ALZHEIMER'S DISEASE
NEUROIMAGING
INITIATIVE

DEFINING ALZHEIMER'S DISEASE

PROCEDURES MANUAL

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Protocol Summary

Title	**Alzheimer's Disease Neuroimaging Initiative 2 (ADNI2)**
Primary Objective	The major goals of ADNI2 are to: 1. Determine the relationships among clinical, imaging, genetic, and biochemical biomarker characteristics of the entire spectrum of Alzheimer's Disease (AD), as the pathology evolves from normal aging through very mild symptoms, to mild cognitive impairment (MCI), to dementia. 2. Inform the neuroscience of AD, identify diagnostic and prognostic markers, identify outcome measures that can be used in clinical trials, and help develop the most effective clinical trial scenarios. 3. Develop improved methods which will lead to uniform standards for acquiring longitudinal multi-site MRI and PET data on patients with AD, MCI, and elderly controls. 4. Perform longitudinal clinical, cognitive, MRI, PET (^{18}F-AV-45 and FDG), and blood and CSF biomarker studies on 550 newly enrolled subjects in four diagnostic categories – cognitively normal (CN), early MCI (EMCI), late MCI (LMCI), and mild AD. Continue these longitudinal studies for approximately 500 LMCI and Cognitively Normal subjects from ADNI1 and approximately 200 EMCI subjects from ADNI-GO for an additional 5 years. 5. Collect blood samples for DNA and RNA extraction. Newly enrolled subjects will also have samples collected for Cell Immortalization and APOE genotyping. 6. Validate the clinical diagnoses and imaging and biomarker surrogates through neuropathological examination of ADNI1, GO and ADNI2 participants who come to autopsy.
Study Design	This is a non-randomized natural history non-treatment study.
Sample Size	550 newly enrolled subjects (150 CN, 100 EMCI, 150 LMCI, 150 mild AD) from approximately 55 sites from the United States and Canada. Approximately 450-500 CN and LMCI subjects will be followed from the original ADNI study. Approximately 200 EMCI subjects will be followed from the ADNI-GO study.
Procedures	All subjects will have clinical/cognitive assessments, biomarker and genetic sample collection, and imaging. A reduced battery of tests is allowable if the subject is not able/willing to complete the full battery after the participant's original Baseline Visit. All MRI and PET scans will be rapidly assessed for quality so that subjects may be rescanned if necessary. All clinical data will be collected, monitored, and stored by the Coordinating Center at University California San Diego. University of Pennsylvania will collect biomarker samples and NCRAD will collect genetic samples. All raw and processed image data will be archived at LONI.

Protocol Summary

Outcome Measures

1. Rate of Decline as measured by: Cognitive tests, Activities of Daily Living, and CDR Sum of Boxes.
2. Rate of conversion will be evaluated among all four groups.
3. Rate of volume change of whole brain, hippocampus, and other structural MRI measures.
4. Rates of change on each specified biochemical biomarker.
5. Rates of change of glucose metabolism (FDG-PET).
6. Extent of amyloid deposition as measured by ^{18}F-AV-45.
7. Group differences for each imaging and biomarker measurement.
8. Correlations among biomarkers and biomarker change.
9. Subgroups analyses: APOE genotype, low CSF Aβ42, positive amyloid imaging with ^{18}F-AV-45.

Schedule of Assessments
(New CN, EMCI, LMCI Participants)

Visit Name	SCREEN	BASELINE	MONTH 3	MONTH 6	ONGOING ANNUAL[1]	ONGOING 6 MONTH INTERIM[1]
Visit Type	**Clinic**	**Clinic**	**MRI**	**Clinic**	**Clinic**	**Phone**
Explain study*	X					
Obtain consent*	X					
Demographics, Family History, Inclusion/Exclusion Criteria*	X					
Medical History, Physical Exam, Neurological Exam, Hachinski*	X					
Vital Signs*	X	X		X	X	
Height*	X					
Screening Labs*	X					
DNA Sample Collection for APOE Genotyping and GWAS*		X				
Cell Immortalization Sample Collection*		X				
American National Adult Reading Test*		X				
Mini Mental State Examination*	X			X	X	
Logical Memory I and II*	X				X	
Everyday Cognition (ECog)		X		X	X	
Montreal Cognitive Assessment (MoCA)*		X		X	X	
Category Fluency (Animals)*		X		X	X	
Trails A & B*		X		X	X	
Boston Naming Test (30-item)*		X		X	X	
Auditory Verbal Learning Test*		X		X	X	
Geriatric Depression Scale	X			X	X	
Clock drawing*		X		X	X	
Neuropsychiatric Inventory		X			X	
Neuropsychiatric Inventory Q				X		X
ADAS-Cog 13 (w/ Delayed Recall & Number Cancellation)*		X		X	X	
Clinical Dementia Rating Scale	X			X	X	
Activities of Daily Living (FAQ)		X		X	X	
Plasma and Serum Biomarker Collection*[4]		X		X	X	
RNA Sample Collection*		X			X	
Concomitant Medications	X	X		X	X	X
Adverse Events	X	X		X	X	X
Diagnostic Summary*	X	X		X	X	
Telephone Check – Participant Status						X
3T MRI Imaging (100%)*	X		X[2]	X	X	
^{18}F-AV-45 Amyloid Imaging (100%)*		X			X[3]	
FDG-PET Imaging (100%)*		X			X[3]	
CSF Collection by Lumbar Puncture (LP) (100%)*		X			X[3]	

* Assessment must be done in-person.

[1] Subjects will be followed for 54 months from baseline, after which they will be asked to consent to additional follow-up under a separate grant and protocol.

[2] Month 3 MRI is timed from Screening MRI .

[3] FDG-PET, ^{18}F-AV-45 Amyloid Imaging, and LP are to be performed only every two years from baseline, as funding permits.

[4] Buffy Coat is removed from plasma sample and shipped to NCRAD for genetic analysis.

Schedule of Assessments
(New AD Participants)

Visit Name	SC	BL	M3	M6	M12	M18	M24	Ongoing 6 Mo. Follow-up[1]
Visit Type	**Clinic**	**Clinic**	**MRI**	**Clinic**	**Clinic**	**Phone**	**Clinic**	**Phone**
Explain study*	X							
Obtain consent*	X							
Demographics, Family History, Inclusion and Exclusion Criteria*	X							
Medical History, Physical Exam, Neurological Exam, Hachinski*	X							
Vital Signs*	X	X		X	X		X	
Height*	X							
Screening Labs*	X							
DNA Sample Collection for APOE Genotyping and GWAS*		X						
Cell Immortalization Sample Collection*		X						
American National Adult Reading Test*		X						
Mini Mental State Examination*	X			X	X		X	
Logical Memory I and II*	X				X		X	
Everyday Cognition (ECog)		X		X	X		X	
Montreal Cognitive Assessment (MoCA)*		X		X	X		X	
Category Fluency (Animals)*		X		X	X		X	
Trails A & B*		X		X	X		X	
Boston Naming Test (30-item)*		X		X	X		X	
Auditory Verbal Learning Test*		X		X	X		X	
Geriatric Depression Scale	X			X	X		X	
Clock drawing*		X		X	X		X	
Neuropsychiatric Inventory		X			X		X	
Neuropsychiatric Inventory Q				X		X		X
ADAS-Cog 13 (w/ Delayed Recall and Number Cancellation)*		X		X	X		X	
Clinical Dementia Rating Scale	X			X	X		X	
Activities of Daily Living (FAQ)		X		X	X		X	
Plasma and Serum Biomarker Collection*[3]		X		X	X		X	
RNA Sample Collection*		X			X		X	
Concomitant Medications	X	X		X	X	X	X	
Adverse Events	X	X		X	X	X	X	
Diagnostic Summary*	X	X		X	X		X	
Telephone Check - Participant Status						X		X
3T MRI Imaging (100%)*	X		X[2]	X	X		X	
^{18}F-AV-45 Amyloid Imaging (100%)*		X					X	
FDG-PET Imaging (100%)*		X					X	
CSF Collection by Lumbar Puncture (LP) (100%)*		X					X	

* Assessment must be done in-person.

[1] Subjects will be followed for 54 months from baseline, after which they will be asked to consent to additional follow-up under a separate grant and protocol.

[2] Month 3 MRI is timed from Screening MRI.

[3] Buffy Coat is removed from plasma sample and shipped to NCRAD for genetic analysis.

Schedule of Assessments

(Follow-Up CN and LMCI Participants from ADNI1, EMCI Participants from ADNIGO)

Visit Name	Initial	Ongoing 6 Month Interim[1]	Ongoing Annual Follow-up[1]
Visit Type	**Clinic**	**Phone**	**Clinic**
Explain study*	X		
Obtain consent*	X		
Demographics*	X		
Medical History*	X		
Vital Signs*	X		X
Mini Mental State Examination*	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
Boston Naming Test (30-item)*	X		X
Auditory Verbal Learning Test*	X		X
Geriatric Depression Scale	X		X
Clock drawing*	X		X
Neuropsychiatric Inventory	X		X
Neuropsychiatric Inventory Q		X	
ADAS-Cog 13 (with Delayed Word Recall & Number Cancellation)*	X		X
Clinical Dementia Rating Scale	X		X
Activities of Daily Living (FAQ)	X		X
Plasma and Serum Biomarker Collection*[4]	X		X
DNA Sample Collection for GWAS (if not previously obtained)*	X		
RNA Sample Collection*	X		X
Concomitant Medications	X	X	X
Adverse Events	X	X	X
Diagnostic Summary*	X		X
Telephone Check – Participant Status		X	
MRI Imaging (100%)[2]*	X		X
^{18}F-AV-45 Amyloid Imaging (100%)*	X[3]		X[3]
FDG-PET Imaging (100%)*	X[3]		X[3]
CSF Collection by Lumbar Puncture (LP) (100%)*	X[3]		X[3]

* Assessment must be done in-person.

[1] Subjects will be followed for 54 months from initial ADNI2 visit, after which they will be asked to consent to additional follow-up under a separate grant and protocol.

[2] All EMCI participants enrolled in ADNI-GO will continue with 3T MRI imaging. All CN and LMCI participants enrolled in ADNI1 will continue with 1.5T MRI imaging unless and until decision made by MRI Core that the site should perform 3T MRIs on all participants.

[3] FDG-PET, ^{18}F-AV-45 Amyloid Imaging, and LP are to be performed every two years, as funding permits.

[4] Buffy Coat is removed from plasma sample and shipped to NCRAD for genetic analysis.

PERSONNEL REQUIREMENTS

The following roles must be assigned, in order to conduct the Alzheimer's Disease Neuroimaging Initiative (ADNI2) Study.

SITE PROTOCOL PRINCIPAL INVESTIGATOR (PI)

This person is responsible for:

- Protect the rights and well-being of study participants.
- Personally conduct or supervise the described study.
- Maintain appropriate staff qualifications including study specific training.
- Adequate staffing resources.
- Medical care of study participants.
- Conduct the study in accordance with Federal Regulations, Internal Conference on Harmonization (ICH) and Good Clinical Practices (GCP).
- Approved protocol (as indicated by signed 1572).
- Communications with IRB.
- Compliance with study protocol.
- Conduct appropriate informed consent of study participants.
- Keep adequate source records and reports.
- Safety Reporting.

The Site PI may also serve as the study physician.

STUDY PHYSICIAN/SITE CLINICIAN

This person is responsible for:

- Conducting or supervising the clinical evaluation of all participants including physical and neurological exams, reviewing adverse events, interpreting lab results, assessing diagnosis at all visits.
- Ensuring that biological samples (CSF, blood) are correctly processed.
- Performing lumbar punctures (if applicable) unless another accredited individual is qualified to do so.

