawing is completed, present the participant with the response form with the model clock drawn at the top and say, **"Copy this clock (point to the model) in the space provided below."**

Allow the participant to work without feedback; interrupt only if the patient starts to scratch out or destroy any of their drawing.

- ➔ If the participant tries to erase or scratch out an error, immediately intervene and gently instruct them to try again. Allow only two attempts on the clock copying task. Although this task is not timed, keep the participant actively engaged in the task; the examiner may use their clinical judgment as to when the task should be abandoned in order to spare the participant undue anxiety or frustration when they are unable to perform the clock copying task.

SCORING

Clock drawings from both the command and copy conditions are scored in the same manner.

Determine if each of the criteria listed below has been met:

1. Approximately circular face. The clock face may be slightly oval, especially if the subject hastily begins to draw. The examiner may always determine that the subject was “too” impulsive and/or careless in their attempt, and re-administer the instructions and have them start over, “taking time to give their best effort.” Do not penalize the subject for tremor. In some cases, participants will draw an “old fashioned” mantle clock or grandfather clock (i.e., with a square clock face). If this occurs, ask the subject to draw a “regular clock.”
2. Symmetry of number placement. One method to assist the examiner in determining if the numbers are symmetrical is to visually “line up” the opposing numbers, e.g., 3-9, 12-6, 4-10. If there are any obvious gaps or misalignments, then the numbers may be considered asymmetrical.
3. Correctness of numbers. All numbers must be present and in the correct order, and inside the face of the clock. If a subject draws the numbers outside the circle, this item would be INCORRECT.
4. Presence of two hands. Two hands (and only two hands) must be present on the clock face to receive credit for this item.
5. Presence of two hands set to ten after eleven. To receive credit for this item, the two hands must be set to the numbers eleven and two and of the appropriate relative lengths (i.e., shorter hand to eleven, longer hand to two). See the examples of scored clock drawings on the next page.

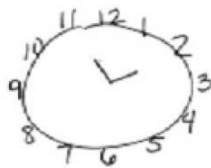


5 points



3 points

- approximately circular face
- presence of 2 hands
- presence of 2 hands, set to 10 after eleven



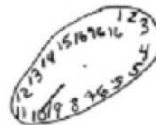
3 points

- circular face
- symmetry of number placement
- presence of 2 hands



3 points

- approximately circular face
- correct numbers
- presence of 2 hands



0 points

Cogstate Brief Battery (CBB) Computerized Testing

The unique ADNI online ID needed for log-in into the CBB will be provided to sites by the coordinating center. Please note that the same ADNI online ID will be used for all computerized testing in ADNI - CBB, and BHR (see BHR section above).

The entire CBB test is made up of four sections and should take about 15 minutes:

1. Detection (DET) Measures of Psychomotor Function
2. Identification (IDN) – Measures of Attention
3. One Card Learning (OCL) – Measure of Learning
4. One Back task (ONB) Measure of Working Memory

ADMINISTRATION

REFER TO COGSTATE MANUAL FOR DETAILS ON SYSTEM SET-UP, SCHEDULING, AND ADMINISTRATION.

The Cogstate Brief Battery (CBB) will be completed in the clinic under the supervision of a certified member and at the participant's home (remote testing).

- ➔ Remote, at home testing, is conducted within 14 days of each In-clinic assessment. Additionally, there will be remote sessions every 3 months in between in-clinic visits.

SCORING

No scoring is needed as these assessments are completed at-home online through the Cogstate website.

Cognitive Change Index (CCI)

The Cognitive Change Index is a subset of items that are focused on memory concerns adapted from a longer panel of self- and informant-report measures originally used to calculate a cognitive complaint index. The Cognitive Change Index is a self-report scale, consisting of 20 items that the subject rates on a scale from 1 to 5 as to whether there has been no change or some degree of change in each of these functions compared to 5 years ago.

SCORING

- ➔ The total score for the entire self -report can range from 20 (no change) to 100 (severe change). Only the first 12 questions that specifically address memory concerns are used to calculate the CCI-Memory Total Score in ADNI2, which has a range from 12 (no change) to 60 (severe change).
- ➔ NOTE: CCI is to be administered for all screening visits (CN, MCI, and AD), and is only used as an inclusion criteria for SMC.

Everyday Cognition

The ECog is a brief questionnaire assessing the participant's capability to perform normal everyday tasks, in comparison to activity levels 10 years prior, on a 5-point scale. Three domains are assessed: Memory, Language and Executive Functioning. For New Participants, the ECog (participant and study partner) are conducted at Baseline, Month 6 and ongoing annual visits. For ADNI1 and/or ADNIGO Follow-Up participants, the ECog is conducted at the initial ADNI-3 visit and ongoing annual visits.

When a participant is unwilling or unable to come into the clinic for ongoing annual visit(s) the ECog should be mailed to the participant and study partner PRIOR to the scheduled visit. The participant and study partner should then mail their completed questionnaires back to the site for data entry.

- Participants and their study partners will independently complete a separate questionnaire, within the clinic, at the time of their ADNI2 in-clinic visits.
- Check all ECog forms before the end of the visit to ensure they are completed fully and, if necessary, direct the participant or study partner to complete the form.
- In some cases, the participant may be too cognitively impaired to complete the form. If this is the case please indicate on question 1 on the Participant ECog questionnaire and collect only the Study Partner questionnaire.
- If the reading level of either the participant or the study partner is low, you may read the items out loud and record their ratings.

INSTRUCTIONS

Ask the participant/caregiver to rate the participant's ability to perform certain everyday tasks now as compared to his/her ability to do these same tasks 10 years ago. In other words, the response should reflect how he/she was doing 10 years ago and indicate any change in the participant's capacity at present.

Ratings should reflect the amount of change on a five-point scale:

1. No change or actually performs better than 10 years ago
2. Occasionally performs the task worse but not all of the time
3. Consistently performs the task a little worse than 10 years ago
4. Performs the task much worse than 10 years ago
5. Participant/caregiver doesn't know.

Financial Capacity Instrument Short-Form (FCI-SF)

PLEASE REFERENCE THE FCI-SF BINDER MATERIALS AVAILABLE IN YOUR FCI-SF KIT OR FCI-SF PORTAL.

ADMINISTRATION

The FCI-SF is a short form that takes about 15 minutes. The rater will need a test-form, test stimuli, administration guide and scoring guide to administer the FCI-SF to study subjects.

There are five sections to the TEST FORM:

1. Mental Calculation
2. Financial Conceptual Knowledge
3. Single Checkbook Register Task
4. Complex Checkbook/Register Task
5. Bank Statement Management

There are a total of 37 performance items administered.

SCORING

Strict time limits are provided on individual items, or on group items, for subjects to provide their answers. These time limits are key to scoring a performance item.

- ➔ 2, 1, 0 scores are given for correct, incorrect, “I don’t know” answers to test items provided within the item time limit.
- ➔ All answers received after the item time limit are given an “OT” (over time) score, whether the subject’s answer is correct, incorrect, “don’t know”, or there is no answer. Treated as a 0.

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.

Geriatric Depression Scale (GDS)

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.

LOGICAL MEMORY TEST I – IMMEDIATE RECALL (STORY “A” ANNA THOMPSON)

This test assesses the ability to recall a short passage or story. The examiner reads the story to the participant in a clear voice. Immediately after hearing the story, the participant is asked to retell the story from memory. The story should be read with adequate volume and clarity for the participant to understand during the presentation. No repetitions are permitted.

It is important for the examiner to get a sense of the participant’s hearing acuity and modulate their voice accordingly. Of note, for the hard of hearing, it is not necessarily helpful to merely increase the volume, but rather change the pitch; a lower pitched voice sometimes is more audible than a loud, high-pitched voice. As with all neuropsychological testing, it is best if the examiner projects his/her voice at the participant, rather down “into” their clipboard.

Use of the alternate story (Greg Fortune) is recommended when a participant is being prescreened for ADNI2, eliminating learning effect when the official screen is conducted using Anna Thompson. If a subject had been tested on the Anna Thompson story within 3 months of screening visit or any subsequent visit where the Logical Memory task is administered under ADNI, the alternative story should be used. Prior approval from the clinical monitor or protocol PI is required in any instance where the alternative story will be administered.

ADMINISTRATION

The following standard instructions are printed on each worksheet and are to be read verbatim.

- Say: “I am going to read to you a little story of just a few lines. Listen carefully and try to remember it just the way I say it, as close to the same words as you can remember. When I am through I want you to tell me everything I read to you. You should tell me all you can remember even if you are not sure. Are you ready?”
- When the examiner has finished reading the story, say to the participant: “Now what did I read to you? Tell me everything and begin at the beginning.”
- Always permit the participant to include additional information by prompting with “Anything else?” Record any additional “bits of information” and score appropriately.
- After the participant appears to be able to recall no more of the story, say: “Later on I will ask you to tell me this story again, so try not to forget it.”

RECORDING

Record the participant’s responses directly on the case report form between the lines of the text. To simplify the process of recording, underline each unit or word that is reported verbatim and

write in above the text units that are reported, but not verbatim. 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.

SCORING

The phrases and words separated by diagonal lines in the passages are treated as items (or units), and each item correctly repeated is worth one point, for a total of 25 points. Non-verbatim responses that are acceptable and receive full credit are listed in the Wechsler Memory Scale-Revised manual, as follows:

LOGICAL MEMORY SCORING GUIDE: ANNA THOMPSON

Story Component	General Rule / Correct Response	Examples of Alternative 1-Point Responses	Examples of 0-Point Responses
Anna	"Anna" or variant of the name	Ann; Annie; Annette	Angela; Allison
Thompson	"Thompson" is required	----	Thompkins; Thomas
of South	"South" (in any context)	from South; who lived in South; who came from the South	----
Boston,	"Boston" (in any context)	who worked in Boston; on a trip to Boston	----
employed	an indication that she held a job	worked; had a job as; who was; who earned a living as	who wanted to be; employed a cook
as a cook	"Cook" or some form of the word is required	who cooked	as a waitress; in the kitchen
in a school	"school" is required	at a high school; by a school	in a hospital; at a company
cafeteria,	"cafeteria" is required	----	lunchroom; dining hall; diner; restaurant; kitchen
Reported	indication that a formal statement was made to someone in authority (in any context)	filed a complaint; said to the police; made a statement; notified the police; called the police; told the police	said; told how
at the City Hall	"City Hall" (in any context)	went to City Hall; called City Hall	----
Station	"Station" in any context, or a word or phrase denoting a police station	police station; train station; stationhouse; police headquarters; precinct house; police department	office; building
that she had been held up	an indication that she had been held up (i.e., gun point or knife)	that someone held her up; that she was in a stick-up	that she was beaten; she was attacked; that she was robbed; she got mugged
on State Street	"State Street" (in any context)	she lived on State Street; on her way to State Street	on some street; State Avenue
the night before	indication that the hold-up occurred the previous night	last night; the previous night	at night; one night; yesterday; the day before

and robbed	indication that a robbery took place	was robbed; her money was stolen; they took her money; someone took her purse	lost her money; somebody took her things
of fifty-six dollars	indication that an amount of money greater than \$49 but less than \$60 was taken from her	fifty-some dollars; fifty-five dollars; about fifty dollars	sixty-five dollars; a lot of money; the police collected fifty-six dollars for her
She had four	"four" is required together with an indication that the children were hers	she was the mother of four	she had two; she had some; there were some
small children,	"children" or a synonym is required	little children; kids; small kids; young children	babies; girls; sons; small boys
the rent was due,	a phrase indicating that the rent was due	she had no paid the rent; she owed for the rent; the landlord had to be paid; she needed money for the rent	she owed money; she needed money; there was no money
and they had not eaten	indication that her children, or the family, were without food	they had gone without food; they were hungry; there was no food; her kids had nothing to eat; she couldn't feed her family	there wasn't much food; they had only a little food; she had not eaten; didn't have money to buy food
for two days.	"two days" is required, or a phrase meaning about two days	for a couple of days; for one or two days; for two or three days	for days; for several days; for a day; for three days
The police,	a word or phrase signifying one or more members of the police department (in any context)	the cops; the policeman; the detectives; the police officer; they (where police is clearly meant)	they (unspecified); some people; her neighbors; somebody
touched by the woman's story	an indication that her story evoked sympathy	were touched; felt sorry for the woman; wanted to help her; were sympathetic; were impressed by her story (implying emotional reaction)	listened to her story; helped her; believed her
took up a collection	a phrase indicating that money was collected	chipped in; collected money; donated; collected some food	gave her some money; found some money
for her.	an indication that the money was collected for her or her children	and gave it to her; for her children; for her family; for them; to help her out	as a gift; to make things better; for food

LOGICAL MEMORY SCORING GUIDELINE: GREG FORTUNE

Story Component	General Rule / Correct Response	Examples of Alternative 1-Point Responses	Examples of 0-Point Responses
Greg	"Greg" or variant of the name; Gregory	Gregory	George; Gary
Fortune	"Fortune" is required		
Captain	"Captain" (in any context) is required	the captain; captain of the team	a player; the team leader; the leader

and quarterback	“quarterback” (in any context) is required	was the quarterback; played quarterback	and a player...; and linebacker...; fullback
for the Atlanta	“Atlanta” (in any context) is required; Atlanta, Georgia	in Atlanta; from Atlanta	
Panthers	“Panthers” is required		
football team	“football” (in any context) is required	was on a football team; football squad; played football...	team; ball team; played ball for...
was injured	indication of injury	got hurt; was injured; was wounded	had trouble
on a fishing trip	indication that he went fishing	while fishing; on a fishing trip	on a trip
After bringing a large	indication that he caught something	while catching...; when reeling in...; as he was landing...	after getting...
bluefish	“Bluefish” or generic variant is required	fish	marlin
aboard his cabin cruiser	indication of both “aboard” and “boat” (in any context)	onto his cabin cruiser; he was aboard his boat; onto his boat; on his yacht; on his cruiser; on board his cruiser boat	on board; onto his deck
it jumped up	indication that the fish jumped	in leapt...; the fish sprang...; it rose up...	the fish moved...; it came at him...
and bit	“bit” or variant is required	bit into; chomped on	grabbed onto
his left	“left” is required		
ring	“ring” is required		fourth; little
finger.	“finger” is required		hand
Even though it took 17	“17” (in any context) is required	they put 17...; he needed 17...	even though he needed...; although he got...
stitches	“stitches” or a variant is required	sutures; he was sewn up...	
to close	“to close” or a variant is required	to seal	to fix; to repair...; to doctor
the wound,	“wound” or variant is required	the cut; the injury; the bite	it; the problem
he was still able to play	indication that he was able to play	he was well enough to play...; it healed up well enough for him to play...; he still got in the game	he couldn’t play...; he wanted to play...; he still went to the game
in Sunday’s game	“Sunday’s game” or a variant is required	the game on Sunday; the football game on Sunday	the weekend game; the game; Saturday’s game
against the Thrashers.	indication that the game was against the Thrashers	when his team played the Thrashers; versus the Thrashers; with the Thrashers	for the Thrashers; against the other team

LOGICAL MEMORY TEST II – DELAYED RECALL (STORY “A” ONLY)

ADMINISTRATION

Administer this test at least 30 minutes and no more than 40 minutes after Logical Memory I- Immediate Recall. Complete other cognitive testing during the interval between Immediate and Delayed Recall.

NOTE: IF THE 30 – 40 MINUTE DELAY PERIOD HAS ELAPSED AND ANOTHER TEST IS BEING ADMINISTERED, INTERRUPT THE ADDITIONAL TEST AND ADMINISTER THE LOGICAL MEMORY II. ONCE THE LOGICAL MEMORY II HAS BEEN FULLY COMPLETED, RESUME THE INTERRUPTED TEST

The following standard instructions are printed on each worksheet and are to be read verbatim. Say, **“Do you remember the little story I read to you a few minutes ago? Now I want you to tell me the story again. Tell me everything; begin at the beginning.”**

If the participant does not recall the story, it is permissible to offer the following reminder which is also printed on the testing worksheets. Say, **“The story was about a woman who was robbed.”** (For Greg fortune say, **The story was about a man who was injured”**)

Do not give any further help other than general encouragement. Note if the reminder was given and do not then give a point for that item (i.e., “robbed”) when scoring. After the participant, has recalled the story, prompt with “Anything else?” Record any additional information recalled and score appropriately.