STUDY COORDINATOR

This person is responsible for:

- Managing the day-to-day conduct of the trial.
- Ensuring accurate administration of all instruments at the site.
- Supervising accurate data collection.
- Preparing, handling, and processing of all laboratory samples.
- Coordinating clinic visits.
- Scheduling visits at MRI and PET centers and schedule assessments and LP procedures.
- Serving as a liaison with the ADCS Clinical Monitor.

Start-Up and General Information

PROJECT INTERVIEWER/PSYCHOMETRIST

- This person will have at least a bachelor's degree in healthcare psychology, social work or a related field, and/or well-documented experience in administering interviews and neuropsychological tests.
- This person may be responsible for administering the ADAS-Cog and/or the CDR.

ADAS ADMINISTRATION

All individuals administering the ADAS must obtain ADAS certification. If an ADAS rater has already completed ADCS certification in the past 5 years, he/she is also certified to conduct the ADAS-Cog for ADNI2. Certification is required for those who are ADAS-naïve and for those certified more than 5 years ago. Certification is a simple process of completing an ADAS questionnaire and scoring better than 75%.

- To request a certification questionnaire please email **adcs-clinops@ucsd.edu**.

After being scored, the rater will receive ADAS certification by email from the ADCS. Certification is valid for 5 years; after this time the rater must recertify.

CDR RATER

All individuals administering the CDR for ADNI must be certified. 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 scores submitted will be compared to the Gold Standard and if the rater passes a certificate will be issued by Washington University.

CDR Certified: For those raters who have been previously certified a refresher is required. This refresher includes five (5) reliability tapes. The scores submitted will be compared to the Gold Standard and if the rater passes a certificate will be issued by Washington University.

CDR Certifcation and Refreshing can be found online at the following url:
http://alzheimer.wustl.edu/cdr/application/step1.htm.

It is important for the CDR rater to remain blinded to the ADAS-Cog data. If the CDR rater is also the PI, the CDR must be completed before viewing and approving the study data collected during the visit.

SIGNATURES

Hard Copy ('Wet') Signatures

The following worksheets must be signed off by a clinician trained in the administration/review of these assessments (only credentials MD, PA, DO or NP).

- Neurological Exam
- Adverse Events and Hospitalizations
- MRI/CT Clinical Read
- Physical Exam
- Lab Results

Study Coordinators with these credentials are allowed to perform and sign off on these assessments.

Electronic Signatures

At each visit a clinician must review and acknowledge that the visit was conducted to his/her satisfaction. The electronic signature is collected by unique user name and password and is the equivalent of a 'wet' signature.

The following eCRFs must be signed off by a clinician (only credentials MD, PA, DO or NP):

- Clinician Verification of Inclusion and Exclusion Criteria Form
- Clinician Review
- Protocol PI Approval (completed by Site Protocol PI at completion of Protocol)

SITE APPROVAL TO BEGIN ENROLLMENT

Before screening begins, a site must meet requirements for ADCS start-up. Meeting Site Approval requirements to begin enrollment will require that you work closely with the ADCS Regulatory, Contracts, Recruitment, and Clinical Operations groups. Please see the Contact Information list at the beginning of this procedures manual for point of contact in these respective areas.

Sites must receive IRB approval within 5 months after the receiving the Final Protocol. In order to meet IRB approval and first screening visit deadlines, please follow Site Approval requirements checklist below.

REGULATORY REQUIREMENTS

- Consent form for ADCS review / approval
- Protocol Signature Sheet (dated 17Sep2010)
- AV45 Protocol Signature Sheet – Amendment 1(dated 16Feb2010)
- AV45 Investigator Brochure Signature Page Version 6 (dated 10May2010)
- AV45 Investigator Brochure Signature Page Version 7 (dated 17Nov2010)
- FDA Form 1572
- ADNIGO/ADNI2 Avid Financial Disclosure Form (required for PI & all sub-investigators listed on the 1572)
- Signed & Dated CV, Medical Licenses and Human Subjects Certifications for PI and all sub-investigators listed on the 1572 (unless previously submitted for the main ADNI study).
- Certificate of Confidentiality ADNI2 Amendment sent to NIA
- Note-To-File (NTF) with CoC tracking number submitted to ADCS RA

NOTE: Originals required for all forms noted above with the exception of CV, Medical Licenses and Human Subject Certifications.

Forms may be downloaded from **ADCS Admin Portal > Regulatory Affairs.** Originals can be FedEx'd to:

ADCS Regulatory Affairs
8950 Villa La Jolla Drive, C227
La Jolla, CA 92037
Tel: 858-677-1545
Reference: ADNI / FedEx Acct # 1595-0531-6

All other documentation can be faxed or emailed: Fax: 858-246-1413 | Email: **adcsra@ucsd.edu**

Start-Up and General Information

CONTRACT REQUIREMENTS

- Master Contract
- Signed Study Agreement

CERTIFICATION AND OTHER ADMINISTRATIVE REQUIREMENTS

- Site Protocol Personnel Log
- Contact Information Form for new personnel
- ADAS-Cog Certification
- CDR Certification (through Washington University, St. Louis)
- MRI Certification
- PET Certification
- Recruitment & Retention Plan (Not required prior to Site Approval)
- Trained Psychometrist and Raters for Neuropsychometric Testing Battery and other assessments

MRI SCAN CERTIFICATION

Any new participating sites for ADNI2 must complete the scanner certification process for 3T MRI. Sites that have been previously certified for ADNIGO do ***NOT*** require recertification unless there has been a change in the 3T MRI scanner or significant software upgrade. The same protocol sequences loaded for ADNIGO will be used in ADNI2.

Site MRI qualification requires a phantom scan and a volunteer scan. Volunteer scanning can be done only AFTER IRB approval. See MRI section for further details.

PET SCAN CERTIFICATION

Any new participating sites for ADNI2 must complete the PET scanner certification process. Sites that have been certified previously for ADNIGO do ***NOT*** require recertification unless there has been a change in PET scanner or change in software paltform.

STUDY SUPPLIES

Once your site receives a 'Site Approval' notification email from adcsra@ad.ucsd.edu to begin enrollment, you will be contacted by ADCS Clinical Operations confirming the supplies needed by your site. The supplies you need will depend on the number of participants you have identified to screen for ADNI2. Additionally, you will need to identify how many follow-up participants will continue on to ADNI2, and which ones will have a LP.

There will be no initial supply distribution and there will be no auto shipments of Screening kits. Please be sure to use the Covance Supply Order form when requesting additional kits. The ADNI Coordinating Center at the ADCS will provide the following supplies for the ADNI2 study:

- DNA, APOE and RNA Collection, Labels and Shipping Supplies.
- Biomarker Collection, Labels and Shipping Supplies.
- Buffy Coat supplies
- CSF Collection and Shipping Supplies (including Sprotte Needles and LP Trays).
- Neuropsychometric Testing Supplies (ADAS Kits, Boston Naming Testing Booklet). These are the same supplies previously provided and used in ADNI1 and ADNIGO. Neuropsychometric Supplies will ***NOT*** routinely be provided to each site as sites are to use one set across ADNI1 to ADNI2.

NOTE: Spanish Neuropsychometric Testing Supplies must be requested by sites. These include Spanish ADAS Word Recall and Recognition, and Spanish Boston Naming Test Booklets.

- Subject binder inserts/tabs, spine and covers. (Actual binders are not being provided by ADCS, rather all sites were provided a start up fund at the start of ADNI2 from the ADCS which is to be used to cover the cost of binders.) Worksheets and Manuals will not be printed for sites. If a paper copy is needed, print the most recent version which is located in the document repository.

Please see the Biofluids section for detailed pictures and descriptions of the kit contents, and a list of items not provided by the ADCS for Lumbar Punctures. Study supplies will be sent to the Study Coordinator. Please keep your Protocol Personnel Log updated so that supplies are sent to the appropriate person.

RESUPPLY

The Covance and ADCS Resupply request forms are available on the document repository under 'forms'.

Request additional Screening Laboratory Kits from Covance by
Fax: **317-616-2352**
or
Email: **resupply.americas@covance.com.**

All other supplies can be requested from the ADCS:
adcs-clinops@ucsd.edu.

ADNI2 SAMPLE VISIT SCHEDULE AND GENERAL GUIDELINES FOR SCHEDULING PARTICIPANT VISITS

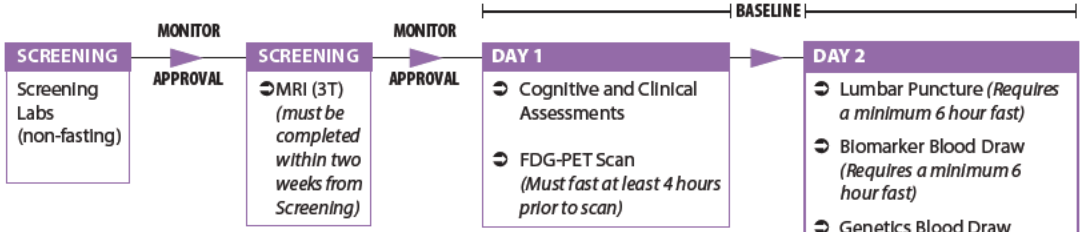
Below are the general guidelines for scheduling visits for ADNI2. More detailed instructions for each visit are in the Visit Procedures Section. In order to ensure standardized outcomes it is important the ADNI2 guidelines for scheduling participant visits are followed. Request any protocol deviations through the Protocol Deviation Form on the EDC.

ADNI 2 SAMPLE VISIT SCHEDULE

GENERAL GUIDELINES:

- ***NEW IN ADNI2:** A total of 2 sets of PET scans 2 years apart *across both* ADNI GO and ADNI 2. PET scans should occur 24 months from the last successful PET scan.
- †**NEW IN ADNI2:** A total of 2 lumbar punctures in ADNI 2. LP should occur 24 months from the last successful LP.
- LP and Biomarker Blood Draws *require* a *minimum* 6 hour fast.
- MRI should occur prior to LP, otherwise the MRI must occur *at least* 3 days after LP
- Subjects must fast for a *minimum* of 4 hours prior to FDG-PET scans
- There must be a *minimum* of 12 hours between the FDG-PET scan and AV-45 PET scan
- If all blood draws are completed at the same time, the RNA sample should *not* be taken first
- If RNA Blood Draw occurs separate from the other blood draws, the red topped evacuation tube should be used to capture the initial blood flow and discarded
- **NEW IN ADNI2:** Buffy Coat extracted from Biomarker Plasma Sample and shipped to NCRAD
- Cell immortalization blood samples are only necessary for new ADNI2 participants at Baseline, unless not previously collected for ADNI1/GO Follow-Ups
- DNA sample collection for APOE/GWAS is not needed if already collected for ADNI GO
- Cognitive assessments should not be done immediately after a blood draw or LP, as this may affect the results
- If LP and PET scan are done on the same day, LP should be completed prior to the FDG or AV-45 PET scan; otherwise there should be at least 12 hours between the LP and the scan.

NEW ADNI2 PARTICIPANT SAMPLE VISIT SCHEDULE (SCREENING AND BASELINE)



NOTE:
- ➲ Baseline must start within 28 days of the Screening visit.
- ➲ Once participants start Baseline they have two weeks to complete all Baseline procedures.

SAMPLE ADNI 2 INITIAL VISIT – CONTINUING PARTICIPANTS FROM ADNI1/GO

After site approval for ADNI 2, CN/MCI participants from ADNI 1 and EMCI participants from ADNI GO should be consented to ADNI 2 at the next annual in-clinic visit.