RECORDING

As specified in the directions for Logical Memory I – Immediate Recall, record the participant’s responses directly on the case report form between the lines of the text. To simplify the process of recording, underline each unit or word that is reported verbatim and write in above the text units that are reported, but not verbatim. Many examiners prefer to tape record the participant’s response and then transcribe any words they may have missed after the session. This is acceptable if appropriate consent has been obtained.

SCORING

Use the same scoring procedure as for Logical Memory I - Immediate Recall. Non-verbatim responses that are acceptable and receive full credit are posted in the document repository.

The Logical Memory II – Delayed Recall score is used to demonstrate abnormal memory function in potential participants. Please see the section on Inclusion/Exclusion Criteria for education-adjusted scores.

IF THE ALTERNATE GREG FORTUNE STORY NEEDS TO BE USED, PLEASE SEE THE WORKSHEET POSTED ON THE DOCUMENT REPOSITORY UNDER SUPPLEMENTAL WORKSHEETS FOR DIRECTIONS ON HOW TO ADMINISTER AND SCORE

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 person administer the MMSE at all appropriate visits
- If the Participant is unable to perform any item, the item should be scored as “Incorrect”
- [REDACTED]
- Prior to administration, ensure that eyeglasses (if needed) are being worn and hearing aid (if needed) are adjusted appropriately
- If the Participant is anxious, it may be helpful to periodically say, “you’re doing fine”
- Since visits are annually, there is less of a concern for a learning effect. Therefore, MMSE Word List 2 [REDACTED] will be used at each annual In-Clinic Visit. If there is a concern for a learning effect, that alternate MMSE Word List ([REDACTED]) can be used; alternate word list can be ordered by completing the online ADNI3 supply order form.

INSTRUCTIONS	SCORING
<p>ORIENTATION: [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>	<p>SCORING: [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>

<p>REGISTRATION: [REDACTED]</p>	<p>SCORING: [REDACTED]</p>
<p>ATTENTION AND CALCULATIONS: [REDACTED]</p>	<p>SCORING: [REDACTED]</p>
<p>DELAYED RECALL: [REDACTED]</p>	<p>SCORING: [REDACTED]</p>
<p>NAMING: [REDACTED]</p>	<p>SCORING: [REDACTED].</p>
<p>REPETITION: [REDACTED]</p>	<p>SCORING [REDACTED]</p>
<p>COMPREHENSION: [REDACTED]</p>	<p>SCORING: A [REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>

<p>READING: [REDACTED]</p>	<p>SCORING: [REDACTED]</p>
<p>WRITING: [REDACTED]</p>	<p>SCORING: [REDACTED]</p>
<p>DRAWING: [REDACTED]</p>	<p>SCORING: [REDACTED]</p>

Montreal Cognitive Assessment (MOCA)

The MOCA was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes.

- ➡ Use a check mark on the worksheet to indicate correct items. The EDC will ask for each item to be entered as correct or incorrect.
- ➡ Record verbatim responses so that scoring can be confirmed by the clinical monitor.

ADN13 SCORING AND TEST ADMINISTRATION DIFFERS SLIGHTLY FROM THE PUBLISHED INSTRUMENT. RATHER THAN CALCULATING A TOTAL SCORE, PLEASE ENTER THE ITEM LEVEL DATA AS SPECIFIED ON THE WORKSHEET AND ECRF.

ALTERNATING TRAIL MAKING:

Instruct the participant: **“Please draw a line, going from a number to a letter in ascending order. Begin here [point to (1)] and draw a line from 1 then to A then to 2 and so on. End here [point to (E)].”**

SCORING:

- Mark as correct if the participant successfully draws the following pattern: 1 - A - 2 - B - 3 - C - 4 - D - 5 - E, without drawing any lines that cross. Any error that is not immediately self-corrected would result in this task being scored as incorrect.
- Note: If a participant starts at 2 rather than 1 they should be instructed to start at 1. Task should be scored as correct if the participant successfully draws the pattern even when starting at 2.

VISUOCONSTRUCTIONAL SKILLS (CUBE):

For Cube and Clock, the participant may be allowed to use an area other than those provided on the MoCA test sheet to reproduce the items (e.g., an additional blank page, with Participant ID and visit date.)

Pointing to the cube. Say: “Copy this drawing as accurately as you can, in the space below.”

Scoring: A correctly executed drawing must meet each criteria:

- Drawing must be three-dimensional
- All lines are drawn
- No line is added
- Lines are relatively parallel and their length is similar (rectangular prisms are accepted)
Place a checkmark on the worksheet next to the cube-drawing task if all criteria are met.

VISUOCONSTRUCTIONAL SKILLS (CLOCK):

A separate blank piece of paper may be used for the MoCA Clock drawing. *Indicate the right third of the space and give the following instructions: “Draw a clock. Put in all the numbers and set the time to 10 after 11.”* Please note that Clock Draw and Copy is repeated again separately in the ADNI battery on a separate piece of paper.

- Do not use the MoCA administration to replace this separate trial of clock draw and copy.

Scoring: Each of the three items must be scored as correct/incorrect based on the following criteria:

- Contour: The clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle).
- Numbers: All clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour.
- Hands: There must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centered within the clock face with their junction close to the clock center.

NAMING:

Beginning on the left, *point to each figure and say: “Tell me the name of this animal”.*

Scoring: Indicate each item is correct with a checkmark: camel or dromedary, (2) lion, (3) rhinoceros or rhino.

MEMORY:

Read a list of 5 words at a rate of one per second, after giving the following instructions: **“This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn’t matter in what order you say them”.**

- ➡ Mark a check in the allocated space for each word the participant CORRECTLY produces on this first trial.

When the participant indicates that she/he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: **“I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time.”**

Put a check in the allocated space for each word the participant recalls correctly after the second trial.

At the end of the second trial, inform the participant that (s)he will be asked to recall these words again by saying, **“I will ask you to recall those words again at the end of the test.”**

Scoring: For the standard MoCA, Trials One and Two are not scored, but for ADNI, these items are entered on the eCRF.

ATTENTION:

DIGIT SPAN FORWARD

Administration: Give the following instruction: “I am going to say some numbers and when I am through, repeat them to me exactly as I said them”. Read the five-number sequence at a rate of one digit per second.

DIGIT SPAN BACKWARD

Administration: Give the following instruction: “Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order.” Read the three-number sequence at a rate of one digit per second.

Scoring: Place a checkmark on the worksheet for each sequence correctly repeated (the correct response for the backwards trial is 2-4-7).

VIGILANCE - LETTERS AND TAPPING:

Administration: Read the list of letters at a rate of one per second, after giving the following instruction: **“I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand”.**

- ➡ Circle any incorrect responses on the worksheet.
- ➡ Record the NUMBER OF ERRORS made (i.e., either a tap on a wrong letter, or failure to tap on an A).

VIGILANCE - SERIAL 7S

Give the following instruction: **“Now, I will ask you to count by subtracting seven from 100, and then, keep subtracting seven from your answer until I tell you to stop.”**

- Give this instruction twice if necessary.

Record participant's verbatim response.

- If a participant makes an error on the first subtraction, but then correctly subtracts 7 from that number, the second subtraction would be considered a correct response. Place a checkmark next to each correct subtraction.

SENTENCE REPETITION

The examiner gives the following instructions: **“I am going to read you a sentence. Repeat it after me, exactly as I say it [pause]: I only know that John is the one to help today.”**

Following the response, say: **“Now I am going to read you another sentence. Repeat it after me, exactly as I say it [pause]: The cat always hid under the couch when dogs were in the room.”**

Scoring:

- A checkmark is given for each sentence correctly repeated. REPETITION MUST BE EXACT.
- Be alert for errors that are omissions (e.g., omitting “only”, “always”) and substitutions/additions (e.g., “John is the one who helped today;” substituting “hides” for “hid”, altering plurals, are all not correct).

VERBAL FLUENCY:

Use the separate page provided in the worksheet packet to record the verbatim responses for this test.

Give the following instruction: **“Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready? [Pause] Now, tell me as many words as you can think of that begin with the letter F [time for 60 sec]. Stop.”**

- Any duplication of words (perseverations) should not be counted as correct words.
- If a participant begins to say proper nouns or numbers you should quickly inform the participant that proper nouns or numbers cannot be used during the task.

Scoring:

- The score is the number of words correctly recalled (i.e., total number of words recalled minus any repetitions, perseverations, intrusions, or variations).

ABSTRACTION

Ask the participant to explain what each pair of words has in common, starting with the example: “Tell me how an orange and a banana are alike”.

- If the participant answers in a concrete manner, then say only one additional time: “Tell

me another way in which those items are alike”.

- If the participant does not give the appropriate response (fruit), say, “Yes, and they are also both fruit.” Do not give any additional instructions or clarification.

After the practice trial, say: “Now, tell me how a train and a bicycle are alike”. Following the response, administer the second trial, saying: “Now tell me how a ruler and a watch are alike”.

Do not give any additional instructions or prompts. Record the participant’s verbatim response.

Scoring - The following responses are considered correct:

- Train-bicycle = means of transportation, means of travelling, you take trips in both.
- Ruler-watch = measuring instruments, used to measure.
- Examples of incorrect responses:
- Train-bicycle = they have wheels.
- Ruler-watch = they have numbers.
- Montreal Cognitive Assessment (MoCA) - (Cont’d)

DELAYED RECALL

Give the following instruction: “**I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember.**” *Give a checkmark for each of the words correctly recalled spontaneously without any cues.*

- For any word not free recalled, prompt the subject with the semantic category cue provided below.
- If the participant does not recall the word after the category cue, give him/her a multiple-choice trial, using the following example instruction, “Which of the following words do you think it was, NOSE, FACE, or HAND?”
- Make a check mark (✓) in the allocated space if the participant remembered the word with the help of a category or multiple-choice cue.

Use the following category and/or multiple-choice cues for each word, when appropriate:

- FACE: category cue: part of the body multiple choice: nose, face, hand VELVET: category cue: type of fabric multiple choice: denim, cotton, velvet CHURCH: category cue: type of building multiple choice: church, school, hospital
- DAISY: category cue: type of flower multiple choice: rose, daisy, tulip
- RED: category cue: a colour multiple choice: red, blue, green

Scoring:

- Place a check mark in the allocated space on the worksheet indicating if recall with no cue, recall with category cue, recall with multiple choice cue or incorrect.

ORIENTATION

Give the following instructions: “**Tell me the date today.**” If the participant does not give a complete answer, then prompt accordingly by saying: “**Tell me the [year, month, exact date,**

and day of the week].” Then say, “Now, tell me the name of this place, and which city it is in.”

- Scoring: *Place a check mark in the allocated space on the worksheet next to each item correctly answered.* The participant must tell the exact date and the exact place (name of hospital, clinic office) to be considered correct.

THE MOCA TOTAL SCORE IS NOT CALCULATED FOR ADNI.

Modified Hachinski

ADMINISTRATION

The form should be administered by a clinician familiar with the study participant’s medical history with the study partner. The completion of the modified hachinski is done using information obtained from the medical history, physical and neurological exams and/or medical records. Indicate if a characteristic is present by checking ‘present’ or ‘absent’.

CLARIFICATION OF TEST ITEMS:

1. Abrupt Onset of Cognitive Impairment

Reported rapid onset with acknowledgement that gradual changes may have also occurred.

2. Stepwise Deterioration of Cognitive Impairment

Cognitive decline, aside from onset, noted to occur over days and followed by plateaus.

3. Somatic Complaints

e.g., headache; tinnitus; chest pain; malaise.

4. Emotional Incontinence

Occasional displays of intense emotional expression such as crying, beyond that which would be considered appropriate to a given situation.

5. History of Hypertension

History of blood pressure of >150/95 for 6 months.

6. History of Strokes

Hemiparesis, aphasia.

7. Focal Neurological Symptoms

Transient dizziness; diplopia lasting hours; seizures.

8. Focal Neurological Signs

Unequal deep tendon reflexes, extensor plantar response, nystagmus.

SCORING

Points are given for each item noted as 'present', for a possible total of 12 points. A total score is derived from the summation of points for each item. The score calculation and automated population may be triggered in the eCRF.

Multilingual Naming test (MINT)

ADMINISTRATION

The MINT is replacing the instrument BNT from ADNI2 Neuropsych battery. The rater will administer the assessment by showing the participant images of 32 items.

[SAY]: **“I am going to show you some pictures of objects, one at a time. Please tell me the name of each object, that is, tell me what it is called. If you cannot think of the name, try to make your best guess. If you don't know what the object is, I will try to help you. DO you have any questions?”**

Allow up to 20 seconds for a response, particularly if the subject is struggling. If the answer is correct, put a check mark in the column “Uncued-correct.”

For items 30 and 31 (mortar, pestle), there is only one picture.

[SAY]: **“On this page there are two things I would like you to name.”** Point to the mortar and say **“What is this called?”** and record the response. Then point to the pestle and say **“What is this called?”** and record the response. Be sure to ask for both items.

ALTERNATE RESPONSES

Item no.	MINT Item	Alternative correct response (s)
3	lightbulb	electric bulb, bulb
10	seesaw	teeter-totter
27	gauge	manometer, barometer

CUEING

If the initial response is incorrect, there are several procedures to follow. Responses to cues are not timed, and if they do not occur immediately, the examiner should move on. When the subject indicates knowledge of the object but cannot name it, it is appropriate to give a phonemic cue (the first few sounds of the word). Knowledge of the word can be assumed if the subject makes a phonemic paraphasia such as “ankle” for “anvil” (substituting a sound within the word, retaining most of its original sounds) or correctly describes the use of the object (e.g., “You use it to mash things up, for “pestle”).

Please take care to provide only the sound of the letter(s) underlined on the response form. Only three-syllable words have the first two letters underlined. The examiner can practice cueing by starting to say each word and suddenly stopping after the first sound.

Sometimes a subject will give a response that indicates lack of visual recognition of the object, that is, misperception (e.g., focusing only on the flame at the top of the candle and saying “fire: or misperceiving the twigs in the nest and saying “hair”). In that instance, a semantic cue should be given since it helps lead the subject to more accurate visual perception of the object. If the response is correct with the semantic cue, it is marked correct in the appropriate column under “Semantic cue”. If it is incorrect it is marked as wrong and the examiner should then move to the phonemic cue. Note, the semantic cue is only given if the subject does not recognize the object.

PROMPTS ALLOWED FOLLOWING SPONTANEOUS RESPONSE ONLY

Subject will often say non-target/alternative names. If that happens there are three prompts you can give to try to elicit the target names as follows:

Prompt 1: **“Can you think of a more specific name?”** (code = S)

Prompt 2: **“Can you think of a more general name?”** (code = G)

Prompt 3: **“Can you think of a different or another name?”** (code = A)

If you use one of these three prompts, indicate this on the coding sheet by writing the relevant code in the Spontaneous Response column.

Examples:

- 1) If the subject gives a circumlocutory or more general response (e.g., for “saw” says “it cuts wood” or “it’s a tool”), use Prompt 1 and write (S) on the coding sheet.
- 2) If the subject gives a more specific name (e.g., for “volcano” says “Its Mt. Vesuvius”) use Prompt 2 and write (G) on the coding sheet.
- 3) If the subject gives an alternative, but not incorrect response (e.g., “dromedary” for “camel”), use Prompt 3 and write (A) on the coding sheet.

Other useful prompts:

Sometimes subjects might tell you other things that they remember about using the object. For example, “My dad had one of those!” If that happens [SAY]:

Prompt 4: **“Can you tell me the name?”**

If the subject gives a correct name, but says it is not that object (e.g., “Well, it’s not a canoe”), cuing proceeds as if the response was incorrect, [SAY]:

Prompt 5: **“Do you know that name?”** or **“Do you know what it is?”**

If the subject is focusing on the wrong part of the picture (e.g. “needle” for “barometer”, or “sky” for “rainbow”), point to what they should be focusing on and [SAY]:

Prompt 6: **“What is the whole thing called?”** or **“What is this part called?”**

SCORING

The total MINT score should be calculated using items up to the point where the subject stopped the test. Items are counted as correct only if spontaneously names or named with a semantic cue if needed (see below). If the subject gives the correct name with a phonemic cue, this is not counted towards the total correct. The reason for this is that this test assesses word retrieval under conditions of full recognition of the object. If the subject is cued to the object’s

identity after an initially faulty recognition and names the item correctly, it is not a word retrieval problem.

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 calculate the total correct score.

Enter the total score on the form, Question 11a. If the test was not completed, enter the appropriate reason code from the key and leave Questions 11b – 11f blank.

For Question 11b, enter the total correct without a semantic cue. For Question 11c, enter the number of semantic cues given. For 11 d, enter the number of items correct with a semantic cue. If no semantic cues were given, enter 88 = Not applicable for Question 11d.

For Question 11e, enter the number of phonemic cues given. For 11f, enter the number of items correct with a phonemic cue. If no phonemic cues were given, enter 88 = Not applicable for Question 11f.

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 another 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 sub questions
- 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 sub questions.
- If the sub questions 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 sub questions as most aberrant.

For example: If the study partner indicates that resistive behavior is particularly problematic when you are asking the sub questions 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 sub questions, 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 sub questions] 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.

Rey Auditory Verbal Learning Test (AVLT)

This is a test of episodic memory that assesses the ability to acquire 15 words across five immediate learning trials, to recall the words immediately after an intervening interference list, and to recall and recognize the words after a 30-minute delay interval. For each trial record verbatim responses. Correct responses are defined as stimulus words recalled correctly by the participant. Please note: pluralization and singularization of an actual stimulus word are counted as correct. Intrusions are defined as any non-stimulus word (i.e. a word that is not on the list) recalled by the participant. Preservations are defined as repetition of a word (either an intrusion or correct stimulus word) in the same trial. The first time a subject recalls a stimulus word it is counted as correct. If later, in the same trial, the same stimulus word is recalled, the second recall is a perseveration. With non-stimulus words, it is considered an intrusion the first time the subject recalls the word and if the same non-stimulus word is recalled again (in the same trial), it is counted as a perseveration.

TRIAL I ADMINISTRATION

After engaging the participant’s attention, the examiner should say, “I am going to read a list of words. Listen carefully, for when I stop you are to repeat back as many words as you can remember. It doesn’t matter in what order you repeat them, just try to remember as many as you can.” The examiner then reads the words aloud. Immediately after the words are read, the participant recalls as many as possible and these are recorded by the examiner.

TRIAL II – V ADMINISTRATION

Immediately after each preceding trial, the examiner says, “Now I am going to read the same words again, and once again when I stop I want you to tell me as many words as you can remember, including words you said the first time. It doesn’t matter in what order you say them, just say as many words as you can remember, whether or not you said them before.” Immediately after the words are read on each trial, the participant recalls as many as possible and these are recorded by the examiner.

LIST B ADMINISTRATION

Immediately after the fifth learning trial, the examiner says, “Now I’m going to read a second list of words. Listen carefully, for when I stop you are to repeat back as many words as you can

remember. It doesn't matter in what order you repeat them, just try to remember as many as you can." Immediately after the words are read on each trial, the participant recalls as many as possible and these are recorded by the examiner.

TRIAL VI ADMINISTRATION

Immediately after the list B trial, the examiner says, "Now tell me all the words you can remember from the first list." The participant recalls as many as possible and these are recorded by the examiner. Note: the words from the original list are NOT read again before recall is elicited on this trial.

30-MINUTE DELAY ADMINISTRATION

After 30-minutes of interpolated testing (timed from the completion of List B recall), the examiner says, "A while ago I read a list of words to you several times, and you had to repeat back the words. Tell me the words from that list." The participant recalls as many as possible and these are recorded by the examiner. Note: the words from the original list are NOT read again before recall is elicited on this trial. Record verbatim all responses. Total correct and total intrusions are recorded on the eCRF.

RECOGNITION ADMINISTRATION

Present the participant with a pencil and the word recognition sheet and say, "Sometimes people can remember more of the words if they see them. Read all these words and circle the ones that you think were on that first list I read...the list I read 5 times to you."

Trail Making

This is a test of processing speed and executive function. Although both Parts A and B depend on visuomotor and perceptual-scanning skills, Part B also requires considerable cognitive flexibility in shifting from number to letter sets under time pressure.

- PART A consists of 25 circles numbered 1 through 25 distributed over a white sheet of 8 1/2" x 11" paper. The participant is instructed to connect the circles with a drawn line as quickly as possible in ascending numerical order.
- PART B also consists of 25 circles, but these circles contain either numbers (1 through 13) or letters (A through L). The participant must connect the circles while alternating between numbers and letters in ascending order (e.g., A to 1; 1 to B; B to 2; 2 to C).

The participant's performance is judged in terms of the time, in seconds, required to complete each Trail. The time to complete Part A (150-second maximum) and Part B (300-second maximum) will be the primary measure of interest (testing is stopped if the maximum time is reached). Both parts of the Trail Making Test are available in multiple forms of equal difficulty for purposes of repeated evaluation.

ADMINISTRATION

PART A: Place the form for Part A sample in front of the participant. Read aloud the instructions:

"There are numbers in circles on this page. Please take the pencil and draw a line from one number to the next, in order. Start at 1 (point to the number), then go to two (point to

the number), then go to three (point to the number) and so on. Please try not to lift the pencil as you move from one number to the next. Work as quickly as you can.”

- If the participant makes an error, mark through the line and go back to the point at which the error was made and say, for example: **“You were at number two. What is the next number?”**
- Wait for the participant’s response and say: **“Please start here and continue.”**
- If the participant completes the sample correctly, go to Test A. Repeat the instructions given for the sample. Start timing as soon as the instruction is given to begin. Stop timing when Trail is completed, or stop participant when maximum time is reached. Allow a maximum of 150 seconds for the test.

PART B: Place the form for Part B sample practice in front of the participant. Read aloud the instructions:

“There are numbers and letters in circles on this page. Please take the pencil and draw a line, alternating in order between the numbers and letters. Start at number 1 (point to the number), then go to the first letter, A (point to the letter), then go to the next number, 2 (point to the number) and then the next letter, B (point to the letter) and so on. Please try not to lift the pencil as you move from one number or letter to the next. Work as quickly as you can.”

- If the participant makes an error, mark through the line and go back to the point at which the error was made and say, for example: **“You were at number two. What is the next letter?”**
- Wait for the participant’s response and say: **“Please start here and continue.”**
- If the participant completes the sample correctly, go to Test B. Repeat the instructions given for the sample. Start timing as soon as the instruction is given to begin. Stop timing when trail is completed or stop participant when maximum time is reached. Allow a maximum of 300 seconds for the test.

SCORING

- Record the total number of seconds to complete Part A, up to a maximum of 150 seconds. If the participant is not finished by 150 seconds, the score is 150.
- Record the total number of seconds to complete Part B, up to a maximum of 300 seconds. If the participant is not finished by 300 seconds, the score is 300.
- For both Part A and Part B, record errors of commission and omission as described below: ‘Errors of commission’ are defined as errors occurring when the participant connects two circles in the incorrect sequence. Each time this occurs, one error of commission is scored.
- ‘Errors of omission’ are defined as errors occurring because the participant failed to draw a connecting line to a given circle in the correct sequence. This only occurs when the participant is very slow and does not complete the task in the time allotted.
- One incorrectly sequenced number/letter may, in rare instances, be counted as both an error of commission and an error of omission (e.g., if the participant incorrectly draws a line to the letter ‘K’, but then never makes it back to that letter in the correct sequence).
- If it is clear that the participant intended to touch a circle but barely missed it, do not count it as an omission. However, caution the participant to touch circles when you first

observe this.

- If the participant passes through another circle while clearly on the way to the next circle in the sequence, caution to avoid touching circles other than the ones intended, and make a note of what occurred on the raw data form, but do not count as an error of commission.
- The participant may be unable to complete this test due to physical problems (e.g., tremor, dystonia). In that event, indicate the reason for incomplete data (i.e., physical problem, other problem, cognitive/behavioral problem, refusal) by completing an additional comment form online, referencing the test not administered and reason.

Chapter 16

Computerized Testing

Cogstate

Separate manual and handout available in the document repository.

Brain Health Registry (BHR)

Whenever possible, please introduce the Brain Health Registry brochure and instructions to the participant **prior to starting the CBB** as participants will be directly introduced to BHR at the conclusion of the CBB.

OVERVIEW

The Brain Health Registry (BHR) is a web-based research study that offers optional online assessments to be completed unsupervised by the participant in their homes. The participant will be invited to register at home for the ADNI-BHR within two weeks of their in-clinic visit. Immediately following their registration, the participant will be asked to take an online brain test, answer a set of questions about their thinking, memory, and day-to-day functioning, and asked to identify and invite their ADNI study partner to the BHR-Study Partner Portal. All of this should take about 15-20 minutes. Subsequently they will receive an email inviting them to return every three months to answer more questions and take repeated tests.

The purpose of ADNI-BHR is to provide valuable insights about whether brain health information collected online can tell us the same thing as information collected in a clinical setting. This information can then be used to design the best assessments for future research studies.

ADMINISTRATION

- ➔ During the in-clinic initial or baseline visit, the clinic personnel will provide an informational BHR brochure to all MCI and CN participants.
- ➔ The clinic personnel will explain the Brain Health Registry to the participant using the brochure for guidance.
- ➔ The clinic personnel will also write the participant's unique ADNI Online ID on the back of the brochure which will be used when the participant registers at home online for the BHR.
- ➔ The unique ADNI online ID can be referenced in your sites listing of unique ADNI online IDs that is provided by the coordinating center. The ADNI online ID will be

logged in the Cogstate eCRF. Please note that the same ADNI online ID will be used for all computerized testing in ADNI, CBB, and BHR. All MCI and CN participants should be assigned an ADNI Online ID, even if they choose to not participate in the CBB. The online ID needs to be entered into the ADNI3 study portal to complete the CBB eCRF (see ADNI3 Data Completion Manual for more information).

- ➔ Clinic personnel should inform the participant that if they lose their BHR brochure, they could contact the clinic site staff to retrieve their ADNI Online ID.
- ➔ Participants who have not yet enrolled in ADNI-BHR, will be re-invited to participate and given supplemental information at their next in-clinic visit.

Clinic personnel will also provide the BHR Study Partner Portal flyer to the study partner of any participant interested in joining the BHR. The Study Partner Portal is a BHR initiative that allows the study partner to answer questions about the participant as well as themselves. Please note the participant will need to join the Brain Health Registry in order to identify and invite the study partner to join the Study Partner Portal.

Additionally, clinic personnel will log the date that the brochure and flyer was given to the participant and study partner in the BHR eCRF. They will also confirm that the ADNI Online ID was provided or the reason that the participant declined the BHR brochure and flyer.

BHR BROCHURES AND STUDY PARTNER FLYERS CAN BE ORDERED USING THE ADNI3 ONLINE SUPPLY ORDER FORM. PLEASE ORDER THE SAME NUMBER OF BROCHURES AND FLYERS AS THE BROCHURE WILL NEED TO BE GIVEN TO EACH CN AND MCI PARTICIPANT AND THE FLYER WILL NEED TO BE GIVEN TO THAT PARTICIPANT'S STUDY PARTNER.

PLEASE NOTE, BHR BROCHURES THAT ARE EDITED WILL NEED TO BE PRINTED LOCALLY. SEND ANY EDITS OF THE BHR BROCHURE TO ATRI REGULATORY AFFAIRS FOR REVIEW/APPROVAL.

INSTRUCTIONS FOR CLINIC PERSONNEL

1. Clinic personnel provide the BHR brochure to the participant and describe the study and how to enroll. Suggested language is provided below:

"The Brain Health Registry (BHR) is welcoming ADNI participants to continue their ADNI experience by completing online assessments! Participation in this study is completely optional and you can withdraw at any time. Brain Health Registry is a web-based ADNI-affiliated research study designed to help find and accelerate treatments for Alzheimer's disease and other brain disorders. Participation is free, easy, and entirely online – it only takes a few minutes to sign up and about an hour a year to participate. More details are here in the brochure!"

2. Clinic personnel write the ADNI Online ID on the BHR brochure.
3. If the ADNI participant accepts the ADNI-BHR brochure, clinic personnel provide and explain the BHR Study Partner Portal flyer to the participant's study partner. Suggested language is provided below:

“A study partner is someone who knows you well, such as a caregiver, family member, or friend, and can answer questions about your health, memory, and day-to-day activities. Having the pair of you participate in ADNI-BHR helps researchers obtain a more complete understanding of cognition and everyday functioning. Study Partners are invited to go to the Brain Health Registry website to answer questions and take brain tests. They also get newsletters and email reminders, and even have the opportunity to join the main Brain Health Registry study. Study Partners and participants will not have access to the information the other person provides. Note- ADNI participants must register and invite the study partner in order to participate.”

4. Clinic personnel log information in the BHR eCRF
5. Clinic personnel assist participant in completing online sign-up form.
 - Participants that complete the Cogstate Brief Battery (CBB) during their in-clinic visit will see a Brain Health Registry invitation page at the end of this test which asks the participant if they would like to learn more about the Brain Health Registry via a link. Once clicked, this link will lead them to a webpage where they can provide their name, email and ADNI Online ID. BHR will then send the participant an invitation email to register for ADNI-BHR at home.
 - Participants who do not complete CBB during their baseline OR do not receive the invitation email after completing the CBB in clinic, can follow the detailed instructions provided on the BHR brochure to register at home.

**NO SCORING IS NEEDED AS THESE ASSESSMENTS ARE COMPLETED AT-HOME
ONLINE THROUGH THE BRAIN HEALTH REGISTRY WEBSITE.**

Chapter 17

Safety Measures

All safety assessments described in this section are administered per the times shown in the Study Schedule of Events, Protocol Appendix 1.

Electrocardiogram (ECG)

An appropriately qualified individual will conduct a standard 12-lead resting ECG. The ECG report must be reviewed, signed, and dated by the site Principal Investigator (or a medically-qualified individual delegated by the PI). There is no central read requirement for the ECG report. If there is a safety concern, please consult with the study team (adni-study@usc.edu).

Those with clinically significant ECG findings will be referred for follow-up as deemed appropriate by the investigator and may be excluded from the study.

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 Study Schedule (See Protocol, Appendix 1, 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 during the ADNI3 Screening Visit.

Chapter 18

Global Unique Identifier

Global Unique Identifier (GUID)

When subjects participate in multiple research studies, GUIDs prevent data of the same subject from being analyzed multiple times. The ADNI GUID Generator creates a Global Unique ID (GUID) for each ADNI participant using his/her full name, date, city, and sex at birth.

To generate the GUID

- ➔ Download the software through the link provided in the Global Unique Identifier (GUID) eCRF located in the ADNI3 EDC study portal.
- ➔ Once the ADNI GUID Generator is downloaded, you simply create the GUID by entering the participant's full name, date, city, and sex at birth into program.
- ➔ The GUID is then entered into the Global Unique Identifier (GUID) eCRF located in the ADNI3 EDC study portal.

ONCE THE GUID HAS BEEN CREATED PLEASE ENTER THE GUID INTO COGSTATE ECRF, EVEN IF THE PATIENT OPTS OUT OF COGSTATE.

Although we do not collect PHI information in the worksheets, this information can be directly entered into the eCRF. If a computer is not easy accessible, write down the information in a blank sheet a paper and ensure this paper is shredded after the information gets entered in the eCRF.

If you have trouble downloading the system please reach out the clinical core for a different system version.

EVERY PARTICIPANT WILL NEED TO HAVE A GUID.