DAY 1
- ➲ Cognitive and Clinical Assessments
- ➲ MRI (3T for ADNIGO Follow-Ups. 1.5 T for ADNI1 Follow-Ups, unless otherwise directed by the MRI Core)
- ➲ *FDG-PET Scan (*Must fast at least 4 hours prior to scan)*

DAY 2
- ➲ †Lumbar Puncture *(Requires a minimum 6 hour fast)*
- ➲ Biomarker Blood Draw *(Requires a minimum 6 hour fast)*
- ➲ Genetics Blood Draw *(RNA, DNA for GWAS, if not previously collected)*
- ➲ Buffy Coat (extract and ship to NCRAD)
- ➲ *AV45 PET Scan *(Must be 12 hours between the two PET scans)*

NOTE:
- ➲ If ADNI 1 participant only agrees to the FDG-PET Scan (not AV45) under ADNI 2, the FDG scan should *ONLY* be conducted if previously done under ADNI 1, otherwise neither scan should be conducted.
- ➲ All Visit 1 procedures must be completed within two weeks.

DATA MANAGEMENT

OVERVIEW

There are three locations for the management of data for the ADNI2 Study.

1. **ADNI2 Clinical Data Portal:** The electronic data capture (EDC) is the primary point of registering a new participant or follow up subject, entering clinical data, signing off on eligibility, obtaining worksheets and procedures manuals.
2. **ADNI LONI Imaging Database:** LONI is the primary interface for imaging data upload. All MRI Scans, FDG PET Scans and AV45 PET Scans are uploaded to LONI.
3. **ADCS Administration Website:** This site is the location where required source documents are uploaded, which includes the MRI clinical reads, laboratory reports, and worksheets. The Query and Support Center for site to pose questions, review and respond to data queries from Coordinating Center.

Accounts for each of these online database are separate. Once an account is issued, access to any of these online databases can take place at any time and from any place internet access is available.

Never share your password with another person. **Every interaction with ADNI online data managment tools is time and date stamped and is traceable to the user who completed the transaction.**

ADNI2 CLINICAL DATA PORTAL / EDC

Activities on the ADNI Clinical Data Portal:

- Assign Participant ID
- Enter Visit Data
- Sign off on Eligibility
- Study Docs: Print Visit Packets, Access Procedures Manuals, SAE Reports, Study Memorandums, and Supply Order Forms.

Navigate to the system using this url: **http://adcs.org/, select ADCS Investigators > Study Resources > ADNI2 EDC**.

Accounts

After Site Approval is received, online accounts will be generated according to the access levels requested on the Protocol Personnel Log. Update the Personnel Log and Contact Information Form as new personnel at your site need online accounts or to remove access for this protocol. Send all updates and questions on access to: **adcs-clinops@ucsd.edu**.

Data Access Level:

View Only:	Allows view access only to site-specific study database.
Enter and update:	Allows user to enter and update data to site-specific study database.
Approval Privileges:	Provides access to approval forms. Credentials required are: MD, PA, DO, or NP. The electronic signature is a binding legal signature.

The following forms require electronic signature:

- Clinician Verification of Inclusion and Exclusion Criteria Form
- Clinician Review
- Site PI Approval (only Site PI can complete this form)

Timeliness Of Data Entry

- Data collected must be entered **promptly** on the ADNI2 Online database (**http://adcs.org/ > ADCS Investigators > Study Resources > ADNI2 EDC**)
- For screening and baseline visits, data must be submitted online within 1-2 business days. All subsequent visit data must be submitted within 5 business days of the visit.

ADNI LONI

Activities on the ADNI LONI Site:

- MRI Image and Phantom Upload
- PET Image and Phantom Upload

Details on accessing and uploading images for ADNI are part of the MRI and PET Technical Manuals. LONI is also the location where publicly-available datasets may be downloaded by users. Please send any questions to: **adni@loni.ucla.edu.**

Navigate to ADNI LONI database using this url: **https://ida.loni.ucla.edu**

ADCS Administration Website:

Activities on the ADCS Administration Site:

- Study File Upload
- Query & Support Center
- Protocol Deviation Review/Approval
- Regulatory Affairs Documents
- Recruitment Documents

Please note that the ADCS Administration Website is a separate URL from the ADNI2 EDC web portal and is a separate login.

To access the Administration Website go to **http://adcs.org. Select ADCS Investigators> Study Resources> ADCS Admin Portal.**

- If you forgot your username or password, please click on "forgot username/password".
- Then enter your email address and click "submit".
- Check your email for the username and temporary password. Follow the instructions included to log-in to admin web portal and update your temporary password to a permanent one.

If you have difficulties logging in to the ADCS Administration Website, email: **adcs-sd@ucsd.edu**.

Study File Upload:

This tool allows users to upload study documents and manage the stored files. The features include the following:

- "Upload" allows you to post Word Docs, JPEG and PDF files for protocols to which you are assigned. These files are saved online and are required for Monitor review. **File size is limited to 4MB**.

Tips for reducing file size of scanned study documents:

- In order to reduce the file size of scanned study documents, use a lower resolution (300dpi or less) and scan documents in grayscale or black and white. Black and white is preferred as it will produce the smallest file size. Use grayscale for documents containing shaded text boxes because these boxes may appear completely black if the document is scanned using black and white.
- Sometimes the file size can be further reduced via the **"Reduce File Size"** command. After opening a PDF, go to the menu bar at the top of the screen and click on **"Document."** Select **"Reduce File Size"** from the drop down menu. If the file is already as small as possible then this command will have no effect. ***(Please note that reducing the file size of a digitally signed document removes the signature.)***
- The **"PDF Optimizer"** also provides settings for reducing the size of PDF files. After opening a PDF, go to the menu bar at the top of the screen and click on**"Advanced."** Select **"PDF Optimizer"** from the drop down menu and another window should pop up. The default settings are usually appropriate for maximum efficiency but some methods of compression may make images unusable in certain situations so experiment with different settings before making changes that cannot be discarded.

NOTE: Upload the worksheet to the appropriate category and only use misc if the worksheet you are uploading does not have it's own category available.

- "View" allows you to search for a stored file uploaded by any user at your site and protocol assignment. The filter may be by "Protocol", "Participant", "Visit" and "Category."
- Files listed in "View" may also be downloaded and printed.
- **IMPORTANT: REMOVE ALL PARTICIPANT IDENTIFIERS (INCLUDING NAME, DOB, MEDICAL RECORD NUMBER) ON ANY FORMS SUBMITTED BY FAX OR UPLOAD TO THE ADCS. USE ONLY THE ADNI PARTICIPANT ID, VISIT NAME AND DATE.**
- If changes or corrections are made to source documents, please rescan and re-upload that section of worksheets with the correction. Uploaded documents may also be deleted by site users.
- The list of required forms by visit is included under the Visit Procedures section of this manual.

If a file is uploaded that should not have been and needs to be deleted, go into **Study File Upload > Upload** and begin entering parameters required for uploading a new document; previously uploaded docs with the same parameters as those selected will appear in the table. The 'Delete' option is available there.

Query & Support Center:
This is a centralized location where you may post queries to ADCS groups, manage the responses, and also receive queries from ADCS groups. The features include the following:

- "Create a New Query" and have it automatically routed to the correct recipient in an ADCS group for response.
- In "Site Inbox", view all queries communicated between users at your site and the ADCS groups. Access to queries is limited by your site and protocol assignment.

Query & Support Center (Cont'd):

- In "My Queries", view only the queries generated by you and ADCS initiated queries responded by you.
- In "Search Queries", find queries associated with your site and protocol assignment. Search according to "Status", "Category", "Protocol", "Created by", and Date intervals and other additional filters.

Check the Query and Support Center every week to ensure that all queries from you and from the coordinator are being reviewed and responded to.

Protocol Deviations
This tool allows you to track a summary of all records entered into the Protocol Deviation eCRF for your site. The deviations are classified by Project Director as decision-pending, denied, approved, or acknowledged. Check the Protocol Deviations Review tool weekly to ensure the Project Director has addressed your deviation requests or documentation.

CLINICAL MONITORING

The Clinical Monitors are the primary communication link between the study sites and the Coordinating Center. Their overarching role is to ensure that sites are GCP-compliant by:

- Evaluating and initiating sites, which includes site capacity and commitment to protecting the health and safety of study participants;
- Approving all potential participants for enrollment into each trial;
- Auditing participant and site records to protect sponsor against fraud;
- Reviewing participant and site records and verifying source records to ensure that clinical trials are being conducted as specified by protocols procedures;
- Reviewing psychometric and behavioral assessments for accuracy of administration and scoring;
- Training site personnel in study procedures as needed;
- Identifying on-site problems in study conduct and helping to determine and implement solutions;
- Serving as ambassadors for the ADNI Coordinating Center when interacting with study sites, and facilitating successful conduct of protocols at each site.

ADCS Clinical Monitors are responsible for Participant Eligibility and Efficacy, with emphasis on screening, baseline, in-clinic evaluation visits and assessments, Safety and Regulatory Compliance, with emphasis on Adverse Events/SAEs, Concomitant Medications, and regulatory documents.

STUDY CLOSE-OUT

ADNI2 data is managed on a separate data portal from the prior ADNI protocol, and all data entry should be kept current on an ongoing basis. This is also important because of the public access to all ADNI data on an ongoing basis.

If a participant ends participation for this protocol or does not consent to follow-up under the next protocol, note the reason for this discontinuation on the early discontinuation and withdrawal form. If possible, a final in-clinic visit should be scheduled. Consult the Project Director on whether MRI or PET imaging should be included in this visit, if the participant agrees to imaging. If a visit is not possible, review all concurrent medications, pre-existing symptoms and adverse events with the participant and study partner; ensure that each record in these logs either has an end date or is marked as 'continuing'.

The closing out of a site is a process and not merely a final and/or routine monitoring visit. Your 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 ADCS 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 clinical monitor will conduct a site close out visit after all participants at the site have completed all follow-up visits and all data queries have been resolved.

During the close-out visit:

- A final review of the regulatory binder is performed.
- CAP / CLIA accreditations are verified.
- Current and signed CV for the PI and all co-investigators are verified.
- FDA form 1572 is verified to ensure it lists all current staff and is signed by the PI.
- Protocol signature log is verified as complete and signed by all site personnel.
- Financial disclosure forms are verified as complete for the PI and all co-investigators.
- All IRB submissions, notifications, and correspondence are verified as present and organized.
- All study memos from the ADCS are verified as present and organized.
- Training records (i.e. EDC, ADAS Rater, CDR rater) are verified.
- All other significant study related documents are reviewed for completeness.
- A final review of AEs/SAEs is conducted to ensure no issues remain.
- Confirmation that all issues/actions from previous monitoring visits are closed.
- Confirmation that all queries in the Query and Support Center have been addressed and are closed.

USE OF MULTIPLE LOCATIONS AT A SINGLE CENTER

Some ADNI sites will use more than one location using the same personnel. The following guidelines have been developed to aid in the decision concerning the use of additional locations at a single center.

Any plan to use more than one location to conduct the ADNI must be approved by Dr. Weiner and Dr. Aisen. The Site Principal Investigator must take responsibility for any additional locations. Also, a single contract will be filed for each center; any exceptions must be approved by both Dr. Aisen and Dr. Weiner.

- A single study coordinator must be used for all locations. This individual must be available to the clinical monitors to answer questions about data entered on the ADNI EDC from all locations. The ADNI Coordinating Center at the ADCS should be immediately notified if there are any changes in the study coordinator.
- Monitoring visits must be carried out at a single location.
- All source documents must be at a single place to avoid the expense of additional travel by the clinical monitors.