Chapter 19

Overview of Sample Collections, Processing and Shipment

BIOFLUIDS GLOSSARY

BLD	Blood (Whole)
CSF	Cerebrospinal Fluid
PL	Plasma
URN	Urine
ACD	Acid Citrate Dextrose
EDT	EDTA (ethylenediaminetetraacetic acid)
SER	Serum
BLD EDT	Whole blood collected in a lavender-top tube
BLD ACD	Whole blood collected in a yellow-top tube (ACD-A)
BLD SER	Whole blood collected in a plain red-top tube
CELL-I	Cell Immobilization Sample
LP	Lumbar Puncture
NCRAD	National Cell Repository for Alzheimer's Disease
PBMC	Peripheral blood mononuclear cell
RBC	Red Blood Cells

All samples described in this section are collected per the times shown in the Study Schedule in the ADNI3 protocol. Ensure the study participant has appropriately consented to sample collections and/or banking procedures before collecting samples. If you have any questions, contact your clinical monitor.

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/>).

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. Please allow up to 7-10 business days to receive supplies.

Biospecimen Collection Schedule

Reminder: CN participants are seen in the clinic every other year unless they are required to come in on an off year for AV-1451 PET imaging and blood draw. MCI and AD are seen in the clinic annually.

NEWLY ENROLLED PARTICIPANTS									
	Safety / Clinical Labs	CSF	Plasma	Serum	Buffy Coat	PBMC & RBC	RNA	Genetics	Cell-Immort.
Screening	✓								
Baseline		✓	✓	✓	✓	✓	✓	✓	✓#
Ongoing Annual Visits		✓*	✓	✓	✓		✓		
Ship samples to:	URMC	UPENN Biomarker Lab			NCRAD				

Cell Immortalization is only collected for New Participants once at Baseline. .

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

ROLLOVER PARTICIPANTS							
	CSF	Plasma	Serum	Buffy Coat	PBMC & RBC	RNA	Genetics
Initial Visit	✓*	✓	✓	✓	✓	✓	✓
Ongoing Annual Visits	✓*	✓	✓	✓		✓	
Ship samples to:	UPENN Biomarker Lab			NCRAD			

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

Recommended Blood Draw Order

ORDER	SAMPLE TYPE		TUBE TYPE	# TUBES x VOLUME (mL)	TOTAL AMOUNT (mL)	SHIPPING TEMP	LAB FOR SHIPPING
1	Blood draw for Plasma		Purple top EDTA	2 x 10	20	Frozen	UPENN
	Buffy Coat	Extracted from plasma sample tube	Cryovials	2 x 2	4	Ambient	NCRAD
	RBC[^]	Extracted from plasma sample tube after buffy coat extraction	Blue cap cryovial + transfer tube	(1 x 2) + (1 x 4)	~4-6	Frozen	NCRAD
2	Blood draw for Genetics[*]		Purple top EDTA	1 x 10	10	Ambient	NCRAD
3	Blood draw for PBMC^{**}		Green top NaHep	1 x 10	10	Ambient	NCRAD
4	Blood draw for Cell Immortalization[#]		Yellow top ACD	2 x 8.5	17	Ambient	NCRAD
5	Blood draw for Serum		Red top serum	2 x 10	20	Frozen	UPENN
6	Blood draw for RNA		PAXgene	3 x 2.5	7.5	Ambient	NCRAD

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

*** Genetic sample collected once upon entry. New Participants at Baseline. Rollovers at Initial Visit.**

Cell Immortalization is only collected for New Participants once at Baseline.

Samples Collected by Visit

SAMPLE TYPE	AMOUNT	SHIPPING TEMP.	ALL COHORTS (NEWLY ENROLLED & ROLLOVER)	LAB FOR SHIPPING
Plasma from blood	20 mL	Frozen	BL/Initial Visit, Ongoing In-clinic	UPENN Biomarker Lab
Serum from blood	20 mL	Frozen	BL/Initial Visit, Ongoing In-clinic	
CSF	20 mL	Frozen	BL/Initial Visit, Ongoing In-clinic*	
Blood for Genetics	10 mL	Ambient	BL/Initial Visit	NCRAD
Blood for Cell Immortalization	2 x 8.5 mL	Ambient	BL	
Blood for PBMC	10 mL	Ambient	BL/Initial Visit#	
Blood for RNA genotyping	3 x 2.5 mL	Ambient	BL/Initial Visit, Ongoing In-clinic	
Buffy Coat	1-2 mL	Ambient	BL/Initial Visit, Ongoing In-clinic	
Blood for RBC	4-6 mL	Frozen	BL/Initial Visit#	

*LP to be performed at Baseline / Initial Visit for all participant types and then again, every two years

Both Rollover and newly enrolled participants will have blood drawn for PBMC collection and extraction of RBC upon entry into the ADNI3 study; longitudinal collection for PBMC and RBC extraction is not required

Sample Identification and Tracking - Labels

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

IMPORTANT to use the appropriate sample labels for each sample type:

- **URMC labels:** Screening Samples
- **NCRAD labels:** Genetic, Cell Immortalization, RNA, Buffy Coat, PBMC, and RBC samples
- **UPENN Labels:** Plasma biomarker sample, Serum biomarker sample and CSF

Clinical Laboratory Samples at screening (URMC)

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

Specimen Label 'Study Name' Site: _____ ID: _____ Date: _____ Time: _____ Kit ID: 1234567 	Study Kit ID:  1234567 Requisition Label
--	---

All Genetic Samples (NCRAD): Genetic, Cell Immortalization, RNA, PBMC, Buffy Coat, and RBC

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

Protocol: <input type="checkbox"/> ADNI3 Subject ID _____ -S- _____ Year of Birth _____ Gender: M / F Collection Date: Mo. / Day / Year Visit: _____
--

When filling out the Visit Field, follow the abbreviations below:

Annual Visit Codes	
CODE	LABEL
BL	New Participant Baseline Visit
INIT	Rollover Initial Visit
Y1	ADNI3 Year 1 Visit
Y2	ADNI3 Year 2 Visit
Y3	ADNI3 Year 3 Visit
Y4	ADNI3 Year 4 Visit
Y5	ADNI3 Year 5 Visit
Y6	ADNI3 Year 6 Visit

All Biomarker Samples (UPENN): plasma, serum and CSF

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

Subject ID #: _____ S _____ Date ____/____/____ Time ____:____ Gender: M or F Biomarkers ADNI3 Red Cap BLD SERUM	Subject ID #: _____ S _____ Date ____/____/____ Time ____:____ Gender: M or F Biomarkers ADNI3 Lavender Cap BLD PLASMA	Subject ID #: _____ S _____ Date ____/____/____ Time ____:____ Gender: M or F Biomarkers ADNI3 CSF License Plate Number:_____
--	--	---

SAMPLE TRACKING

Important to double check that all samples are sent to the appropriate laboratory:

- All genetic samples (Genetic, Cell Immortalization, RNA, Buffy coat, PBMC, and RBC) are shipped to **NCRAD**
- All biomarker samples (plasma, serum, and CSF) are shipped to **UPENN**

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

The Genetic sample collection worksheet collects data related to Genetic, Cell Immortalization, RNA, Buffy coat, PBMC, and RBC. Biomarker sample collection worksheet collects data related to plasma, serum, and CSF. Both worksheets 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 ADNI3 web portal must be completed on the day of each visit.

NOTIFY NCRAD THE DAY THE SAMPLES ARE SHIPPED. NCRAD WILL NOT BE ABLE TO ACCEPT ANY SHIPMENTS ON SATURDAY OR SUNDAY.

UNDER NO CIRCUMSTANCES CAN PBMC SAMPLES BE DRAWN AND SHIPPED ON A FRIDAY.

GENETIC SAMPLES (NCRAD): GENETIC, CELL IMMORTALIZATION, RNA, BUFFY COAT, PBMC, AND RBC

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

NCRAD SHIPPING ADDRESS:

**Kelley Faber
National Cell Repository for AD
980 W Walnut St R3 C102
Indianapolis, IN 46202**

NCRAD HELPDESK:

**alzstudy@iu.edu
Tel: (800) 526-2839
Fax: (317) 278-1100**

BIOMARKER SAMPLES (UPENN): PLASMA, SERUM AND CSF

UPENN SHIPPING ADDRESS:

**ADNI BIOMARKER CORE LABORATORY
7 Maloney South
University of Pennsylvania Medical Center
3400 Spruce Street
Philadelphia, PA 19104**

UPENN HELPDESK

**Email: ADNI@uphs.upenn.edu
Fax: 215-349-5092**

Sample Quality Checks

In addition to being tracked online in the ADNI3 web portal, the condition and number of samples received will be tracked by the Biomarker Core 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. Please ensure the reason why the sample was not obtained is provided.
 - Sample Collection: Biomarker Samples serum/plasma and CSF
 - Sample Collection: Genetic Samples - RNA, Cell immortalization, Buffy coat, PBMC, and RBC

Chapter 20

Clinical Laboratory Samples at Screening (URMC)

URMC – Safety Labs (Fasting Not Required)

URMC will provide screening laboratory kits for the ADNI3 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 per the Study Schedule. The URMC Laboratory Manual is posted to the study folder in Box. For ADNI3, safety labs **DO NOT** require that the subject fast prior to lab collection.

SAFETY CLINICAL LAB KIT CONTAINS:

- Tubes (expiration date noted on outside of box)
 - 3.5 mL yellow top tube for chemistry panel - TSH
 - 4.0 mL purple top tube for hematology & differential panel
 - 2 mL red top tube for vitamin B12
 - 10 mL orange top tube for urine panel
 - 2 x 5 mL brown top tubes for shipment of blood sample for chemistry panel and shipment of vitamin B12 sample
- Requisition (bar coded). Use black or blue ink, and send white copy to URMC
- Labels (bar coded). USE ONLY THE LABELS WITH THE REQUISITION, or samples could be lost
- An extra barcode label is included in case one is misplaced or lost
- Vacutainer holder with needle guard
- Needle and holder
- Diff-safe (Be sure to REMOVE this from the tube before shipping)
- Slides with blue slide mailer
- Pipettes
- Test tube sleeve
- Absorbent material
- Bag with sleeve for requisition
- Gel-pack (Do not put specimens into the gel; wrap the whole gel pack around the specimens)

YOU WILL NEED TO PROVIDE:

- | | |
|--------------|------------------------|
| ➤ Tourniquet | ➤ Dry ice |
| ➤ Bandage | ➤ Gauze |
| ➤ Alcohol | ➤ Urine collection cup |

REQUISITIONS:

- Use black or blue ink, as URM uses other colors for coding
- Do not mix up the bar-coded labels, as these are linked to a specific requisition form
- Fill in all the blanks
- Put the white original copy of the requisition with the ambient specimen. If only a frozen specimen is sent, put the white original with the frozen specimen. Place the requisition in the sleeve of the sample bag
- Use military, or 24-hour clock
- Dates use the international convention: DD_MMM_YYYY. (Example: 01_JAN_2011)

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

Clinical Laboratory Reports

URM will fax 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 URM
- 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 URM. 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 URM.

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 URMCLaboratory 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: LABSRSS@URMC.ROCHESTER.EDU**

Chapter 21

Genetic Sample Collection: Genetics, PBMC, Cell Immortalization, RNA and Buffy Coat (NCRAD)

For reference, you can visit the NCRAD website for guidance on genetic sample collection. Please visit www.NCRAD.org and 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.

Sample Collection for Genetics/DNA Testing

Blood samples will be collected for Genetics at the Baseline Visit for Newly Enrolled Participants and at Initial Visit for Rollover Participants.

- Genomic/Genetic studies will be done by using the single 10 mL EDTA (lavender top) tube of whole blood will be collected at Baseline/Initial Visit
- ApoE genotyping will only be done for the Newly Enrolled participants, using the same 10 mL whole blood sample.

Begin by confirming the subject consented to DNA testing and sample storage per their informed consent. **Next**, complete the information on the Genetic label for the EDTA (lavender top) tube.

- Ensure all fields on the label are complete, using a ballpoint pen or permanent marker.
- Securely place the label onto the 10 mL EDTA (lavender top) tube BEFORE the blood draw.

BLOOD COLLECTION:

Lavender top 1x 10 mL EDTA tube of whole blood will be collected; gently mix by inversion, 10 - 12 times, to assure that the EDTA anticoagulant is well-mixed with the whole blood sample.

Sample Collection for PBMC

Whole Blood Collection for extraction of PBMC: Sodium Heparin (green top) Blood Collection Tube (10 ml). One green top tube is collected at Baseline for all Newly Enrolled Participants after passing screening criteria for this study, and at Initial Visit for Rollover Participants; longitudinal collection of PBMC is not required. In other words, PBMC will not be collected in Ongoing Annual Visits.

BLOOD COLLECTION:

- Place completed Genetic tube label on the Sodium Heparin (green top) Blood Collection Tube (10 ml).
- Using a blood collection set and a holder, collect blood into the Sodium Heparin (Green-Top) Blood Collection Tube (10 ml) using your institution's recommended procedure for standard venipuncture technique

- 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.
- **CRITICAL STEP:** Immediately after blood collection, gently invert/mix (180-degree turns) each tube 8-10 times.
- Ship the unprocessed tube ambient to NCRAD the day of the participant visit.

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

Sample Collection for Cell Immortalization

Blood samples will be collected for Cell Immortalization at Baseline Visit for all Newly Enrolled Participants after passing screening criteria for this study.

Begin by confirming the participant consented to DNA testing and sample storage per their informed consent. **Next**, complete the information on the genetic label for each of the ACD-A (yellow top) tubes. Ensure all fields on the label are complete, using a ballpoint pen or permanent marker. Securely place the label onto each ACD-A (yellow top) tube before the blood draw. Whole blood will be collected in two 8.5 mL ACD-A (yellow top) tubes.

BLOOD COLLECTION:

ACD-A 1 x 8.5 mL ACD-A (yellow top) tubes of whole blood will be collected; gently mix by inversion, 6-10 times, to assure complete mixing of the blood sample with the anticoagulant Acid Citrate Dextrose.

Sample Collection for RNA

In order to measure gene expression across time, an RNA sample will be collected at Baseline and Ongoing Annual Visits across all Newly Enrolled Participants. Rollover Participants will have a RNA sample collected at the Initial Visit and then Ongoing at annual follow-up visits. Whole blood will be collected in three 2.5 mL PAXgene Blood RNA tubes.

Begin by confirming the subject consented to RNA testing and sample storage per their informed consent. **Next**, complete the information on the Genetic label for each of the PAXgene Blood RNA tubes. Ensure all fields on the label are complete, using a ballpoint pen or permanent marker. Securely place the label onto each tube before the blood draw.

BLOOD COLLECTION:

PAXgene Blood RNA kits are provided by the ATRI.

- Ensure that the PAXgene Blood RNA tube is at room temperature prior to use.
- 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)

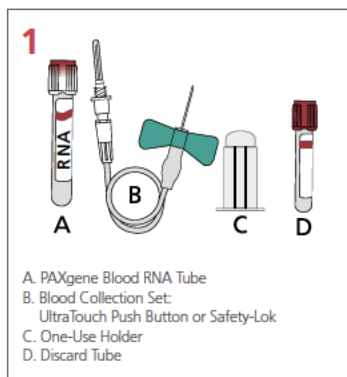
by ATRI)

PAXGENE TUBE SHOULD BE THE LAST TUBE DRAWN AND AFTER A SERUM TUBE. IF SERUM IS NOT DRAWN, THEN USE THE “DISCHARGE TUBE”.

- 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.
- Hold the PAXgene Blood RNA tube vertically, below the blood donor’s arm, during blood collection.
- 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.
- Gently invert the PAXgene Blood RNA tube 8 to 10 times.
- Store the PAXgene Blood RNA tube upright at room temperature.

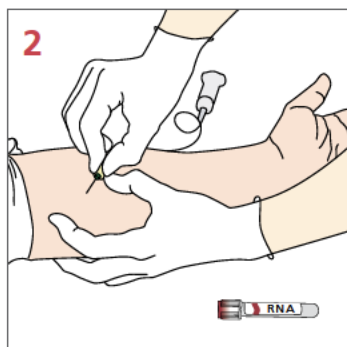
How to Collect Blood Using the PAXgene® Blood RNA Tube

For Molecular Diagnostic Testing



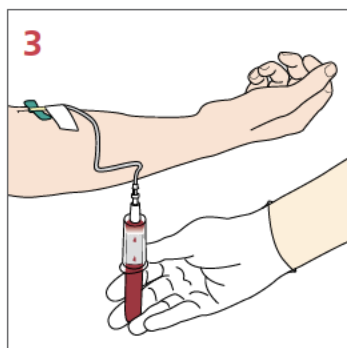
Required Items:

- 1a. Ensure that the PAXgene Blood RNA Tube (A) is at room temperature (18°C–25°C) prior to use and is properly labeled with patient identification.
- 1b. 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” (D) 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.



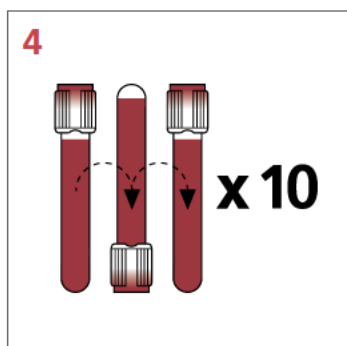
Venipuncture:

2. Using a blood collection set such as the BD Vacutainer UltraTouch Push Button or BD Vacutainer Safety-Lok Blood Collection Set (B) and the One-Use Holder (C), perform venipuncture using your institution’s recommended procedure for standard venipuncture.



Blood Collection:

- 3a. Hold the PAXgene Blood RNA Tube vertically, below the blood donor’s arm, during blood collection.
- 3b. 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.



After Blood Collection:

- 4a. Gently invert the PAXgene Blood RNA Tube 8 to 10 times.
- 4b. Store the PAXgene Blood RNA Tube upright at room temperature (18°C–25°C) for a minimum of 2 hours and a maximum of 72 hours before processing or transferring to refrigerator (2–8°C) or freezer (–20°C).*

Before Blood Collection



After Blood Collection



Ref #	Product Description
762165	PAXgene® Blood RNA Tube
367365	BD Vacutainer® UltraTouch™ Push Button Blood Collection Set
367281 (US) 367286 (CE)	BD Vacutainer Safety-Lok™ Blood Collection Set
364815	BD Vacutainer One-Use Holder
367812 (US) 368975 (CE)	BD Vacutainer Plus Plastic Serum Tube (Discard Tube)

BD Customer Service / Orders:
888.237.2762 (North America)

www.PreAnalytiX.com



*Refer to PAXgene Blood RNA Tube product circular.
PAXgene and PreAnalytiX are registered trademarks of PreAnalytiX, Hombrechtikon, CH ©2016 PreAnalytiX GmbH
All other trademarks are property of Becton, Dickinson and Company.
06/16 VS9339

PreAnalytiX GmbH, Feldbachstrasse, 8634 Hombrechtikon, CH



A QIAGEN / BD Company

Preparing Genetic, PBMC, Cell Immortalization, & RNA sample shipment to NCRAD

COMPLETION OF SAMPLE COLLECTION - GENETIC WORKSHEET:

Ensure all fields on the Genetic Sample Collection worksheet: DNA, PBMC, Cell Immortalization, RNA, Buffy Coat, and RBC, located in the worksheet packet is complete. Note that there is one worksheet that covers the data required for the genetic, PBMC, cell immortalization, RNA, Buffy Coat, and RBC sample collection. The name of the individual who packaged and shipped the blood specimen, along with their phone number and email needs to be listed on the worksheet. Additionally, please list in the comments section of the worksheet any issues that occurred during the blood draw, with packaging or any temperature excursions.

TEMPERATURE & SHIPPING REQUIREMENTS:

NCRAD SHIPPING ADDRESS:

Kelley Faber
National Cell Repository for AD
980W Walnut St R3C102
Indianapolis, IN 46202

NCRAD HELPDESK:

alzstudy@iu.edu
Tel: (800) 526-2839
Fax: (317) 278-1100

NCRAD sample	Shipping temperature	Shipping timeframe	Allowed days for shipping	Friday blood draw allowed? (only in instances where blood draw on Friday is unavoidable)
Genetic	Ambient - never refrigerate	Samples should be received by NCRAD within 24 hours of collection	Monday - Thursday; NCRAD cannot accept any shipments on Saturday or Sunday	Yes; EDTA (lavender top) tube for genetics sample needs to be stored at room temperature (20-25 degrees Celsius) from Friday until Monday and must be shipped out no later than Monday to NCRAD
PBMC	Ambient - never refrigerate	Once drawn, sodium heparin tubes must be shipped the day of collection. This is to ensure the specimen has the most viable cells available at extraction	Monday - Thursday; NCRAD cannot accept any shipments on Saturday or Sunday	NO Friday shipments! Not an option. If there is a baseline / initial visit that occurs on Friday, please ensure that the participant is brought back on Monday - Thursday
Cell Immort.	Ambient - never refrigerate	Samples should be received by NCRAD within 24 hours of collection	Monday - Thursday; NCRAD cannot accept any shipments on Saturday or Sunday	Yes; ACD-A (yellow top) tube for cell immortalization sample needs to be stored at room temperature (20-25 degrees Celsius) from Friday until Monday and must be shipped out no later than Monday to NCRAD
RNA	Ambient (unless drawn on Friday)	Samples must be received by NCRAD within 24 hours of collection	Monday - Thursday; NCRAD cannot accept any shipments on Saturday or Sunday	Yes; PAXgene Blood RNA tubes will need to be held at room temp for 2 hours and then placed in -20 or -80 Celsius freezer over the weekend and then shipped frozen (on dry ice)

NOTIFYING NCRAD:

The day the blood sample is shipped to NCRAD you must FIRST fax a copy of the completed Genetic Sample Collection worksheet to (317) 278-1100 or email a copy of the completed worksheet to NCRAD at alzstudy@iu.edu.

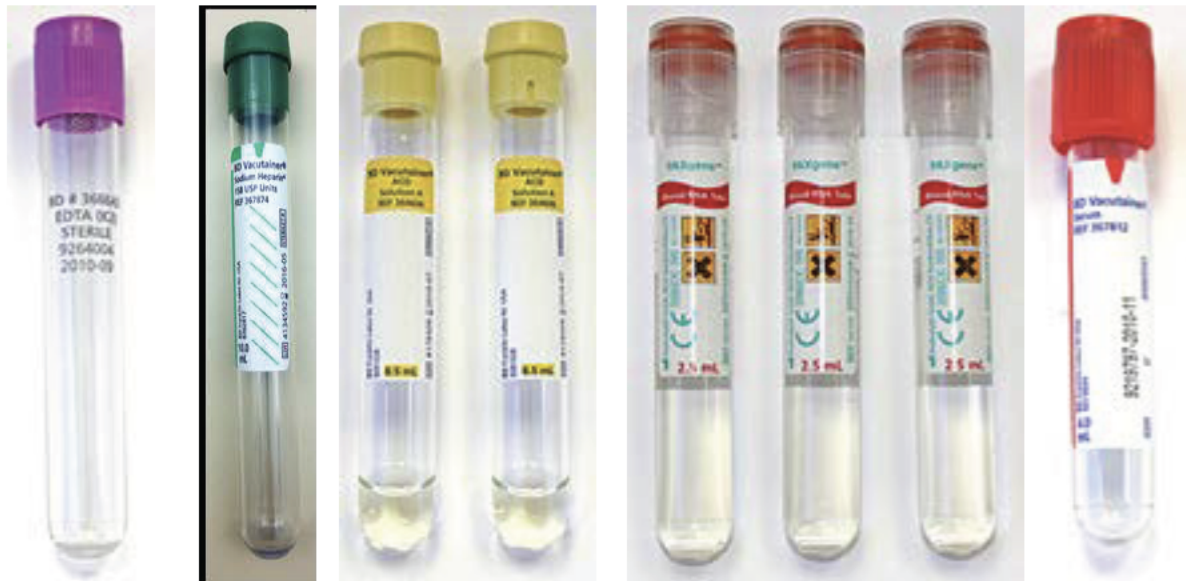
ADDITIONALLY, BE SURE TO INCLUDE A COPY OF THE GENETIC SAMPLES WORKSHEET WITH THE SHIPMENT

SAMPLE TRACKING:

Complete the Genetic Sample Collection electronic case report form (eCRF) located in the ADNI3 web portal immediately after sample collection. Remember to include any issues that occurred during the sample collection with packaging or temperature excursions in the visit comments section of the eCRF.

NCRAD Packaging & Shipping (Genetics, PBMC, Cell Immortalization, & RNA)

TUBE TYPES



Genetics	PBMC	Cell Immortalization	RNA (tilde line indicates the fill line)	Discharge <i>(only use if RNA is drawn first, then discharge)</i>
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Samples are shipped by Federal Express – Priority Overnight (Monday – Thursday) at ambient temperature 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, please complete the online ADNI3 Supply Order Form

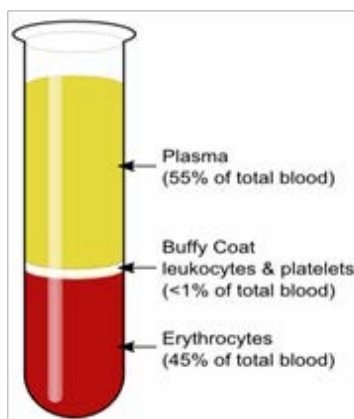
- Ensure that the NCRAD/Genetic label has been attach to each tube prior to collecting sample. Please use a ballpoint pen or permanent marker
- Genetics samples shipping supplies include:
 - 1 medium 95kPa canister,
 - Biohazard symbol label
 - Aquí-Pak segmented absorbent pouch
 - Biological Substance Category B label
 - Cushioning material (bubble bag)
 - Shipping box
 - List of contents card
- Insert all tubes into tube sleeves
- **NEVER INSERT DISCHARGE TUBE INTO TUBE SLEEVE.** If used, the discharge tube should be discarded
- Carefully roll up sleeve, insert into canister and wrap **OUTSIDE** canister in bubble wrap
- Fill out the list of contents card
- Place card and canister into shipping box
- Fill out NCRAD FedEx Air-bills I and attach to box

MAKE SURE A COPY OF THE SAMPLES COLLECTION – GENETICS WORKSHEET IS INCLUDED WITH THE SHIPMENT

Buffy Coat & RBC Sample Extraction Sent to NCRAD

Buffy coat extraction should follow each biomarker 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.

The buffy coat is the thin layer in between the red blood cells and plasma after centrifugation of the lavender-top tubes used for plasma sample collection during the biomarker lab procedures.



BUFFY COAT EXTRACTION

- Extract the buffy coat from the 2 lavender-top EDTA tubes that are used for the biomarker lab blood draw.
- After the lavender-top EDTA tubes have been centrifuged at 3000 rpm transfer the plasma into the 13mL plastic transfer tube.
- Using sterile gloves and a sterile pipette, extract the buffy coat from one of the lavender-top EDTA tubes and aliquot it into one of the 2mL cryogenic vials.
- Repeat this process for the second lavender-top EDTA tube and the remaining, empty 2mL cryogenic vial.

IT IS VERY NORMAL TO 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.

- Complete the information on the genetic label. Ensure all fields on the label are complete using a ballpoint pen or permanent marker. Securely place the label onto each cryogenic vial.
- The label will be larger than the vial and should be dovetailed rather than wrapped around the tube in order to view all information on the label

RED BLOOD CELL (RBC) EXTRACTION

RBC extraction should follow buffy coat extraction. For all participant types, RBC pellet will be saved at Baseline for all Newly Enrolled Participants after passing screening criteria for this study, and at Initial Visit for Rollover participants; longitudinal collection of RBCs is not required.

- Complete the information on the genetic label. Ensure all fields on the label are complete using a ballpoint pen or permanent marker. Securely place the label onto each cryogenic vial.
- For the 2ml cryovial, the label will be larger than the vial and should be dovetailed rather than wrapped around the tube in order to view all information on the label.

Extract the RBC pellet from the EDTA tube after the buffy coat has been extracted. Using a STERILE pipette, carefully transfer 1ml of the RBC pellet into 1, 2.0ml aliquot tube with a blue cap. The remaining 2-4ml of the cell pellet will be transferred into a 4.0 ml transfer tube with a blue cap.

Preparing Buffy Coat & RBC Sample Shipment to NCRAD

COMPLETION OF SAMPLE COLLECTION - GENETIC WORKSHEET:

Ensure all fields on the Genetic Sample Collection worksheet: DNA, PBMC, Cell Immortalization, RNA, Buffy Coat, and RBC, located in the worksheet packet is complete. Note that there is one worksheet that covers the data required for the genetic, PBMC, cell immortalization, RNA, Buffy Coat, and RBC sample collection. The name of the individual who packaged and shipped the blood specimen, along with their phone number and email needs to

be listed on the worksheet. Additionally, please list in the comments section of the worksheet any issues that occurred during the blood draw, with packaging or any temperature excursions.

TEMPERATURE & SHIPPING REQUIREMENTS:

NCRAD SHIPPING ADDRESS:

**Kelley Faber
National Cell Repository for AD
980 W Walnut St R3 C102
Indianapolis, IN 46202**

NCRAD HELPDESK:

**alzstudy@iu.edu
Tel: (800) 526-2839
Fax: (317) 278-1100**

NCRAD Sample	Shipping temperature	Shipping timeframe	Allowed days for shipping	Friday blood draw allowed? (only in instances where blood draw on Friday is unavoidable)
Buffy Coat	Ambient (unless drawn on Friday)	Samples must be received by NCRAD within 24 hours of collection	Monday - Wednesday; NCRAD cannot accept any shipments on Saturday or Sunday	Yes; place cryogenic buffy coat vials in -20 to -80 Celsius freezer over the weekend and then ship frozen (on dry ice)
RBC	Frozen - freeze immediately by transferring to a -80 Celsius freezer. If samples cannot be immediately transferred to a -80 Celsius freezer, prepare enough dry ice for immediate freezing	Store samples in -80 Celsius freezer until ready to ship	NCRAD prefers Monday - Wednesday to prevent any issue with FedEx delays	Can be drawn on Fridays, stored frozen over the weekend and shipped Monday - Wednesday

NOTIFYING NCRAD:

The day the buffy coat and RBC is extracted and shipped to NCRAD you must FIRST fax a copy of the completed Sample Collection: Genetic samples to (317) 278-1100 or email a copy of the completed worksheet to NCRAD at alzstudy@iu.edu.

ADDITIONALLY, BE SURE TO INCLUDE A COPY OF THIS WORKSHEET WITH THE SHIPMENT

SAMPLE TRACKING:

Complete the Genetic Sample Collection eCRF located in the ADNI3 web portal immediately after the visit. Remember to include any issues that occurred during the extraction of the buffy coat, with packaging or temperature excursions in the visit comments section of the eCRF.

BUFFY COAT EXTRACTED FROM EACH OF THE LAVENDER-TOP BIOMARKER TUBES MUST BE PLACED IN SEPARATE CRYOGENIC VIALS, FOR A TOTAL OF 2 CRYOGENIC VIALS BEING SHIPPED TO NCRAD.

DEPENDING ON THE NUMBER OF SPECIMEN TUBES AT A GIVEN VISIT BEING SHIPPED TO NCRAD, THE BUFFY COAT VIALS MAY NOT FIT IN THE EXISTING AMBIENT SHIPPER USED FOR DNA AND RNA (AS THE SHIPPER HOLDS UP TO 6 SPECIMEN TUBES). IN SUCH CASES A SMALLER AMBIENT SHIPPER IS BEING PROVIDED BY THE ATRI TO SHIP THE BUFFY COAT TO NCRAD.