RECRUITMENT AND RETENTION

The ADCS Recruitment and Retention Team has a host of ADNI2 recruitment materials available to assist with site efforts. These include:

- Flyer
- Trifold Brochure
- Bookmark
- Health fair package consisting of 60 inch x 24 inch vinyl indoor-outdoor banner with grommets for mounting, and an 11 x 17 laminated poster on foam core material with a cardboard easel-type support so that it can be displayed on a desk. (It is a larger version of the flyer) These can be ordered separately.
- Physician Pocket Cards (also known as Doc Cards)
- Informational PET Pamphlet
- Informational MRI Pamphlet
- Lumbar Puncture Participant Handout
- Dear Colleague Letter
- Letter to the Editor
- Professional PowerPoint
- Community PowerPoint

For ADNI2 Recruitment, we are working with GYMR, a communications firm specializing in issues affecting public health such as Alzheimer's disease. Our teams are working together to implement marketing and communications strategies to help increase awareness of the ADNI2

study and help recruit participants at the study sites nationwide. The outreach efforts on a national front include:

- An online/social media campaign – This includes an Alzheimer's Disease Research Facebook page dedicated to ADNI until recruitment is complete. Tweets about the study on the ADCS Twitter account, ADCSComm. Outreach to bloggers reaching a range of audiences, including a variety of regions, seniors, caregivers and baby boomers, Alzheimer's specific, health, women's interest and moms.
- National advertising in various magazines, outreach to national columnists, NPR and local public radio stations.
- Outreach to national third party healthcare provider and consumer advocacy organizations.
- Distribution of ready-to-run newspaper articles to thousands of hometown community newspapers across the country.
- Study information page on ADCS.org website that features contact information for all sites participating in ADNI2.
- Blurb placed in the Alzheimer's Disease Information Network E-Newsletter distributed to over 3,000 subscribers

The advertisement mentioned above is a printed public service announcement (PSA).

In addition to our national outreach, the National Institutes of Aging (NIA) has released a formal announcement of ADNI2. Lastly, materials to use in sites' local communities include a localized press release and tailorable Craigslist posting. GYMR, the communications agency hired to assist with ADNI2 has sent tool kits to each site.

RETENTION

To assist retention efforts, the quarterly ADNI Exclusive newsletters for participants in ADNI1 and ADNIGO will be distributed to ADNI2 participants as well. Also, study sites have the option to utilize a participant "Welcome" letter from Dr. Weiner that thanks all ADNI GO participants (newly enrolled eMCI and continuing ADNI1 participants) and describes this third phase of ADNI in addition to briefly touching upon testing procedures involved. Mugs with the ADNI logo have been distributed. We have various informational materials that sites can utilize on the ADCS Library Tools List. Finally, we are distributing handmade lap-size quilts to help with retention. They will be shipped to sites upon request as you enroll new participants.

Contact Us

Most of the materials mentioned above are available on the ADNI2 toolkit or on the ADCS Admin website. Please contact the ADCS Recruitment and Retention Team at **brainlink@ucsd.edu** for any requests, questions, comments or suggestions. Also, sites should send all IRB approvals regarding recruitment and retention materials to the email address above.

New Enrollees: Screening Procedures

SUMMARY

The purpose of the ADNI2 screening 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. The MRI will be conducted only for participants who meet eligibility criteria for all other screening assessments as determined by both a site investigator and ADCS clinical monitor.

Eligibility will be determined according to the Inclusion/Exclusion criteria outlined later in this section and confirmed by an ADCS clinical monitor before the participant can be brought back for Baseline.

The following items will be covered in this section:

Key Reminders

- The window from Screening to Baseline is 28 days.
- Participants must meet all inclusion/exclusion criteria.
- Complete Data Entry within 3 business days of the screen, including Laboratory Reports.
- Monitor approval is required prior to conducting the Screening 3T MRI scan.
- Scan must be approved before proceeding to Baseline.

1. PARTICIPANT IDENTIFIERS

The ADNI Participant ID (PTID) consists of the ADCS 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 will begin at 4001.

Example: A participant from site 900 who is the third subject assigned for ADNI 2 is 900_S_4003.

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, while uploading to the LONI database.

New Enrollees: Screening Procedures

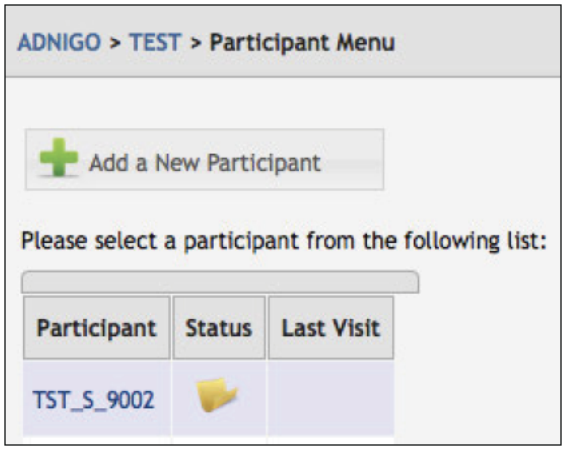
IMPORTANT: **Participant IDs may only be assigned once consent is signed. Assign the ID on the day of screening whenever possible. Once assigned, IDs cannot be removed from the ADNI Clinical Portal.**

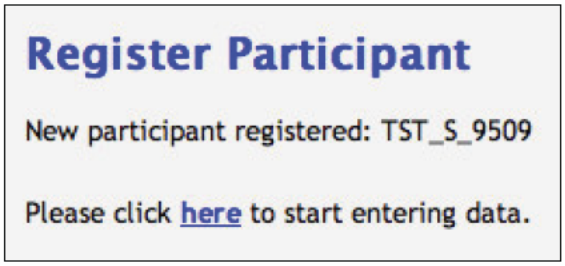
TO ASSIGN AN ADNI PTID FOR NEW PARTICIPANTS:

- Log on to the ADNI Clinical Data Portal:

  adcs.org/ADCSInvestigators/StudyResources/ADNI2EDC

- From 'EDC', click on 'Add a New Participant'.
- Answer 'No' to the question 'Was Subject previously enrolled in ADNI?'.
- The new participant ID will be displayed on the following screen.

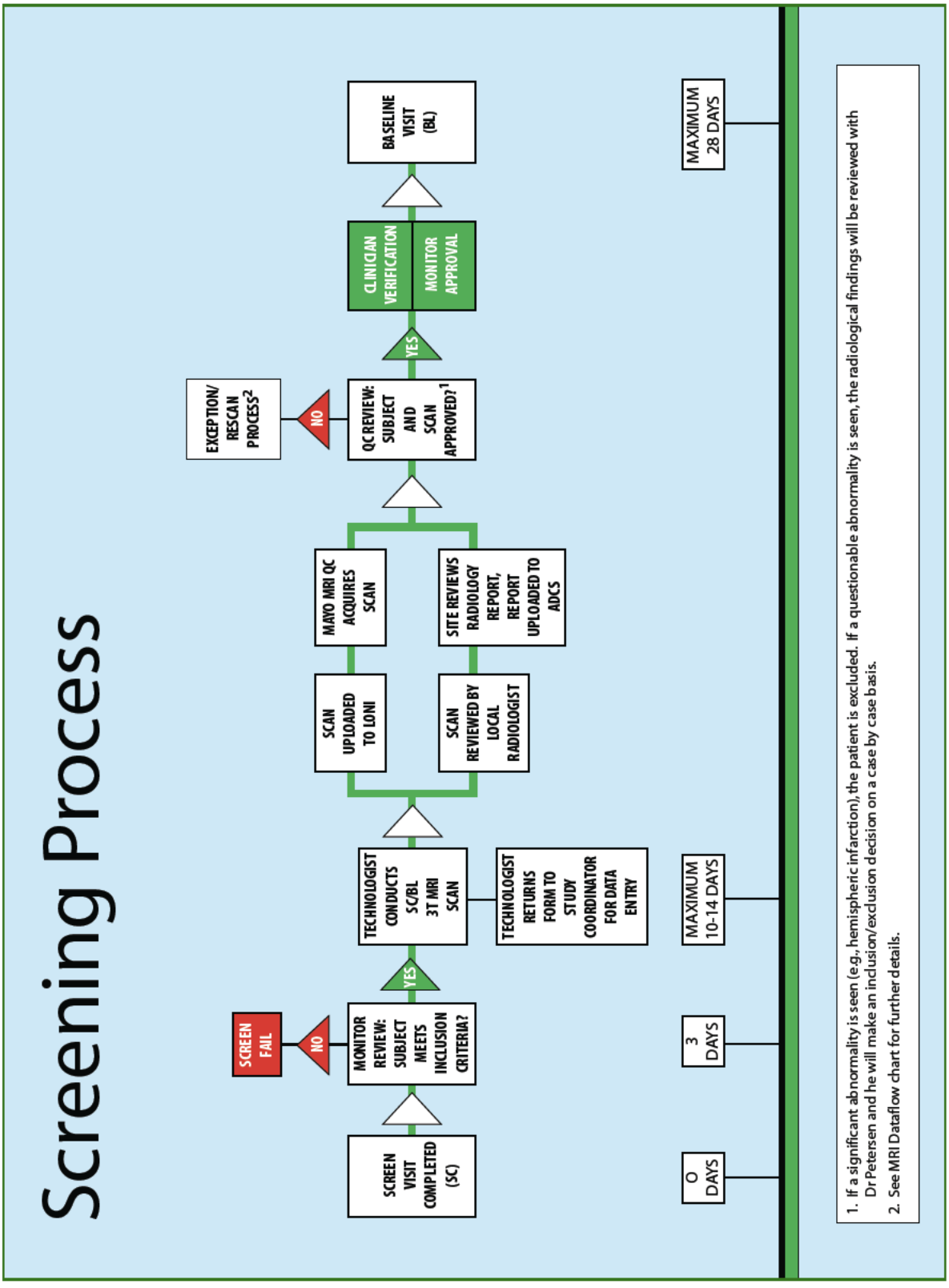




Enter Registry as soon as possible after a visit is initiated

1. Indicate participant status as active (even for participants who screen fail).
2. Visit type as standard for those that complete their first ADNI2 visit (even if the participant screen fails).
3. The examination date is the date the first part of the ADNI2 screening visit was completed.
4. If a participant is a rescreen, indicate "yes" for "Is this a rescreen" and enter the previous participant ID in the subsequent field.

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


Screening Process
SCREEN VISIT COMPLETED (SC)
MONITOR REVIEW: SUBJECT MEETS INCLUSION CRITERIA?
NO
SCREEN FAIL
YES
TECHNOLOGIST CONDUCTS SC/BL 3T MRI SCAN
TECHNOLOGIST RETURNS FORM TO STUDY COORDINATOR FOR DATA ENTRY
SCAN UPLOADED TO LONI
SCAN REVIEWED BY LOCAL RADIOLOGIST
MAYO MRI QC ACQUIRES SCAN
SITE REVIEWS RADIOLOGY REPORT, REPORT UPLOADED TO ADCS
QC REVIEW: SUBJECT AND SCAN APPROVED?1
NO
EXCEPTION/ RESCAN PROCESS2
YES
CLINICIAN VERIFICATION
MONITOR APPROVAL
BASELINE VISIT (BL)
0 DAYS
3 DAYS
MAXIMUM 10-14 DAYS
MAXIMUM 28 DAYS
1. 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 Dr Petersen and he will make an inclusion/exclusion decision on a case by case basis.
2. See MRI Dataflow chart for further details.

New Enrollees: Screening Procedures

2. DATA FLOW

Please see the data flowchart on the previous page for an illustration of this process.

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.
- Enter all data in the ADNI2 Clinical Data Portal within 3 business days of screen:

  adcs.org/ADCSInvestigators/StudyResources/ADNI2EDC

- Upload worksheets in the Administration Portal:

  adcs.org/ADCSinvestigators/study resources/ADCSAdmin Portal/StudyFileUpload

- Enter Clinician Verification after completing review of all required Screening Assessments.

MONITOR REVIEW:

- ADCS Clinical Monitors will review all data entered in the EDC and study documents uploaded to ADCS Admin Portal.
- Clinical Monitor enters all queries on the ADCS Admin Portal/Query and Support Center.
- Resolve or reply to all queries.
- Upon satisfactory resolution of queries, clinical Monitor approves screen for 3T MRI.

3T MRI SCAN:

- Conduct as soon as Screen Visit is monitor approved.
- Ensure Participant and Study Partner have the MRI Pamphlet with Appointment Reminder and Directions.
- Ensure MRI Center has current MRI Technologist manual and MRI Scan Information Form for this participant.
- Upload Scan to LONI day of scan (see MRI Training Manual for details.)
- Enter MRI Scan Information form in EDC on day of scan:

  adcs.org/ADCSInvestigators/StudyResources/ADNI2EDC

- Email monitor that scan has been conducted and entered in the EDC system.
- Upload copy of de-identified Radiology Report/Clinical Read as soon as it has been reviewed/signed off by Study Clinician:

adcs.org/ADCSinvestigators/study resources/ADCSAdminPortal/StudyFileUpload

Ensure any identifers are blacked out on the copy uploaded to the ADCS including Medical Record numbers, telephone numbers, and date of birth.

New Enrollees: Screening Procedures

MRI QC REVIEW:
MRI Quality Control at Mayo Clinic (MRI QC) will review the scan and confirm eligibility in the EDC by completing the MRI inclusion eCRF.

CLINICIAN VERIFICATION:
Site Clinician completes the Clinician Verification form verifying eligibility only after reviewing the 3T MRI Radiology Report/Clinical Read.

MONITOR APPROVAL:
The Clinical Monitor completes the Monitor Eligibility only after confirming:

1. Site Clinician approval
2. MRI QC Approval

IMPORTANT REMINDERS:

- 3T MRI may **NOT** be conducted until screen approved by both clinician and monitor
- Baseline may **NOT** be conducted until 3T MRI approved by Mayo MRI QC group, clinician and monitor.
- Baseline visit (in-clinic assessment) must start within 28 days of screening visit. There are an additional 2 weeks to complete other Baseline procedures (e.g. FDG PET, AV45 PET, LP).

DO NOT CONTINUE TO BASELINE UNTIL MONITOR ELIGIBILITY IS CONFIRMED!

3. SCREEN FAILURES AND RESCREENS

All participants who sign consent must be assigned an ADNI2 ID, even if a Screening Visit is not completed. Indicate whether a participant is screen fail on the Clinician Verification form.

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

1. Registry (Reminder: For all participants, even those who screen fail, the participant status should be 'active,' and visit type as 'standard').
2. Participant Demographics
3. Clinician Verification
4. Study Summary
5. Publicity Tracking

Before scheduling a rescreen, contact your clinical monitor for approval. There is a minimum of 2 months required before a rescreen can be scheduled. Rescreens must be assigned a new ADNI2 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 monitor whether the alternate Logical Memory story should be used for the rescreen.

New Enrollees: Screening Procedures

4. Inclusion Criteria: NEW Participants – CN, EMCI, LMCI, AD

	CN	EMCI	LMCI	AD
1	Subject must be ***free of memory complaints***, verified by a study partner, beyond what one would expect for age	Subject ***must have a subjective memory concern*** as reported by subject, study partner, or clinician	Same as EMCI	Same as EMCI
2	Normal memory function documented by scoring above education adjusted cutoffs on the Logical Memory II subscale (Delayed Paragraph Recall, Paragraph A only) from the Wechsler Memory Scale –Revised (the maximum score is 25): **a. ≥9 for 16 or more years of education** **b. ≥5 for 8-15 years of education** **c. ≥3 for 0-7 years of education**	Abnormal memory function documented by scoring within the education adjusted ranges on the Logical Memory II subscale (Delayed Paragraph Recall, Paragraph A only) from the Wechsler Memory Scale –Revised (the maximum score is 25): **a. 9-11 for 16 or more years of education** **b. 5-9 for 8-15 years of education** **c. 3-6 for 0-7 years of education**	Abnormal memory function documented by scoring within the education adjusted ranges on the Logical Memory II subscale (Delayed Paragraph Recall, Paragraph A only) from the Wechsler Memory Scale –Revised (the maximum score is 25): **a. ≤8 for 16 or more years of education** **b. ≤4 for 8-15 years of education** **c. ≤2 for 0-7 years of education**	Same as LMCI
3	Mini-Mental State Exam score between **24 and 30** (inclusive). (Exceptions may be made for subjects with less than 8 years of education at the discretion of the project director)	Same as CN	Same as CN	Mini-Mental State Exam score between **20 and 26** (inclusive) (Exceptions may be made for subjects with less than 8 years of education at the discretion of the project director)
4	Clinical Dementia Rating = **0**. Memory Box score must be **0**	Clinical Dementia Rating = **0.5**. Memory Box score must be at least **0.5**	Same as EMCI	Clinical Dementia Rating = **0.5 or 1.0**
5	**Cognitively normal**, based on an absence of significant impairment in cognitive functions or activities of daily living	**General cognition and functional performance sufficiently preserved such that a diagnosis of Alzheimer's disease cannot be made** by the site physician at the time of the screening visit	Same as EMCI	NINCDS/ADRDA criteria for **probable AD**

4. Inclusion Criteria: NEW Participants – CN, EMCI, LMCI, AD (Cont'd)

	CN	EMCI	LMCI	AD
6	Stability of Permitted Medications for 4 weeks. In particular, subjects may: a. Take stable doses of antidepressants lacking significant anticholinergic side effects (if they are not currently depressed and do not have a history of major depression within the past 1 year). b. Estrogen replacement therapy is permissible c. Gingko biloba is permissible, but discouraged d. Washout from psychoactive medication (e.g., excluded antidepressants, neuroleptics, chronic anxiolytics or sedative hypnotics, etc.) for at least 4 weeks prior to screening	Stability of Permitted Medications for 4 weeks. In particular, subjects may: a. Take stable doses of antidepressants lacking significant anticholinergic side effects (if they are not currently depressed and do not have a history of major depression within the past 1 year). b. Estrogen replacement therapy is permissible c. Gingko biloba is permissible, but discouraged d. Washout from psychoactive medication (e.g., excluded antidepressants, neuroleptics, chronic anxiolytics or sedative hypnotics, etc.) for at least 4 weeks prior to screening **e. Cholinesterase inhibitors and memantine are allowable if stable for 12 weeks prior to screen**	Same as EMCI	Same as EMCI

New Enrollees: Screening Procedures

Additional Inclusion Criteria: All Diagnostic Categories

7. Geriatric Depression Scale less than 6.
8. Age between 55-90 (inclusive).
9. Study partner is available who has frequent contact with the subject (e.g. an average of 10 hours per week or more), and can accompany the subject to all clinic visits for the duration of the protocol.
10. Visual and auditory acuity adequate for neuropsychological testing.
11. Good general health with no diseases expected to interfere with the study.
12. Participant is not pregnant, lactating, or of childbearing potential (i.e. women must be two years post-menopausal or surgically sterile).
13. Willing and able to participate in a longitudinal imaging study.
14. Hachinski less than or equal to 4.
15. Completed six grades of education or has a good work history (sufficient to exclude mental retardation).
16. Must speak English or Spanish fluently.
17. Willing to undergo repeated MRIs (3Tesla) and at least two PET scans (one FDG and one Amyloid imaging) and no medical contraindications to MRI.
18. Agrees to collection of blood for GWAS, APOE testing and DNA and RNA banking.
19. Agrees to collection of blood for biomarker testing.
20. Agrees to at least one lumbar puncture for the collection of CSF.

New Enrollees: Screening Procedures

5. Exclusion Criteria: NEW Participants – CN, EMCI, LMCI, AD

	CN	EMCI	LMCI	AD
1	**Any significant neurologic disease**, such as Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities	**Any significant neurologic disease other than suspected incipient Alzheimer's disease**, such as Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities.	Same as EMCI	**Any significant neurologic disease other than Alzheimer's disease**, such as Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities.

Additional Exclusion Criteria: All Diagnostic Categories

2. Screening/baseline MRI scan with evidence of infection, infarction, or other focal lesions. Participants with multiple lacunes or lacunes in a critical memory structure are excluded.
3. Presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments or foreign objects in the eyes, skin or body.
4. Major depression, bipolar disorder as described in DSM-IV within the past 1 year. Psychotic features, agitation or behavioral problems within the last 3 months which could lead to difficulty complying with the protocol.
5. History of schizophrenia (DSM IV criteria).
6. History of alcohol or substance abuse or dependence within the past 2 years (DSM IV criteria).
7. Any significant systemic illness or unstable medical condition which could lead to difficulty complying with the protocol.
8. Clinically significant abnormalities in B12, or TFTs that might interfere with the study. A low B12 is exclusionary, unless follow-up labs (homocysteine (HC) and methylmalonic acid (MMA)) indicate that it is not physiologically significant.
9. Residence in skilled nursing facility.
10. Current use of specific psychoactive medications (e.g.,certain antidepressants, neuroleptics, chronic anxiolytics or sedative hypnotics, etc.). Current use of warfarin (exclusionary for lumbar puncture).

New Enrollees: Screening Procedures

Additional Exclusion Criteria: All Diagnostic Categories (Cont'd)

11. Investigational agents are prohibited one month prior to entry and for the duration of the trial.
12. Participation in clinical studies involving neuropsychological measures being collected more than one time per year.
13. Exclusion for amyloid imaging with ^{18}F –AV-45: Current or recent participation in any procedures involving radioactive agents such that the total radiation dose exposure to the participant in any given year would exceed the limits of annual and total dose commitment set forth in the US Code of Federal Regulations (CFR) Title 21 Section 361.1.
14. Exceptions to these guidelines may be considered on a case-by-case basis at the discretion of the protocol director (Dr. Petersen).

GENERAL RULE: Any history of cancer five years prior to screening is exclusionary (history of skin melanoma is not exclusionary)

Inclusion Criteria: Follow-Up Participants

1. Must have been enrolled and followed in ADNI1 for at least one year or enrolled in ADNIGO with original diagnosis of Cognitively Normal (CN), Mild Cognitive Impairment (MCI), or Early Mild Cognitive Impairment (EMCI) regardless of whether a diagnostic conversion has occurred since initial enrollment in ADNI.
2. Willing and able to continue to participate in an ongoing longitudinal study. A reduced battery of tests is allowable if the participant is not able/willing to complete the full battery.
3. Study partner is available who has frequent contact with the participant (e.g., an average of 10 hours per week or more), and can accompany the participant to all clinic visits for the duration of the protocol.

Exclusion Criteria: Follow-Up Participants

1. Participants will not be able to participate in amyloid imaging with ^{18}F-AV-45 (florbetapir F 18) if the following is true: Current or recent participation in any procedures involving radioactive agents such that the total radiation dose exposure to the participant in any given year would exceed the limits of annual and total dose commitment set forth in the US Code of Federal Regulations (CFR) Title 21 Section 361.1.

New Enrollees: Screening Procedures

6. EXCLUDED MEDICATIONS

PLEASE NOTE:

This is not a complete list of all excluded medications. For drugs not included here, please bring to the attention of your monitor prior to screening.

1. Current use of Warfarin
2. Antidepressants with anti-cholinergic properties are excluded.
3. Regular use of narcotic analgesics (>2 doses per week) within 4 weeks of screening.
4. Use of neuroleptics with anti-cholinergic properties (e.g., chlorpromazine, thioridazine) within 4 weeks of screening.
5. Chronic use of other medications with significant central nervous system anticholinergic activity within 4 weeks of screening (e.g., diphenhydramine).
6. Use of Anti-Parkinsonian medications (including Sinemet, amantadine, bromocriptine, pergolide, selegeline) within 4 weeks of screening.
7. 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).
8. 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.