NCRAD Packaging & Shipping (Buffy Coat & RBC)

BUFFY COAT

- ➔ Using sterile procedures (gloves and STERILE pipette) extract Buffy Coat layer from the lavender-top EDTA tubes used for plasma biomarker sample collection



- ➔ Fill out NCRAD label and attach to cryogenic vials. Ensure label is dovetailed to not obscure any information on the label. Please use a ballpoint pen or permanent marker
- ➔ Buffy Coat sample shipping supplies include:
 - 1 small 95kPa canister,
 - Biohazard symbol label
 - Aquipak segmented absorbent pouch
 - Biological Substance Category B label
 - Cushioning material (bubble bag)
 - Shipping box
 - List of contents card
- ➔ Insert the 2 mL cryogenic vials into tube sleeve
- ➔ Carefully roll up sleeve, insert into canister and wrap **OUTSIDE** canister in bubble wrap
- ➔ Fill out the list of contents card
- ➔ Place card and canister into shipping box
- ➔ Fill out NCRAD FedEx Air-bill and attach to box

The buffy coats can be tricky to obtain so we have some additional resources to offer: https://www.ncrad.org/resource_adni2.html. Please follow the link to the page and review

the “buffy coat instructions” tab. In addition, we have videos for other studies that show extracting a buffy coat but the plasma extraction instructions differ from ADNI. Please only use this video for watching the buffy coat process and discard the plasma related details: https://www.ncrad.org/resource_artfl_lefftds.html.

RED BLOOD CELLS (RBC)

- Using sterile procedures (gloves and STERILE pipette) extract RBCs (after Buffy coat extraction) from the lavender-top EDTA tubes used for plasma biomarker sample collection
- Fill out NCRAD label and attach to cryogenic vials. Ensure label is dovetailed to not obscure any information on the label. Please use a ballpoint pen or permanent marker
- Place the 1, 2.0ml aliquot tube with a blue cap, and the 4.0 ml transfer tube with a blue cap immediately freeze by transferring to a -80 Celsius freezer. If samples cannot be immediately transferred to a -80 Celsius freezer, prepare enough dry ice for immediate freezing
- Place blue cap cryovials into segmented absorbent sleeve
- Place segmented absorbent sleeve into 95kPa shipping bag. Place into bubble wrap bag
- Place bag directly onto dry ice in Styrofoam shipper and fill rest of box with dry ice
- Cover Styrofoam box and place into cardboard box
- 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 SAMPLES COLLECTION – GENETICS WORKSHEET IS INCLUDED WITH THE SHIPMENT

Chapter 22

Biomaker Sample Collection: Plasma & Serum (UPENN)

Plasma and serum for biomarkers will be collected at Baseline / Initial Visits and Ongoing In-clinic follow-up visits for all participant types (New Participants and Rollovers).

FASTING OVERNIGHT (MINIMUM 6 HOURS) IS REQUIRED FOR PLASMA, SERUM, AND CSF SAMPLE COLLECTION

- ➔ Only water is permitted until blood draws and the lumbar puncture are completed.

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

Next, complete the information on the 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 serum and lavender top tubes for plasma) PRIOR to transfer of biomarker samples.

THE BIOMARKER 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 for Serum and Plasma:

TUBES 1 AND 2: 10 ML PLAIN RED-TOP TUBES FOR SERUM SAMPLES

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. Estimate blood volume and record on the ADNI Biomarker Samples form.
4. Allow the blood to clot for 30 minutes at room temperature in a vertical position.
5. Centrifuge the tube at room temperature within one (1) hour of collection. Spin for 15 minutes using the Sorvall T 6000D Centrifuge (rotor H-1000B swinging bucket rotor) at 3000 rpm (1500 rcf) with the brake on, or in another centrifuge at a comparable rcf.
6. 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 SER and place this on one 13 mL plastic transfer tube (red screw cap) standing in a tube rack in the vertical position.

IMPORTANT TO USE THE CORRECT SERUM UPENN LABEL AND SHIP ALL SERUM SAMPLES TO UPENN

7. Using a STERILE pipette carefully transfer serum from each of the two red-top tubes into the bar code-labeled 13 mL plastic transfer tube, then firmly cap with the red screw cap.

8. After the serum has been transferred to the plastic bar-code labeled tube and capped, place the red screw-capped BLD SER-labeled tube upright in dry ice and allow to completely freeze.

TUBES 3 AND 4: 10 ML LAVENDER-TOP TUBES FOR PLASMA SAMPLES

1. Write the Subject Identification Number on the side of the tubes prior to drawing blood.
2. Collect blood until each tube is full; gently mix by inversion, 10-12 times.
3. Estimate blood volume and record on the ADNI Biomarker Samples form.
4. Centrifuge the tube at room temperature within one (1) hour of collection. Spin for 15 minutes using the Sorvall T 6000D Centrifuge (rotor H-1000B swinging bucket rotor) at 3000 rpm (1500 rcf) with the brake on, or in another centrifuge and rotor at a comparable rcf.
5. 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 EDT PL and place this on one 13 mL plastic transfer tube (lavender top screw cap) standing in a tube rack in the vertical position.

**IMPORTANT TO USE THE CORRECT PLASMA UPENN LABEL AND SHIP ALL
PLASMA SAMPLES TO UPENN**

6. Using a STERILE pipette carefully transfer plasma from each of the two lavender- top blood tubes into the bar code-labeled 13 mL plastic transfer tube, and firmly cap with the lavender screw cap.
7. After the plasma has been transferred to the plastic labeled tube and capped, place the lavender screw-capped BLD EDT PL-labeled tube upright in dry ice and allow to completely freeze.

COMPLETION OF SAMPLE COLLECTION: BIOMARKER SAMPLES – SERUM / PLASMA WORKSHEET

Ensure all fields on the Biomarker Samples worksheet (serum/plasma) 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, please list in the comments section of the worksheet any issues that occurred during the blood draw, with packaging or any temperature excursions.

TEMPERATURE REQUIREMENTS:

Plasma and serum samples should be placed on dry ice immediately and allowed to freeze and shipped on dry ice.

NOTIFYING UPENN:

The day the serum and plasma is collected and shipped to UPENN, you must FIRST fax a copy of the completed Biomarker Sample Collection: Plasma, Serum, CSF to (317) 278-1100 or email a copy of the completed worksheet to UPENN at ADNI@uphs.upenn.edu.

SAMPLE TRACKING:

Complete the Biomarker Sample (serum/plasma) eCRF located in the ADNI3 web portal immediately after sample collection. Remember to include any issues that occurred during the sample collection, with packaging or temperature excursions in the visit comments section of the eCRF.

**MAKE SURE A COPY OF THE BIOMARKER SAMPLES COLLECTION –
SERUM/PLASMA WORKSHEET IS INCLUDED WITH THE SHIPMENT**

UPENN Packaging & Shipping (Plasma, Serum)

Since all biomarker samples (serum, plasma, and CSF) are shipped to UPENN frozen on dry ice, please refer to CSF Chapter for plasma/serum shipping and packaging Instructions (next chapter).

SHIPPING:

- ➔ FedEx all biomarker biofluid samples the **SAME DAY on DRY ICE** by Federal Express,
- ➔ Priority Overnight shipping (Monday-Thursday).
- ➔ For those instances in which a Friday study visit is necessary, CSF, plasma and serum samples should be placed in a -80 degree Celsius freezer until Monday and shipped on dry ice to UPENN. If a -80 degree Celsius freezer is not available, a -20 degree Celsius freezer is acceptable.
- ➔ Pre-Paid Federal Express Air-bills and frozen shippers will be provided by ATRI. If your site needs additional UPENN Air-bills or frozen shippers, please complete the ADNI3 online Supply Order Form.
- ➔ Complete the Biomarker Samples Online Form before shipping samples.
- ➔ Print a pdf of the completed form and include a copy with the shipment.

UPENN SHIPPING ADDRESS:

ADNI BIOMARKER CORE LABORATORY
7 Maloney South
University of Pennsylvania Medical Center
3400 Spruce Street
Philadelphia, PA 19104

UPENN HELPDESK

Email: ADNI@uphs.upenn.edu
Fax: 215-349-5092

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

Chapter 23

Cerebral Spinal Fluid (CSF) Collection

General Guidelines:

- Begin by confirming participant consented to lumbar puncture (LP) before scheduling the procedure and again prior to performing procedure.
- For all participants, CSF will be collected at Baseline / Initial Visit and every two years thereafter.
- CSF samples should be collected in the morning before breakfast and after an overnight fast.
- Only water is permitted until blood draws and the lumbar puncture are completed.
- If LP and PET scan are done on the same day. LP should be completed prior to the PET scan; otherwise there should be at least 12 hours between LP and PET scan.
- Do NOT use any extension tubing due to the tendency of manufactured plastic tubing to bind beta amyloid peptides and other important AD biomarkers.
- If LP was attempted but unsuccessful in obtaining CSF, a second attempt under fluoroscopy (if deemed appropriate by site clinician) is allowed.
- LP under fluoroscopy is permitted, if needed. Site personnel should advise the subject that use of fluoroscopy (x-rays) involves exposure to radiation.
- Subjects taking an anti-platelet agent (e.g. aspirin) may, at the discretion of the site clinician, be discontinued from that agent for a period of time prior to lumbar puncture and/or continue off agent for a period of time post LP. Participants who are taking anticoagulants (e.g. warfarin (Coumadin) and/or dabigatran (Pradaxa)) may not undergo an LP and are not suitable to participate in this substudy.
- Each study participant or a person designated to speak for them will be contacted by phone one day after the LP to confirm participant well-being and to query about any adverse events.

PREVENTION OF POST-LUMBAR PUNCTURE HEADACHE:

- Use of a Sprotte 22g atraumatic spinal needle using gravity drip method and careful technique are optimal for reducing post-LP headache risk.
- Having the subject refrain from exertion (e.g. exercise, housework, gardening, lifting, sexual activity or any other strenuous activities) for 24 hours after the LP is helpful.
- Increasing fluid intake for 24 hours after LP is helpful.

MILD-TO-MODERATE HEADACHE AFTER A LUMBAR PUNCTURE:

Mild to moderate headache following lumbar puncture usually resolves within 3-4 days with the above treatment. If the headache becomes severe, posturally sensitive (relieved by supine posture), or is accompanied by nausea, vomiting, tinnitus and/or visual disturbances, it will likely require additional treatment with an epidural blood patch. This usually relieves the headache immediately. An anesthesiologist typically performs the epidural blood patch.

TREATMENT OF MILD TO MODERATE HEADACHE:

- Limit physical activity as much as possible.
- Oral fluids and caffeine are helpful. Drinking a can of Mountain Dew soft drink (for example) is preferable to coffee (which has some diuretic activity)
- Tylenol should be used for symptomatic relief. If a subject cannot tolerate Tylenol, ibuprofen should be used. Avoid aspirin. If these do not relieve the headache, Tylenol with codeine or equivalent could be considered.

SEVERE HEADACHE AFTER A LUMBAR PUNCTURE:

Severe headache which may be accompanied by nausea, vomiting, tinnitus, and/or visual disturbances and which is relieved by supine posture requires epidural blood patch to provide rapid relief. This type of headache most commonly occurs on the morning following LP, when the person arises from bed. Posturally-sensitive severe post-LP headache can last as long as a week even with bedrest and analgesics if not treated with epidural blood patch.

IT IS HIGHLY RECOMMENDED THAT EACH SITE IDENTIFY AN ANESTHESIOLOGIST AHEAD OF TIME WHO IS AGREEABLE TO PERFORMING AN EPIDURAL BLOOD PATCH FOR ANY SUBJECT WHO EXPERIENCES SEVERE POST LUMBAR PUNCTURE HEADACHE

TIPS FOR CLINICIANS PERFORMING LUMBAR PUNCTURE: OPTIMIZING PATIENT COMFORT AND MINIMIZING RISK OF ADVERSE EVENTS:

- Talk the patient through the procedure - no surprises.
- Use adequate local anesthesia. Use the 25g 5/8" needle and inject lidocaine to raise a skin wheal. Then inject lidocaine using the pattern of a square - first the center and then to all 4 corners. Advance the needle approximately 1/2 its length in two stages. Then change to the longer 1 1/2" 25g needle. Again, use the same pattern - be sure to draw the needle back out nearly all the way out to change direction. Advance the needle approximately 1/2" per "pass". Be sure to draw back on the syringe before injecting every single time to make sure you are not in a blood vessel. The subject may feel pressure but should feel no sharp pain from the introducer or spinal needle if adequate local anesthesia is used.
- If the subject is thin, do not insert the deep infiltration needle. Use only about 2/3 of the length (to prevent entering the subarachnoid space with anything other than the Sprotte spinal needle).
- Be sure to give post-LP care instructions verbally to subject.

CSF Collection Supplies

Gravity drip using a 22g Sprotte needle is the recommended method for CSF collection **with no extension tubing**, though sites may prefer the suction method, and/or, a differing

needle.

Lumbar Puncture Materials provided by ATRI:

Universal (VWR) Medical Lumbar Puncture Trays (all sterile components):

- 1 Tray
- 1 Needle 22G
- 1 Needle 24G Sprotte
- 1 Needle 25G
- 1 RX Lidocaine 1%
- 2 Tubes – 14ml
- 2 Tubes – cryovials
- 1 Drape
- 2 Label
- 3 Gauze
- 2 Blunt filter needles
- 2 3ML Luer-lok Syringes
- 1 Wrap
- 5 Syringes 5 ml
- 1 Needle 20G
- 1 Needle stick pad cube
- 1 Insert
- 3 Pipette
- 2 Towels
- 1 Tray 3 (compartment SM molded)
- 1 Bandage
- 3 Sponges
- 2 25G x 5/8” Safety Needles
- 1 Ampule Cracker

Each LP tray will have a Ziploc bag attached containing:

- 1 Absorbent Sleeve
- 1 Bubble Wrap Bag
- 95kPa biohazard shipping transport bag
- 2 Clear 13cc Sarstedt Polypropylene tubes

The following “stock” items will also be used and are NOT provided by the ATRI:

- Sterile gloves in correct size for person performing the LP (one plus extras for backup)
- Blue pad (one plus extras for backup)
- Bottle of Betadine solution (not Betadine scrub)
- Individually wrapped alcohol wipes
- Sharps container
- *Attached needle is used for drawing up lidocaine, but NOT for injecting it*
- Sterile 4 x 4 gauze pads (extra)
- Extra adhesive bandages (Band-Aid)
- Clean washcloths and towels
- Dry ice

THE BELOW SUPPLY LIST FOR LUMBAR PUNCTURE SUPPLIES FOR ARE PROVIDED BY THE ATRI AND CAN BE ORDERED BY FILLING OUT THE ONLINE SUPPLY ORDER FORM

SUMMARY OF CSF SUPPLIES:

Item	Purpose	QTY
US SITES		
LP Trays by VWR	CSF collection by gravity/drip or suction/syringe	1
Falcon 14 mL sterile polypropylene tubes	Lumbar Puncture: Gravity/Drip Method. Shipping of CSF to UPENN Biomarker Core	2 (if requested)
CANADIAN SITES		
LP Trays by Carefusion	CSF collection by gravity/drip or suction/syringe	1
22g Sprotte Needle w/Introducer by Pajunk	For sites that request this type of needle for LP/CSF collection by gravity/drip. Recommended by ATRI	1 (if requested)
24g Sprotte Needle w/Introducer by Pajunk	For sites that request this type of needle for LP/CSF collection by suction.	1 (if requested)
Sterile Syringe, 5cc , Norm-ject Henke Sass Wolf/Air-Tite Products	Lumbar Puncture: Suction Method	5 (if requested)
Lidocaine Needle by BD Vacutainer	Administration of Lidocaine	1
Externally threaded 2 mL Cryogenic Vial by Thermo Scientific	Shipping of CSF to local labs	2
Falcon 14 mL sterile polypropylene tubes	Lumbar Puncture: Gravity/Drip Method. Shipping of CSF to UPENN Biomarker Core	2 (if requested)
Samco Sterile pipette	Aliquot 2ml of CSF to cryogenic vials for local lab ONLY	3

COMPLETION OF CSF LABEL & BIOMARKER SAMPLE WORKSHEET

Complete the information on the UPENN label for CSF collection. Ensure all fields on the CSF label are complete using a ball-point pen or permanent marker and place each of these on two 13 mL polypropylene transfer tubes (clear screw cap) PRIOR to transfer of CSF samples.