EXPANDED LIST ON FOLLOWING PAGES

New Enrollees: Screening Procedures

NARCOTIC ANALGESICS: Not allowed within 4 weeks prior to screening

GENERIC NAME	BRAND NAME
Hydromorphone	Dilaudid
Oxycodone/Acetaminophen	Percocet
Oxycodone/Aspirin	Percodan
Propoxyphene/Darvon and its variations	
Narcotics that contain codeine or morphine	

NEUROLEPTICS: Not allowed within 4 weeks prior to screening

Chlorpromazine	Thorazine
Fluphenazine	Prolixin
Loxapine	Loxitane
Perphenazine	Etrafon, Trilafon
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine
Clozapine	Clozaril
Haloperidol	Haldol

Use of the following is permitted if dose is stable for 4 weeks prior to screening:

Aripiprazole	Abilify
Olanzapine	Zyprexa
Quetiapine	Seroquel
Risperidone	Risperdal (up to 2mg/day)
Ziprasidone	Geodon
Haloperidol	Haldol

ANTICHOLINERGIC AGENTS: Not allowed within 4 weeks prior to screening

Amantadine	Symmetrel
Benztropine	Cogentin
Cyproheptadine	Periactin
Dicyclomine	Bentyl
Diphenhydramine	Benadryl, Sominex 2
Diphenoxylate with Atropine	Lomotil
Hydroxyzine	Vistaril, Atarax
Hyoscyamine	Levsin
Meclizine	Antivert, Bonine
Prochlorperazine	Compazine
Trihexyphenidyl	Artane
Trimethobenzamide	Tigan

New Enrollees: Screening Procedures

ANTIPARKINSONIAN MEDICATIONS: Not allowed within 4 weeks prior to screening

GENERIC NAME	BRAND NAME
Bromocriptine	Parlodel
Deprenyl/Selegilene	Eldepry
Levodopa	Sinemet
Pergolide	Permax
Pramipexole	Mirapex

INVESTIGATIONAL DRUGS: Not allowed within 4 weeks of screening

SEDATIVES/BENZODIAZEPINES: Not Allowed Within 4 Weeks Of Screening

Chlordiazepoxide	Librium
Clonazepam	Klonopin
Diazepam	Valium
Flurazepam	Dalmane
Meprobamate	Miltown
Triazolam	Halcion

Allowed if on stable doses 4 weeks prior to screening:

Alprazolam	Xanax
Buspirone	Buspar
Chloral Hydrate	Noctec
Lorazepam	Ativan
Oxazepam	Serax
Temazepam	Restoril
Trazodone	Desyrel
Zaleplon	Sonata
Zolpidem	Ambien

ANTIHYPERTENSIVE AGENTS WITH FREQUENT CNS SIDE-EFFECTS: Not allowed within 4 weeks

Clonidine	Catapres

New Enrollees: Screening Procedures

7. PERMITTED MEDICATIONS

1. Cholinesterase inhibitors and memantine are permitted if the dose is stable for 4 weeks prior to screening.
2. Use of estrogen and estrogen-like compounds is allowed if the dose has been stable for 4 weeks prior to screening.
3. 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 (Dr. Petersen).

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.

New Enrollees: Screening Procedures

8. SCREENING ASSESSMENTS

- Explain study
- Obtain consent
- Demographics (Participant and Study Partner)
- Family History
- Inclusion and Exclusion Criteria
- Medical History
- Physical Exam
- Neurological Exam
- Hachinski
- Vital Signs
- Height
- Screening Labs (hematology, chemistry panel, urinalysis, B12, TSH)
- Mini Mental State Examination
- Logical Memory I and II
- Geriatric Depression Scale
- Clinical Dementia Rating Scale
- Concurrent Medications
- Pre-Existing Symptoms Checklist and Log
- Adverse Events
- Publicity Tracking
- Diagnostic Summary
- Autopsy consent discussion
- MRI (3T) - Screening MRI only to be conducted after confirmation from clinician and monitor that the subject has met all other inclusion/exclusion criteria.

9. SCREENING BLOOD DRAWS

New participants must have screening blood draws to aid in assessing eligibility. Screening kits are provided by Covance; please refer to the clinical laboratory samples section in the Biofluids Section of the Procedures Manual for more detailed information, as well as the Covance Lab Manual posted to the document repository.

Laboratory reports must be revised, signed and filed in the source documents for monitor review.

10. PRIVATE MD NOTIFICATION

As soon as a screened participant meets approval, send a letter to his/her private MD, notifying the MD of the participant's involvement and outlining the ADNI procedures. Consent from the participant is required before sending information to their private MD. Each site should include in the letter to the MD the name and telephone number of a site physician who is available to answer any questions about ADNI. A sample letter and protocol synopsis is available in the document repository.

11. BASELINE VISIT:

KEY REMINDERS

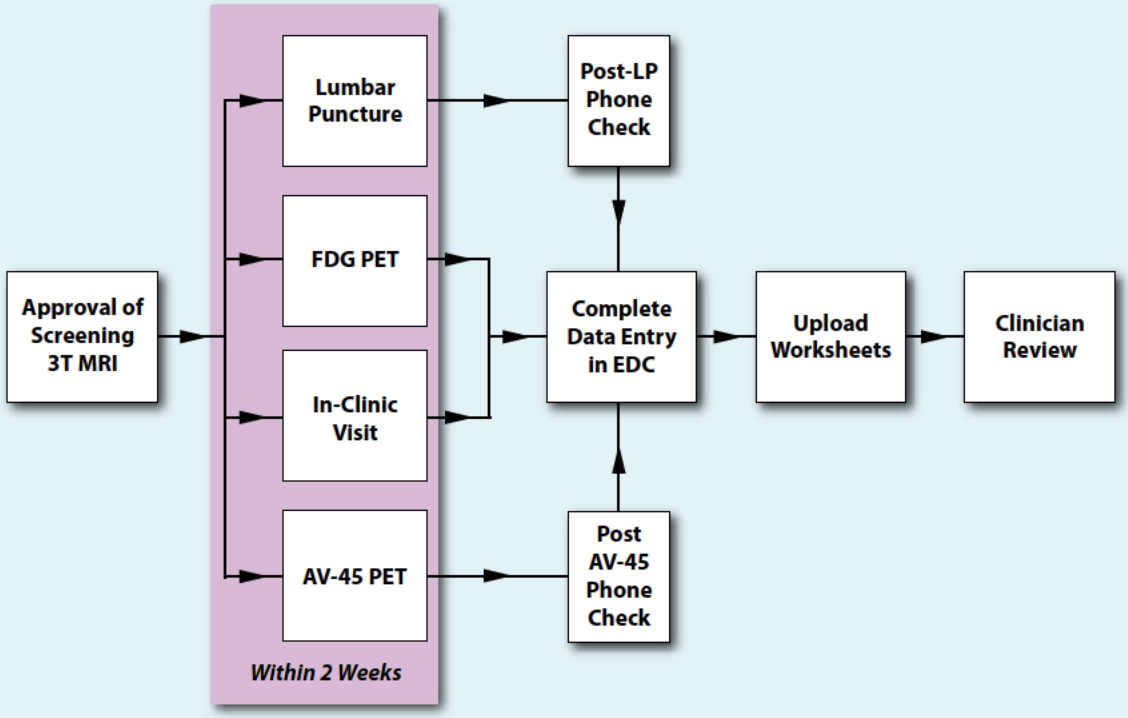
- The window from Screening to Baseline is 28 days.
- Participants must meet all inclusion/exclusion criteria.
- Complete Data Entry within 5 business days of the visit.

DATA FLOW

Before conducting any Baseline assessments, the Screening 3T MRI is reviewed and approved by:

- Local Radiologist
- ADNI MRI QC (MRI Inclusion ECRF)
- Clinical Monitor

IMPORTANT: **If baseline assessments are conducted prior to obtaining full approval, the site may not be compensated for these.**



More detailed Data flow for LP, FDG, PET, AV-45 PET under these separate procedures sections.
Rules for Scheduling Imaging Procedures and LP can be found under Start-Up and General Information

11. BASELINE VISIT (Cont'd)

DATA FLOW (Cont'd)

Once the Baseline visit begins, you have 2 weeks to complete all baseline procedures. Please refer to the Sample Visit Schedule under the Overview Section of this manual for rules on scheduling Lumbar Puncture, AV-45 PET and FDG-PET scans in relation to the Baseline in-clinic visit.

Keep in mind that the CSF, Plasma and Serum collected for Biomarker analysis are after at least a 6 hour fast. Buffy Coat is extracted from Plasma tubes and shipped ambient to NCRAD. ***Cognitive assessments should NOT be scheduled while the participant is fasting, or immediately after an LP or imaging session.***

Complete Data entry within 5 business days of the Baseline visit. Scan and Upload worksheets in the Administration Portal:

adcs.org/ADCSinvestigators/studyresources/ADCSAdminPortal/StudyFileUpload

BASELINE ASSESSMENTS

- Plasma and Serum Biomarker Collection *
- CSF Collection *
- Genetic Sample Collection (DNA, RNA, Cell Immortalization)
- Neuropsychological Battery (follow order of assessments on worksheets)
- MoCA
- ADAS-Cog 13
- Everyday Cognition - Participant and Study Partner Self-Report
- Neuropsychiatric Inventory
- Functional Assessment Questionnaire
- Vital Signs
- Concurrent Medications Review
- Diagnostic Summary
- Adverse Event
- FDG PET Scan *
- AV-45 PET Scan
- AV-45 24-48 Hour Follow-Up
- Post LP phone call
- Clinician Review
- Autopsy consent discussion

* Fasting

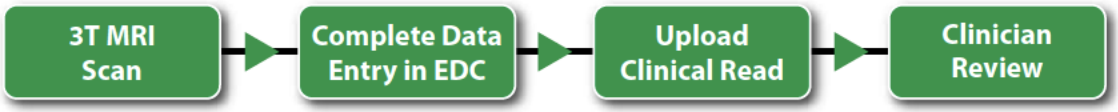
New Enrollees: Baseline and Follow-Up Procedures

12. MONTH 3 VISIT:

KEY REMINDERS

- The Month 3 visit is scheduled 3 months from the date of the Screening MRI scan.
- A clinical read must be reviewed and uploaded for central ADNI review.

DATA FLOW



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

adcs.org/ADCSinvestigators/studyresources/ADCSAdminPortal/StudyFileUpload

If Adverse Events or changes to Concurrent Medications are reported at this visit, enter these in the appropriate form.

MONTH 3 ASSESSMENTS

- 3T MRI Scan
- Clinician Review

THE FOLLOWING WORKSHEETS MUST BE UPLOADED FOR MONTH 3:

- MRI Report: Site Clinical Read - 3.0T
- MRI

If updates made:

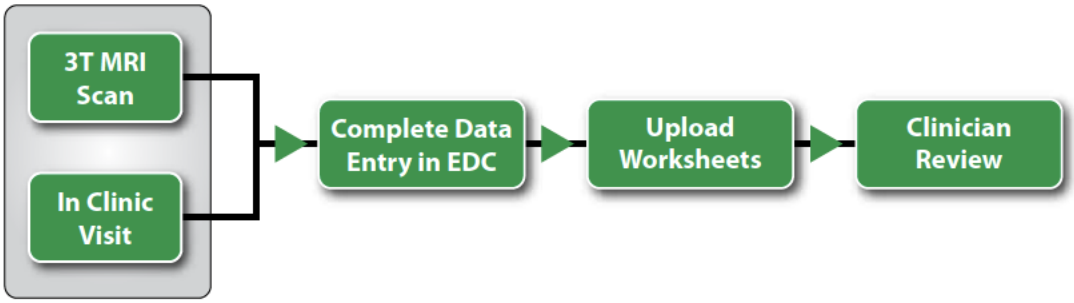
- Adverse Events/Hospitalizations Log
- Concurrent Medications

13. MONTH 6 VISIT:

KEY REMINDERS

- The Month 6 visit is scheduled 6 months from the date of the Baseline in-clinic visit.

DATA FLOW



Within 2 Weeks

New Enrollees: Baseline and Follow-Up Procedures

13. MONTH 6 VISIT (Cont'd)

Plasma and Serum collected for Biomarker analysis are after at least a 6 hour fast. Buffy Coat is extracted from Plasma tubes and shipped ambient to NCRAD. ***Cognitive assessments should NOT be scheduled while the participant is fasting.***

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

adcs.org/ADCS investigators/studyresources/ADCSAdminPortal/StudyFileUpload

MONTH 6 ASSESSMENTS

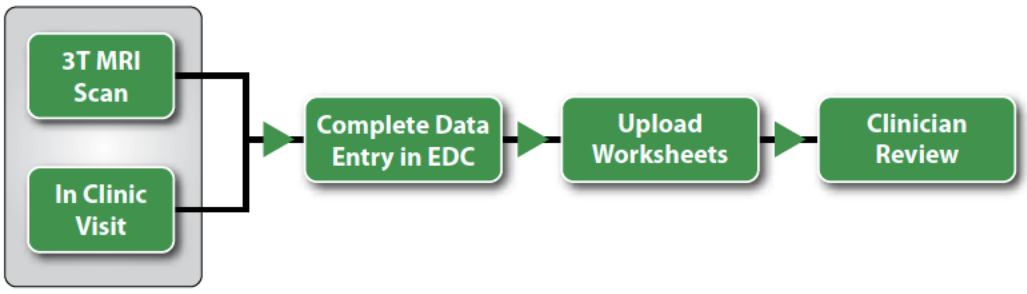
- Plasma and Serum Biomarker Collection *
- Neuropsychological Battery (follow order of assessments on worksheets)
- MoCA
- ADAS-Cog 13
- Everyday Cognition - Participant and Study Partner Self-Report
- Clinical Dementia Rating
- Geriatric Depression Scale
- Neuropsychiatric Inventory Q
- Functional Assessment Questionnaire
- 3T MRI Scan
- Vital Signs
- Concurrent Medications Review
- Diagnostic Summary
- Adverse Event Review
- Clinician Review
- Autopsy Consent Discussion

* Fasting

14. ANNUAL IN-CLINIC VISIT

KEY REMINDERS

- The annual in-clinic visit is scheduled annually from the date of baseline, not 12 months from the previous in-clinic visit.



Within 2 Weeks

14. ANNUAL IN-CLINIC VISIT (Cont'd)

Plasma and Serum collected for Biomarker analysis are after at least a 6 hour fast. Buffy Coat is extracted from Plasma tubes and shipped ambient to NCRAD. ***Cognitive assessments should NOT be scheduled while the participant is fasting, or immediately after an LP or imaging session.***

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

adcs.org/ADCSinvestigators/studyresources/ADCSAdminPortal/StudyFileUpload

ANNUAL IN-CLINIC VISIT ASSESSMENTS

- Plasma and Serum Biomarker Collection *
- Genetic Sample Collection (RNA)
- Neuropsychological Battery (follow order of assessments on worksheets)
- MoCA
- ADAS-Cog 13
- Everyday Cognition - Participant and Study Partner Self-Report
- Clinical Dementia Rating
- Geriatric Depression Scale
- Neuropsychiatric Inventory
- Functional Assessment Questionnaire
- 3T MRI Scan
- Vital Signs
- Concurrent Medications Review
- Diagnostic Summary
- Adverse Event Review
- Clinician Review
- Autopsy Consent Discussion

In addition to the above, the following procedures should be performed every two years as funding permits:

- AV-45 PET Scan
- FDG-PET Scan*
- CSF Collection*

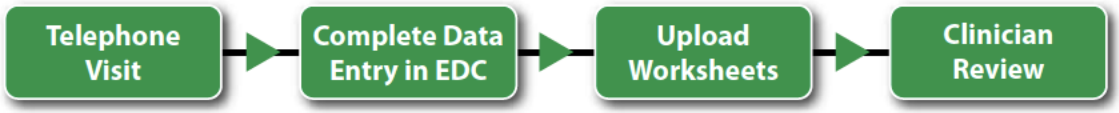
* Fasting

15. 6 MONTH INTERIM TELEPHONE CHECK

KEY REMINDERS

- The 6 month interim telephone visits will be timed at 18, 30, 42 and 54 months from the **BASELINE VISIT**.
- The purpose of these visits is to retain contact with the participant and study partner to assess change in cognition and address possible Adverse Events that may have occurred since the last in-clinic visit.

DATA FLOW



Complete Data entry within 5 business days of the visit. Scan and Uploadworksheets to the Administration Portal:

adcs.org/ADCSinvestigators/studyresources/ADCSAdminPortal/StudyFileUpload

6 MONTH INTERIM TELEPHONE CHECK ASSESSMENTS

- Concurrent Medications Review
- Adverse Event Review
- Neuropsychiatric Inventory Q
- Participant Status
- Clinician Review

AD PARTICIPANTS - ONGOING FOLLOW-UP

Newly enrolled AD participants will be seen until the Month 24 Clinic visit. After that, telephone checks only will be performed at six-month intervals to obtain key demographic and participant status information as well as to discuss provisional autopsy consent and logistical support for autopsy.

Follow-Up Participants: CN, LMCI, EMCI Visit Procedures

SUMMARY

Consent will be obtained before any portion of the initial ADNI2 visit begins. There is no screening visit for continuing participants and no prior approval necessary before the MRI scan is conducted.

The following items will be covered in this section:

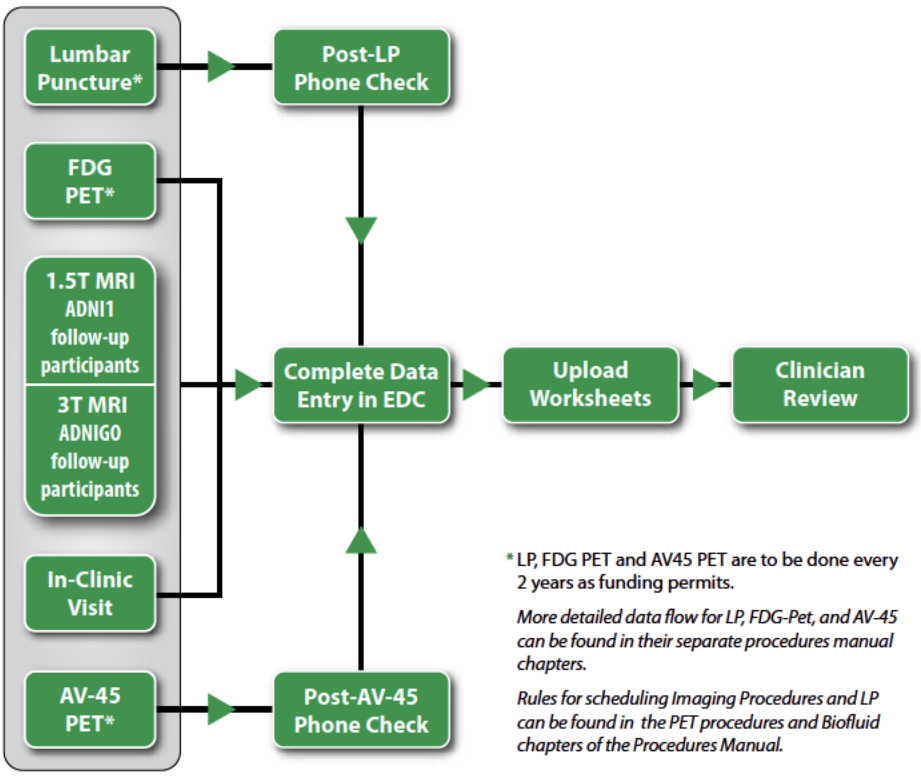
1. INITIAL ADNI2 VISIT AND FOLLOW-UP VISITS
2. 6 MONTH INTERIM TELEPHONE CHECK

1. INITIAL ADNI2 VISIT AND FOLLOW-UP VISITS

KEY REMINDERS

- Must have been enrolled and followed in ADN1 for at least one year with original diagnosis of Cognitively Normal (CN), Mild Cognitive Impairment (MCI), or enrolled in ADNIGO with original diagnosis of Early Mild Cognitive Impairment (EMCI) regardless of whether a diagnostic conversion has occurred since initial enrollment in ADNI.
- Participants should be approached at their annual in-clinic visit to enroll in ADNI2. For new enrollees under the ADNIGO study that means at month 12 the participant should be approached for ADNI2 and if consented would proceed to ADNI2 at that time and no longer be a participant in ADNIGO.
- 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.

DATA FLOW



Follow-Up Participants: CN, LMCI, EMCI Visit Procedures

1. INITIAL ADNI2 VISIT AND FOLLOW-UP VISITS (Cont'd)

Participant should enroll in the ADNI2 study on their projected annual in-clinic time point. The initial visit assessment can occur ± 2 weeks from the target time point. Please refer to the Sample Visit Schedule under the Overview Section of this manual for rules on scheduling Lumbar Puncture, MRI, AV-45 PET and FDG-PET scans in relation to the in-clinic visit.

Keep in mind that the CSF, Plasma and Serum collected for Biomarker analysis are after at least a 6 hour fast. Buffy Coat is extracted from Plasma tubes and shipped ambient to NCRAD. ***Cognitive assessments should NOT be scheduled while the participant is fasting, or immediately after an LP or imaging session.***

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

adcs.org/ADCSinvestigators/studyresources/ADCSAdminPortal/StudyFileUpload

INITIAL ADNI2 VISIT AND FOLLOW-UP VISIT ASSESSMENTS

- Explain Study†
- Obtain Consent†
- Demographics†
- Medical History†
- Genetic Sample Collection (DNA†, RNA)
- Plasma and Serum Biomarker Collection *
- CSF Collection *
- Neuropsychological Battery (follow order of assessments on worksheets)
- MoCA
- ADAS-Cog 13
- Everyday Cognition - Participant and Study Partner Self-Report
- Clinical Dementia Rating
- Geriatric Depression Scale
- Neuropsychiatric Inventory
- Functional Assessment Questionnaire
- Vital Signs
- Concurrent Medications Review
- Diagnostic Summary
- Adverse Event
- 1.5T MRI (ADNI 1 follow up participants)/ 3T MRI (ADNI GO follow up participants)
- FDG PET Scan *
- AV-45 PET Scan
- AV-45 24-48 Hour Follow-Up
- Post LP phone call
- Clinician Review
- Autopsy Consent Discussion

Due to funding limitations, there are specific timing rules on when an LP, FDG PET Scan and AV-45 PET Scan should be conducted. Please ensure to review the PET procedures and Biofluids section of the Procedures Manual for detailed instructions.

† These assessments are unique to the initial ADNI2 visit; all others are done at the initial ADNI2 visit and subsequent annual in-clinic visits

* Fasting

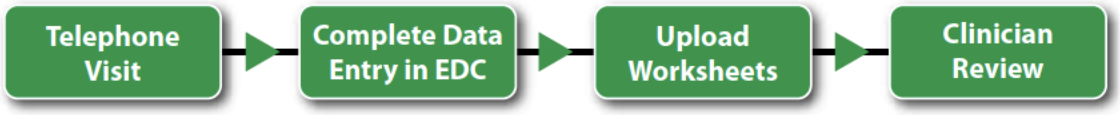
Follow-Up Participants: CN, LMCI, EMCI Visit Procedures

2. 6 MONTH INTERIM TELEPHONE CHECK

KEY REMINDERS

- The 6 month interim telephone visits will be timed at 6, 18, 30, 42 and 54 months from the initial ADNI2 visit.
- The purpose of these visits is to retain contact with the participant and study partner to assess change in cognition and address possible Adverse Events that may have occurred since the last in-clinic visit.
- The next annual in-clinic visit is scheduled annually from the date of the original baseline visit from ADNI1 or ADNIGO, not 12 months from the previous in-clinic visit.