Ensure all fields on the biomarker samples worksheet located in the visit packet are complete. Ensure the Bar Code License Plate and FedEx tracking number are included on the worksheet. Additionally, please list in the comments section of the worksheet any issues that occurred during the CSF collection, with packaging or any temperature excursions.

Subject ID #: _____ S _____ Date ____/____/____ Time ____:____:____ Gender: M or F Biomarkers ADNI3 Red Cap BLD SERUM	Subject ID #: _____ S _____ Date ____/____/____ Time ____:____:____ Gender: M or F Biomarkers ADNI3 Lavender Cap BLD PLASMA	Subject ID #: _____ S _____ Date ____/____/____ Time ____:____:____ Gender: M or F Biomarkers ADNI3 CSF License Plate Number: _____
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Remember to copy down the License Plate number to match the other labels.

PROCESSING THE CSF FOR SHIPPING

- Ensure that all necessary equipment and supplies are available ahead of time.
- When gravity drip method is used for lumbar puncture, the CSF is drawn in four 7 mL collection tubes (or 5 mL syringes if using suction method).
- Ensure to aliquot the first 2 mL of CSF for local laboratory testing
- Transfer the remaining 18 mL of CSF into the 13 mL polypropylene clear-capped transfer tubes.
- Immediately freeze CSF samples that will be shipped to UPENN upright on dry ice for at least 20 minutes before being packaged. 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.

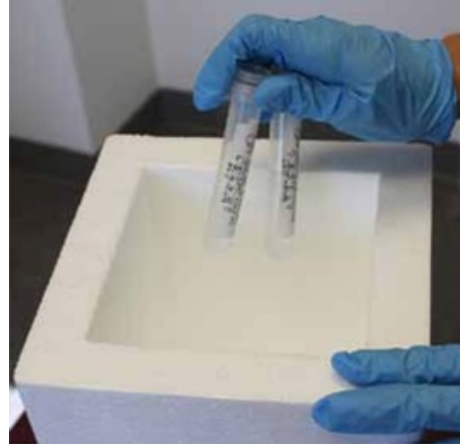
A LUMBAR PUNCTURE INFORMATION SHEET IS AVAILABLE WHICH INCLUDES INSTRUCTIONS FOR THE SUBJECT TO TAKE HOME. TO REQUEST A COPY, PLEASE EMAIL: ATRI-CLINOPS@USC.EDU

UPENN Packaging & Shipping (CSF, Serum, Plasma)

MAKE SURE TO NOTIFY THE UPENN BIOMARKER CORE THE DAY SAMPLES ARE SHIPPED BY FAXING OR EMAILING THE SAMPLE COLLECTION WORKSHEET – SEE SHIPPING DETAILS BELOW



1. Biomarker shipping supplies.



2. Place the four 14 ml tubes (1 serum, 1 plasma, and 2 CSF) upright in dry ice and allow to completely freeze.



3. Place 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.



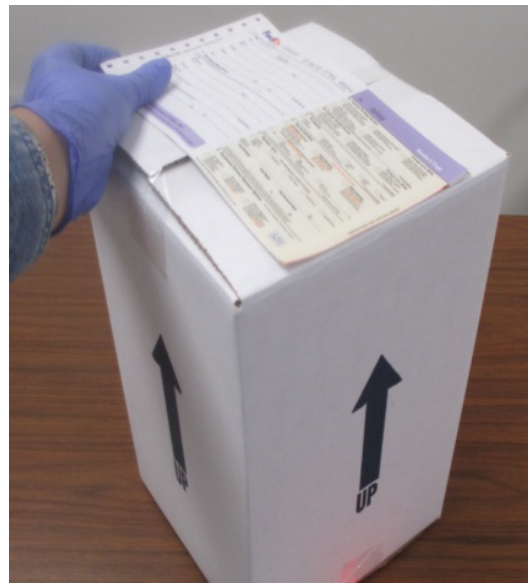
5. Place bag directly on to dry ice in Styrofoam shipper and fill rest of box with dry ice.



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:

- FedEx all biomarker biofluid samples the **SAME DAY on DRY ICE** by Federal Express,
- Priority Overnight shipping (Monday-Thursday).

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

- For those instances in which a Friday study visit is necessary, CSF, plasma and serum samples should be placed in a -80 degree Celsius freezer until Monday and shipped on dry ice to UPENN. If a -80 degree Celsius freezer is not available, a -20 degree Celsius freezer is acceptable.
- Pre-Paid Federal Express Air-bills and frozen shippers will be provided by ATRI. If your site needs additional UPENN Air-bills or frozen shippers please complete the ADNI3 online Supply Order Form.
- Complete the Biomarker Samples Online Form before shipping samples.
- Print a pdf of the completed form and include a copy with the shipment.

UPENN SHIPPING ADDRESS:

ADNI BIOMARKER CORE LABORATORY
7 Maloney South
University of Pennsylvania Medical Center
3400 Spruce Street
Philadelphia, PA 19104

UPENN HELPDESK

Email: ADNI@uphs.upenn.edu
Fax: 215-349-5092

SAMPLE TRACKING:

- Enter the sample collection data on the Biomarker Samples and Method of CSF collection electronic case report forms located in the ADNI3 web portal immediately after sample collection.
- Make sure to enter the Bar Code License Plate (one per visit) and FedEx tracking number.
- Print a copy of the completed form and include it with the shipment.
- To order additional Biomarker kits, please fill out the ADNI3 online Supply order form.

Chapter 24

Adverse Event (AE) & Serious AE Reporting

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). 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.

Adverse Event (AE)

An **Adverse Event (AE)** is any adverse change from the participant's 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 REGARDLESS OF THE INVESTIGATOR'S
ATTRIBUTION TO STUDY PROCEDURE.**

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 ECGs, 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

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 pending or in the absence of a diagnosis). If/when a diagnosis is subsequently made, update the AE verbatim term to reflect the name of the condition (diagnosis); the initial signs/symptoms should be referenced in the comments section along with the date that the diagnosis was made. If a diagnosis is made after the abnormal lab finding has itself resolved, the AE = diagnosis of condition can be linked to the abnormal lab finding AE.

- An abnormal test finding should **NOT** be reported as an AE if any of the following criteria are met:
 - Abnormal test is a repeat of a previous lab abnormality, and still doesn't meet of any of the above criteria for AE
 - Test result is determined to be an error
 - An imaging finding reveals a congenital anomaly that has been asymptomatic and is likely to remain so [in which case, the finding would be added to the Initial Health Assessment (IHA) list]

Serious Adverse Event (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 | ➤ Disability or permanent damage |
| ➤ Life-threatening | ➤ Congenital anomaly/birth defect |
| ➤ Hospitalization or prolongation of existing hospitalization (but not a planned elective procedure for an IHA and not necessarily an emergency room visit) | ➤ Important medical events |

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

Serious Adverse Event Outcomes

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
- Skilled nursing facilities
- Hospice
- Nursing homes
- Respite care
- 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. **Hospitalization or Prolongation of Hospitalization is NOT an event term.** Record events that occur during a hospitalization and are considered an AE or SAE.

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)
- Admission to the Emergency Department and treatment was less than 24 hours

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

Collection and Reporting of AEs and SAEs

Special note regarding Rollover participants from ADNI2:

- For Rollover participants, report AEs and SAEs that occurred during the dates of onset while the participant was still enrolled in ADNI3 Data Portal (i.e., onset dates that predate Rollover to ADNI3). The following needs to be followed.
 - The instructions for AE data entry are to use the date of reporting, as opposed to the onset date of the AE.
 - Any AEs that were reported to you DURING ADNI3 to be entered into the ADNI3 EDC, as opposed to going back into the ADNI2 EDC to report them.
- 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.
- In ADNI2, four forms were used upon entry into the study to assess medical history and adverse events (Medical History checklist, Medical History log, Pre-existing checklist, and Pre-existing log). In ADNI3 those forms have been removed, and replaced by the Initial Health Assessment form. In other words, ongoing AEs from ADNI2 should be entered as IHA in ADNI3 at initial visit
- If an event is resolved, sites should update the ADNI2 database and it should NOT be reported as ADNI3 initial health condition (unless it is clinically significant medical history)
- If a prior AE recurs or worsens after participant signs consent for ADNI3, then it should be reported as a new AE

COLLECTING REPORTS FOR ALL PARTICIPANTS:

Collect and document all AEs/SAEs that occur after CONSENT and up to 30 days after the last study visit, 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 (clinic and telephone 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: 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? [This may lead to reporting a change in severity on the previously entered AE, as opposed to creating a new AE related to the original one.]
- 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. A new medication added for an IHA that worsened during the study would indicate the need to post a new AE.
- 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). List the diagnosis that led to a procedure, not the procedure itself.
5. Fulfill local IRB requirements

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. For more details, see the ADNI3 Data Entry Manual.

AE/SAE Reporting General Notes

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).

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.

The site clinician should be involved in choosing the verbatim term for all AEs. Diagnoses are preferred to lists of symptoms. Each AE eCRF results in one AE item coded, so an event with multiple diagnoses may require the completion of more than one eCRF. Site coordinators may list a key symptom if a diagnosis is still pending, while listing related symptoms in the Comments/Narrative section.

- **Example:** The study partner relates that the participant felt dizzy before retiring to sleep, then fell on rising during the night to the toilet. Neither the dizziness nor the immediately subsequent fall led to a trip to the hospital nor new dysfunction. Acceptable interim terms would include:
 - Dizziness (with ‘fall’ in Comments/Narrative)
 - Fall (with ‘preceded by dizziness’ in Comments/Narrative)

Later, the verbatim term would be updated to diagnosis, such as “Hypotension” or “Adverse Reaction to Blood Pressure Medication.” If there were a hospitalization as a result of the fall, it might be better to list 2 AEs: dizziness – not serious because it did not lead to the hospitalization and fall – serious because it led to hospitalization. Because the AE MedDRA coding system allows us to differentiate a fall from someone merely tripping from a fall caused by some other condition, some might prefer to enter the dizziness associated with fall in Comments.

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), update the AE to reflect the name of the

condition (diagnosis); the initial signs/symptoms should be referenced in the Comments/Narrative section.

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 consider listing the cause and the injury/accident as a set of compound events.

➔ **Example:** The participant has an IHA of osteoporosis. At some time during the study, she develops back pain that is months later diagnosed as a stress fracture of the lumbar spine. Acceptable interim verbatim terms would include:

- New AE = Lower back pain (unrelated to osteoporosis at the time of entry)
- Later, change of this AE to L4 stress fracture, related to IHA = osteoporosis.
- Neither of the AEs above would be listed as serious unless debilitating to the participant or leading to hospitalization or surgery.

A fracture that led to hospitalization or that rates as a Serious Adverse Event may be separable from a related AE.

Example: The participant is involved in a car accident. On examination in the emergency room, he is noted to have a ruptured spleen and undergoes an emergent splenectomy.

- New AE = passenger in a motor vehicle accident
- 2nd new AE = ruptured spleen, serious, with splenectomy noted in Comments

When in doubt, consult with the Medical Monitor via email for how to list a related series of adverse events. See section below for more information on compound events.

If the diagnosis is already in the IHA list and the surgery/procedure was elective or planned, the IHA should be updated with a resolution date or comment, as opposed to the AE of a procedure being listed.

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)

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) that persists longer than a day and which may or may not be related to a...
- **Subsequent fall** (AE2) resulting in a ...
- **Wrist fracture** (AE3)

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 ADNI3 Data Entry Manual for guidance.

Provide an Event Cease Date if the Event Outcome is:

- Recovered/Resolved
- Recovered/Resolved with sequelae

Complete the Date of Death field if the event is 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.

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. <i>An Event Cease Date has been given.</i>
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. <i>An Event Cease Date has been given.</i>
Fatal	Death has occurred and is possibly related to the event. <i>An Event Cease Date has been given.</i>
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 ADNI3 Data Entry Manual.

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.

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 and should be recorded in the Change Log Report.

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. Clinician judgement should be used when determining if single events previously reported transition in severity and should be recorded in the Change Log Report.

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.

RELATEDNESS

The investigator is responsible for determining whether or not an event is related to specific study procedures or “other study procedure(s)”. “Other study procedure(s)” refers to any other procedure outside of those specified that may have a causal relationship to the AE.

RELATEDNESS	DESCRIPTION
Not Related	There is no evidence of a causal relationship and a causal relationship cannot be reasonably attributed to the study treatment or procedures. The event is clearly due to extraneous causes.
Unlikely Related	A poor temporal relationship exists between the event onset and administration of study drug. The event could easily be explained by the subject’s clinical state, intercurrent illness, or concomitant therapies.
Possibly Related	A relationship cannot be ruled out with certainty and the event may be related. There is some evidence to suggest a causal relationship but the influence of other factors may have contributed to the event, such as the participant’s clinical condition or concomitant treatment.
Probably Related	The event is likely related to the study procedure. There is evidence to suggest a causal relationship, such as reasonable temporal sequence from study procedures. The influence of other factors is unlikely.
Definitely Related	The event is clearly related to the study procedure. There is clear evidence to suggest a causal relationship. The influence of other factors can be ruled out.

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.

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”.

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.

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 (SEE CHAPTER 2-PERSONNEL REQUIREMENTS-LIST OR ROLES, FOR CREDENTIALS).

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/ STUDY TEAM MEMBER (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

CLINICIAN

- Signs off on some worksheets and EDC, like neurology exam, physical exam, Adverse Events
- Clinicians can only sign off in EDC if they have EDC sign off privileges as indicated in their personnel sheet.

REGULATORY CONTACT (DELEGATED AS APPROPRIATE BY PI)

- All SAEs available for sites to file. As soon as reports are available sites will be alerted.
- Monitors will check that all reports are filed properly

ATRI

- Regularly and promptly review and evaluate all information related to the safety and effectiveness of the study medication as it is obtained from the Investigator (21 CFR 312.32b)
- Keep Investigators informed about new observations related to study medication, particularly those that pertain to adverse effects and safety
- Notify Investigators of any adverse experiences associated with the study procedures that are both serious as well as unexpected and any findings from tests in lab animals that could suggest a significant risk for human subjects (21 CFR 312.32c).

Chapter 25

Magnetic Resonance Imaging (MRI)

Summary and Timing of MRI Scans

- ➔ MRI's in this study will be performed using a 3.0 Tesla magnet at screening
- ➔ Imaging scans are used for eligibility determination at screening (after PI or designee has verified that screening visit meets eligibility requirements and monitor has authorized proceeding to MRI)
- ➔ An MRI scan is also performed at ongoing in-clinic visits

Sedation is allowed at the discretion of the site clinician. Refer to the protocol for requirements regarding timing of use of sedating medications relative to administration of cognitive tests.

For technical details regarding MRI, refer to the MRI Tech Manual located on the study portal document repository.

MRI Scanner Qualification

All participating sites must complete the MRI scanner qualification process in order to receive approval to begin screening participants for ADNI3.

- ➔ Both a phantom and volunteer scan will be needed for site approval.

SCANNER QUALIFICATION FOR ADNI2 DOES NOT TRANSFER TO THIS STUDY.

For volunteer scans require for certification, sites may use their own local imaging center consent forms, if available, or email ATRI Regulatory Affairs for a template.

The procedures for site qualification, participant scanning, as well as image upload instructions are described in the MRI Technical Manual posted in the study data portal.

During the course of the study, if the scanner used for ADNI3 has hardware/software upgrades (or a different scanner is requested to be used for ADNI3), immediately contact the MRI Imaging Core. Depending on the impact of the upgrade, the scanner may need to be re-qualified BEFORE additional subjects can be screened.

THE SAME MRI SCANNER QUALIFIED FOR THE STUDY MUST BE USED FOR ALL MRI SCANS DURING THE COURSE OF THE STUDY. IF THE SAME MRI SCANNER IS NOT USED, THE SCAN MAY NOT BE REIMBURSED AND THE PARTICIPANT MAY NEED TO BE RE-SCANNED USING THE QUALIFIED SCANNER.

MRI Pamphlet for Participants

Informative pamphlets describing imaging procedures are available to provide to participants:

- ➔ The MRI pamphlet includes basic information about an MRI scan. It briefly describes how participants can best prepare for the MRI scan and outlines ways participants can reduce anxiety during the procedure.

- Before distributing the MRI pamphlet, use the space provided on the back page to write in the specifics of the MRI appointment (date, day of the week, time, and place). If the MRI scan will be conducted at a facility other than where clinical appointments are held, provide the participant and study partner with detailed directions to the radiology site. Distribute the MRI pamphlet to participants when the MRI scan is scheduled in order to allow plenty of time for the participant to review this information before the scan appointment.
- In addition, remind the participant to bring the pamphlet to the MRI appointment and display it when checking in. This will ensure that the participant is scanned with the appropriate MRI protocol sequence.
- The pamphlet is posted to the document repository. IRB approval is required prior to distribution to participants.

MRI Scan Contraindications

Use the MRI Screening Form posted in the document repository to assess the presence of metal in the participant's body and help determine whether or not the participant is eligible to be scanned. Anyone with a firm understanding of the participant's medical history (the participant, caretaker, or study partner) may fill out the MRI Screening Form.

THE MRI SCREENING FORM SHOULD BE COMPLETED DURING PRESCREENING. IF A PARTICIPANT IS NOT ELIGIBLE TO BE SCANNED THEY SHOULD NOT BE SCHEDULED TO SCREEN FOR THE STUDY.

If the participant or study partner checks "yes" next to any items on the MRI Screening Form please be sure to inform the MRI Center about the metal items that have been identified. Try to get as much information about the metal object(s) so your MRI Center can best assess whether or not an MRI would be safe for the participant.

In addition, if a participant indicates that he or she is claustrophobic please try to discuss the level of discomfort an MRI may pose. Some participants might be claustrophobic but are willing to undergo an MRI. It is preferred that participants who are uncomfortable with MRI scans not be included in this study. If the participant decides that the anxiety associated with MRI is too uncomfortable and they wish to terminate the scan, then the examination will be ended at that time. There will be no attempt to coerce participants to complete exams they are uncomfortable with. According to the protocol, sedation can be used in rare cases if deemed appropriate by the site clinician. If sedation is used, it should be noted in the MRI Scan Information Form. Refer to the excluded medications section of the protocol for details of timing of administration of sedating medications relative to cognitive testing.

THE MRI SCREENING FORM IS ONLY INTENDED TO SCREEN FOR MRI CONTRAINDICATIONS. IT SHOULD BE KEPT IN THE PARTICIPANT'S FILE BUT PLEASE DO NOT SUBMIT THE FORM TO ATRI.

MRI Scanning Protocol

All participants **MUST** be scanned using the ADNI3 MRI core scanning protocol. **DO NOT make any adjustments to this protocol** unless requested to do so. For details on the imaging acquisition and image upload instructions please refer to the MRI Technical Manual posted in the document repository in the study data portal.

Local Read

A local read conducted by qualified personnel at the site is required. At screening, the site PI, or designee, will review the local read results to determine if the participant meets eligibility requirements.

Procedure Overview and Data Flow

Prior to any scanning for this study, establish a process for the study site to obtain the MRI Scan Information form and/or imaging data from the MRI Center in a secure, timely manner.

PRIOR TO THE SCAN:

- ➔ At Screening for New participants, ensure that the PI or Clinician has reviewed the participant's Screening Visit and has deemed that the subject is eligible to proceed to the MRI scan
- ➔ Be sure that the MRI Screening form is completed and/or reviewed for changes
- ➔ Provide the participant with an MRI pamphlet that includes appointment time
- ➔ Provide the participant and study partner with travel directions and information for parking
- ➔ Coordinate with the MRI center: re-confirm the appointment date/time and convey that the patient is a participant in the ADNI3 study

ON THE DAY OF THE SCAN:

- ➔ Ensure that the MRI Technician has a copy of the MRI PET Scan Information form. A copy of this form is located in the appropriate study visit worksheet packet posted to the study data portal. The Study Coordinator should complete the top section of the form and the MRI Technician should complete the remainder of the form during the scan.

WITHIN 24 HOURS AFTER THE SCAN:

- ➔ Upload the MRI Scan to LONI
- ➔ Obtain the MRI Scan Information form from the MRI Technician
- ➔ Complete the MRI Scan Information eCRF in the ADNI3 Study Data Portal

AS SOON AS POSSIBLE AFTER THE SCAN:

- ➔ Ensure that a local clinical read of the MRI has been reviewed by the site PI or clinician/designee

MRI Data Archive

As described in detail in the MRI Tech Manual, MRI scan data is transferred to LONI database immediately after the MRI scan; however, every MRI conducted for ADNI3 study must be archived at the MRI facility following local standard practice in order to safeguard the MRI data in the event that data transfer is interrupted or incomplete. The coordinating center will request additional transfers or copies of the data as needed. ATRI recommends retaining all data, documents and other records for seven (7) years following primary publication of study results.

Chapter 26

Positron Emission Tomography (PET)

For technical details regarding PET please refer to the ADNI3 PET Tech Manual located in the document repository.

EACH SCAN MUST BE DONE ON A SEPARATE DAY OR AT LEAST 12 HOURS AFTER A PRIOR SCAN.

Types of PET Scans:

AMYLOID PET

- Florbetapir amyloid PET: All Rollover participants will receive amyloid PET scan with florbetapir upon entry into the study and then again, every two years.
- It is important that all Rollover participants continue on Florbetapir for longitudinal comparability
- Florbetaben (FBB) amyloid PET: Newly enrolled participants will receive amyloid PET scan with FBB upon entry into the study and then again, every two years.
- If you are a site that is not able to get FBB tracer delivered, you will conduct the amyloid PET scan with florbetapir.

FDG PET

- Performed during Initial Visit or Baseline Visit for MCI and AD participants.
- A 4-hour minimum or overnight fast is required.
- Prior to the scan a blood glucose measurement will be made by fingerstick and scans may be postponed or rescheduled if the reading is > 180 mg/dL.

AV-1451/TAU PET

- On all participants, AV-1451 PET is conducted at the first and last year
- AD will have a AV-1451 PET scan at each visit (AD participants are seen for three years for a total of 3 tau PET scans)
- Normal and MCI Participants, 20% of amyloid-negative and 80% of amyloid-positive will be randomly selected for two additional AV-1451 PET scans. Those selected for more tau PET scans will have a total of **4 scans**

SEDATION IS NOT ALLOWED FOR ANY OF THE PET SCANS

PET Scanner Qualification

All new participating sites must complete the PET scanner qualification process in order to receive approval to screen participants for ADNI3. If using an ADNI2 scanner without major upgrades, no certification scans will be required. Otherwise, a Hoffman phantom will be required. The procedures for the PET scanner qualification process, dose preparation and administration, imaging acquisition and reconstruction parameters, as well as image upload instructions are described in the ADNI3 PET Technical Manual posted in the document repository.

During the course of the study, if the scanner used has hardware/software upgrades (or a different scanner is requested for use), immediately contact the University of Michigan PET QC Team. Depending on the impact of the upgrade, the scanner may need to be re-qualified BEFORE a participant can be scanned.

CHANGING THE ORIGINAL SCANNER DURING THE COURSE OF THE STUDY IS HIGHLY DISCOURAGED. PLEASE USE THE SAME SCANNER QUALIFIED AT THE START OF THE STUDY ACROSS ALL PARTICIPANTS AND FOR THE DURATION OF THE ENTIRE STUDY.

PET Scan Contraindications

All participants who consent to PET scan(s) must be queried to assure that they do not have specific contraindications to PET which include:

- ➔ Inability to cooperate/claustrophobia (**sedation is not allowed for either type of PET scan**)
- ➔ Inability to lie on the scanner for the scan duration

PET Pamphlets for Participants

Informative pamphlets describing PET imaging procedure are available to provide to participants:

- ➔ The pamphlet includes basic information about the PET scan. They briefly describe how participants can best prepare for the scan and outline ways participants can reduce anxiety during the procedure.
- ➔ Before distributing the pamphlet, write in the specifics of the scan appointment (date, day of the week, time, and place). If the scan will be conducted at a facility other than where clinical appointments are held, provide the participant and study partner with detailed directions to the radiology appointment location. Distribute the pamphlet to participants when the associated PET scan is scheduled in order to allow plenty of time for the participant to review this information before the scan appointment.
- ➔ Remind the participant to bring the pamphlet to the PET appointment and display it when checking in. This will ensure that the participant is scanned with the appropriate PET protocol.
- ➔ The PET pamphlets are posted to the document repository. IRB approval is required

prior to distribution to participants.

Radiotracers

NO TRAINING IS REQUIRED FOR ORDERING RADIOTRACERS, HOWEVER PLEASE REVIEW THE PIRAMAL FBB ORDER SLIDE DECK AND AVID CLINICAL SUPPLIES GUIDENCE DOCUMENTS FOR ORDERING INFORMATION.

FLORBETAPIR PET

The AVID Radiopharmaceuticals Clinical Supplies Guidance Document IIT Florbetapir is posted in the document repository. Florbetapir F18 (^{18}F -AV-45 Injection) can be ordered by filling out the Dose Request Form.

- ➡ Dose should be requested within 5 business days in advance of the scan date.

Refer to the ADNI3 study contact sheet for more contact information. Individual doses may need to be ordered a number of days in advance of the PET scan. Consult with your local vendor representative for ordering details.

FLORBETABEN (FBB) PET

The Piramal Neuraceq (florbetaben F18 injection) dose order slides are posted in the document repository. Order forms are unique to each site. Please use the Sample order provided in your site folder, located in the ADNI3 document repository.

Refer to the ADNI3 study contact sheet for contact information. Individual doses may need to be ordered a number of days in advance of the PET scan. Consult with your local vendor representative for and questions or issues you may encounter.

There a few sites that do not have a NEURACEQ Florbetaben F18 manufacturing site close enough to their site clinic, so instead Avid's AMYVID (Florbetapir F18) tracer will be provided to New participants. ATRI will inform sites when/if a manufacturing site becomes available in their area.

TAU PET

The AVID Radiopharmaceuticals Clinical Supplies Guidance Document IIT AV-1451 is posted in the document repository. ^{18}F -AV-1451 (^{18}F -AC-45 Injection) can be ordered by filling out the Dose Request Form.

- ➡ Dose should be requested within 5 business days in advance of the scan date.

Refer to the ADNI3 study contact sheet for contact information for more contact information. Individual doses may need to be ordered a number of days in advance of the PET scan. Consult with your local vendor representative for ordering details.

FDG PET

FDG injection is to be provided by your local radiology center.

Quality Review

The University of Michigan QC Team will conduct an initial QC within 2 business days of all PET scans uploaded to LONI. The initial quality check will include:

- ➔ Ensuring the scan was uploaded to the study data portal appropriately
- ➔ Checking the PET scan date against visit registry date
- ➔ Checking compliance with the PET scan naming requirements (e.g. leaving PID out of header and proper format of participant ID in the Patient Name field of the image header)
- ➔ Checking compliance with the PET scan procedures (e.g. proper positioning of participant, correct protocol and scanner settings)

It is possible that scans will need to be reprocessed or repeated due to failed QC. If required, repeat scans must be scheduled within four weeks of the original scan date.

Procedure Overview and Data Flow

Prior to any scanning for this study, establish a process for the study site to obtain the PET Scan Information form and/or imaging data from the PET Center in a secure, timely manner.

PRIOR TO THE SCAN:

- ➔ Ensure that the PI or Clinician has reviewed the participant's MRI and has deemed that the subject is eligible to proceed to the PET scan
- ➔ Place dose order and ensure dose availability prior to the subject's appointment (Note: dose orders may need to be placed a number of days in advance of the scan appointment.)
- ➔ **FDG:** Remind study participant to fast at least 4 hours prior to FDG scanning session
- ➔ Coordinate with the PET center: re-confirm the appointment date/time and convey that the patient is a participant in the ADNI3 study.
- ➔ Provide the subject with the PET pamphlet that includes appointment time
- ➔ Provide the participant and Study Partner with travel directions and information for parking
- ➔ Verify no contraindications have arisen.

ON THE DAY OF THE SCAN:

- ➔ Ensure that the PET technologist has a copy of the PET scan information form. A copy of this form is located in the appropriate study visit worksheet packet posted to the study data portal. The Study Coordinator should complete the top section of the form before the scan and the PET Technologist should complete the remainder of the form during the scan.

WITHIN 24 HOURS AFTER THE SCAN:

- ➔ Upload the PET scan to LONI
- ➔ Obtain the PET Scan Information form from the PET Technologist
- ➔ Complete the corresponding PET Scan Information eCRF

PET Data Archive

As described in detail in the PET Tech Manual, the PET scan imaging data is transferred to LONI database immediately after the PET scan. However, every PET scan conducted must be archived at the imaging site and must include all raw and processed study PET data. ATRI recommends retaining all data, documents and other records for seven (7) years following primary publication of study results.

Revision History

Version 3.0

Dated: 2017JUNE26

LOCATION	DESCRIPTION OF SIGNIFICANT REVISIONS
THROUGHOUT	Corrected spelling, formatting, and grammatical errors
CHAPTER 3: CERTIFICATION, TRAINING AND EXPERIENCE	Clarified that a person requesting EDC access to sign off on participant eligibility must have required credentials as outlined
CHAPTER 4: RECRUITMENT & RETENTION	Added recruitment tools, including adni3.org personalized pages
CHAPTER 7: NEW ENROLLEE BASELINE & LONGITUDINAL FOLLOWUP	Updated annual visit labels in the visit schedule to match ICF
CHAPTER 8: INIITAL ROLLOVER VISIT & LONGITUDINAL FOLLOWUP	Updated annual visit labels in the visit schedule to match ICF
CHAPTER 9: CONVERTERS	Reorganized chapter to be clearer on the various scheduling scenarios
CHAPTER 12: PARTICIPANT TRANSFERS	New chapter added
CHAPTER 14: SAMPLES COLLECTIONS PROCESSING & SHIPMENT	Clarified that upon entry all participants, Rollover and Newly enrolled, need a 10-mL blood draw (purple EDTA) for genetic analysis
CHAPTER 16: COMPUTERIZED TESTING	BHR section separated into its own chapter
CHAPTER 17: SAFETY MEASURES	Separated into its own chapter

CHAPTER 18: GLOBAL UNIQUE IDENTIFIER	Separated into its own chapter
CHAPTER 19: OVERVIEW OF SAMPLE COLLECTIONS, PROCESSING AND SHIPMENT	Clarified that Cell Immortalization should only be collected for new participants Added a new table on Visit Codes which should be used for completing NCRAD labels.
CHAPTER 21: GENETIC SAMPLE COLLECTION: GENETICS, PBMC, CELL IMMORTALIZATION, RNA AND BUFFY COAT (NCRAD)	Added language to emphasize PBMC should not be collected on a Friday Added website tool and videos to further explain procedure for collecting buffy coat
CHAPTER 22: BIOMARKER SAMPLE COLLECTION: PLASMA & SERUM (UPENN)	Updated NCRAD label image to show the license ID
CHAPTER 23: CEREBRAL SPINAL FLUID (CSF) COLLECTION	Coagulation test was removed
CHAPTER 24: MAGNETIC RESONANCE IMAGING (MRI)	New chapter added
CHAPTER 25: POSITRON EMISSION TOMOGRAPHY (PET)	New chapter added
CHAPTER 24: ADVERSE EVENT & SERIOUS ADVERSE EVENTS REPORTING	Added instruction on AE reporting for Rollover Participants. Ongoing AEs from ADNI2 should be entered in the IHA form in ADNI3 at Initial Visit