DATA FLOW



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

adcs.org/ADCSinvestigators/studyresources/ADCSAdminPortal/StudyFileUpload

6 MONTH INTERIM TELEPHONE CHECK ASSESSMENTS

- Concurrent Medication Review
- Adverse Event Review
- Neuropsychiatric Inventory Q
- Participant Status
- Clinician Review

Telephone Visit Option

TELEPHONE VISIT OPTION

The following participants are eligible for telephone-only follow-up:

1. MCI or Control originally enrolled in ADNI1 and/or EMCI originally enrolled in ADNIGO who is not willing to return for in-clinic visits.
2. ADNI2 new enrollees who have completed all baseline assessments under ADNI2 but 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 for two reasons:

1. The longitudinal data on such participants is extremely valuable.
2. The degree of participants not continuing into ADNI2 from ADNI1 is alarming.

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

PLEASE NOTE: 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.

TELEPHONE VISIT (REPLACEMENT OF IN-CLINIC VISITS) ASSESSMENTS

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

Pre-Existing Symptoms Checklist and Log

The Pre-Existing Symptoms Checklist is completed at screening. Any condition or symptom present must be entered in the Pre-Existing Symptoms Log which is then reviewed and updated at every visit. Details about the symptoms should be captured on the Pre-Existing Symptoms Log under "Description of Symptom." If episodic symptoms associated with the medical conditions listed on the Medical History form have occurred during the three months prior to the initial visit, these symptoms should also be captured on both the Pre-Existing Symptoms Checklist and the Pre-Existing Symptoms Log.

For continuing participants from ADN1 or ADNIGO please use the same procedures outlined above, where the Pre-Existing Symptoms Checklist is completed at entry into ADNI2 (initial ADNI2 visit). Any condition or symptom present must be entered in the Pre-Existing Symptoms Log which is then reviewed and updated at every visit.

EXAMPLE: The participant reports knee pain at the screening visit, which the study partner states is due to osteoarthritis. Record this on the Medical History form as 'Osteoarthritis' and on the Pre-Existing Checklist select 'present' to musculoskeletal pain, with details of this pain recorded on the Pre-Existing Symptoms Log.

Wherever possible, use medical terminology and a diagnosis for documenting symptoms. Do not record Pre-Existing Symptoms in the participant's, or study partner's, own words. Enter details for all symptoms marked "Present" on the Pre-Existing Symptoms Checklist on the Pre-Existing Symptoms Log.

- Enter both the symptom number and name on the Pre-Existing Symptoms Log.
- Date of onset may be estimated if necessary. An estimated Month is required if the symptom began within the same calendar year.

EXAMPLE: If participant reports pain, elaborate on location of pain – "Pain in right foot".

At each subsequent visit, review the Pre-Existing Symptoms Checklist with the participant and study partner and:

- If the symptom has ceased, enter the date the symptom ceased on the Pre-Existing Symptoms Log.
- If the symptom has worsened in chronicity or severity from the participants screening visit or initial visit under ADNI2, enter the date the symptom changed in the "Date Ceased" box on the Pre-Existing Symptoms Log and create a new Adverse Event on the AE / Hospitalization Log and ***NOT*** an entry on the pre-existing symptoms checklist /log.
- If the symptom is still present at the end of the study, check the box on the Pre-Existing Symptoms Log under "CONT'G AT FINAL FOLLOW UP?"

NOTE: If a symptom has improved in chronicity or severity from screening, do not create a new entry.

All new symptoms and Pre-Existing symptoms that have worsened in chronicity or severity *MUST* be recorded as an Adverse Event, and *SHOULD NOT* be added to the Pre-Existing Symptoms Log.

Pre-Existing Symptoms Checklist and Log

If, after the screening visit or initial visit under ADNI2, a participant and/or study partner reports a symptom that should have been recorded at the screening visit, but was overlooked at the time, then record the symptom as a Pre-Existing symptom, not an Adverse Event. Upon determination that this symptom was clearly in existence prior to consent, site personnel should then update the following worksheets:

1.	Pre-Existing Symptoms Checklist: Any symptom that was previously recorded as "absent" should be checked as "present".
2.	Pre-Existing Symptoms Log: Any missed symptom(s) should be added to the form with all the necessary information, such as symptom number, description, severity, chronicity, date of onset and date ceased (if applicable).

- If the participant or study partner is unsure (or if the symptom began after consent but they forgot to report it), then it should be reported as an Adverse Event.

ADNI1 AND ADNIGO FOLLOW-UP PARTICIPANTS

In general, once an ADNI1 or ADNIGO participant signs the consent for ADNI2 everything starts anew. Review the participant's medical history, concurrent medications, and symptoms present during the initial visit. Record any existing symptoms, or those present in the past three months, on the Pre-Existing Symptoms Checklist. Provide details for each existing diagnosis or symptom on the Pre-Existing Symptoms Log.

Medical History: Review the participant's medical history during the initial ADNI2 visit. All significant/relevant medical history will need to be documented in the source worksheets and/or research chart, as well as entered in the ADNI2 EDC. If a subject had an adverse event during ADNI1 or ADNIGO that was associated with a disease or condition, this would now be captured as medical history under ADNI2.

Adverse Events: Once a subject signs the consent for ADNI 2 any subsequent event that is not a part of medical history or not noted on the Pre-Existing Symptoms Checklist at the screening or initial visit would be considered an AE. Additionally, any disease/symptom that has worsened in severity or chronicity from intake would be considered an AE. Any AEs that were ongoing during the last visit under ADNI1 or ADNIGO would be considered medical history (since they began prior to consenting to ADNI2) and if the AE is present during the screening visit or initial visit under ADNI2 to then this should be captured on the Pre-Existing Symptoms Checklist and Pre-Existing Symptoms Log.

Updating the ADNI1 and/or ADNIGO EDC systems: The general rule is anything that occurred while the subject was under consent for ADNI1 and/or ADNIGO should be reported and updated in the respective EDC system. If an adverse event resolved from the time of the last ADNI1 or ADNIGO visit to the time of the initial ADNI2 visit, the end date should be entered in the ADNI1/GO EDC system (which ever study which the AE occurred under) and the condition (if applicable) should be recorded as medical history in the ADNI2 EDC system. Additionally if a concurrent medication for the adverse event was taken during the time of consent to ADNI 1 and/or ADNI GO and has since been discontinued, the date of discontinuation of the concurrent medication should be entered in the appropriate EDC system and the medication would not be reported in the ADNI2 (unless the medication was taken within 3 months of the initial ADNI2 visit).

Pre-Existing Symptoms Checklist and Log

SYMPTOMS OF POTENTIAL CONCERN

Some symptoms on the checklist may be particularly difficult to interpret. Other complaints are commonly voiced in vague language. When recording symptoms under "Description of Symptom" on the Pre-Existing Symptoms Log use the Symptoms of Potential Concern below as a guide to defining the symptoms in terminology that is as specific as possible.

SYMPTOMS OF POTENTIAL CONCERN	
Abdominal Discomfort	Describe discomfort: epigastric burning; lower abdominal fullness; cramping, etc.
Dizziness	If you can determine that the participant is actually experiencing light-headedness, vertigo, drowsiness, palpitations, confusion, poor concentration, etc., report the more specific symptom. If you cannot obtain a better understanding of this symptom and do not feel that it requires further investigation, please add NOS (or "not otherwise specified") to your comments. If the dizziness is part of a symptom complex that requires further investigation, add this information in a comment.
Chest Pain	This complaint should always elicit further questions to determine if further investigation is needed. Please indicate if you feel the etiology is most likely cardiac, pulmonary, gastrointestinal or musculoskeletal.
Fall	Anytime you record a fall, please comment on the circumstance, when possible, i.e., tripped on rug; stood up, felt faint and fell; worsening gait apraxia; attempted to walk without cane. Also, if you have recorded a wrist fracture or other such trauma, ask if it was associated with a fall.

It will not be possible to reliably determine whether adverse symptoms that occur during the study are attributable to study procedures, the progression of disease, other causes, or a combination of these. For the purpose of study monitoring, all new symptoms and all symptoms that worsen in frequency or severity will be reported as adverse events.

Adverse Events and Hospitalizations

ADVERSE EVENT (AE)

An adverse event is any adverse change from the subject's baseline (screening visit or initial visit) condition including clinical or laboratory tests, or abnormalities that occur during the course of the study after consent. ***Adverse events will be collected from the time of informed consent until the end of the study.***

Example:

- Clinically significant adverse changes in clinical status and physical exams.
- Any complaint associated with such an abnormal finding.
- New symptoms and pre-existing symptoms that have worsened in frequency or severity even if the event was not caused by the treatment or study procedure.
- Recurrence of a previously resolved condition.

COLLECTION AND DOCUMENTATION

- Begins at the time of participant ***CONSENT***.
- Screen for adverse events at each study visit including interim telephone calls.
- Document any new condition, recurrence of a previously resolved condition, or worsening of an existing condition as an AE.

All Adverse Events and Serious Adverse Events must be reviewed and signed off by a qualified clinician (MD, PA, DO , NP). Only clinicians with these credentials are allowed to sign off on these assessments.

AE CHECKLIST

At each visit after screening or the initial ADNI2 visit for continuing participants the AE checklist is to be reviewed with the study participant and partner. The intent of the worksheet is to engage site staff in a conversation with the participant/partner about potential adverse events. If any new symptom is present or worsening of a pre-existing symptom has occurred, **"yes"** should be checked on the AE checklist and details are entered on the AE/Hospitalization Log.

EVENT

The AE/H form is designed for reporting one adverse event (AE) per online form. If the AE is a known diagnosis, enter the diagnosis in the box labeled "Event." If an AE is reported to the interviewer as a group of symptoms for which there is no apparent unifying diagnosis, each symptom should be listed as a separate AE. If you believe a group of symptoms may be related to one diagnosis but no diagnosis has yet been determined, use the Comments section to clarify your suspicions and indicate whether or not a work-up is underway.

When symptoms, rather than diagnoses, are recorded, the interviewer should be as specific as possible. If a subject reports abdominal discomfort, try to clarify and record a more specific complaint (i.e., epigastric burning or lower abdominal cramping). If a subject complains of dizziness the interviewer should probe for more specifics: (i.e., lightheadedness, vertigo, drowsiness, palpitations, confusion, poor concentration). Once a diagnosis is known for a symptom, this should be entered on the Adverse Event.

EVENT (Cont'd)

An adverse event should be reported as a diagnosis ***OR*** symptom in one report. Reporting a symptom and the diagnosis, e.g. ,"right hemiparesis" and "stroke", on two separate CRFs would result in double reporting of a single event.

Symptoms and Diagnoses should not be recorded in the subject/study partner's own words. Each entry into 'Event' (diagnosis or symptom) should be as specific as possible, and linked to a body system. The subject/study partner's description can be noted under 'Comments'. To clarify the text entered in 'Event' the site should also use parenthesis around any words that should be used as keywords in coding the Adverse Event.

For events that are also behaviors (i.e. "repeatedly washes and combs hair") the word 'behavior' is a keyword so it should be added under 'Event' and placed in parenthesis. If the entry is not key-worded it could become coded incorrectly.

Where possible, the interviewer should probe for the cause of Adverse Events.

Examples:

- Participant reports 'feeling bloated'.

  Event: Bowel Gas, Comments: 'feeling bloated'.

- Participant reports 'fuzzy feeling'.

  Event: Sleepiness, Comments "subject reports 'fuzzy feeling' which is explained as drowsiness in the afternoon".

- Participant reports "itching back and stomach."

  Event: Itching (Skin), Comment: 'back and stomach.'

- Participant is seen at the ER for chest pain and is diagnosed with severe indigestion.

  Event: Indigestion, Comment: Seen in ER, reported chest pain.

- Participant falls and bruises hip (2 Adverse Events).

  Event: Fall, Comment: tripped over the rug, was not wearing glasses.

  Event: Bruised hip, Comment: due to fall.

COMMENTS

Use the Comments section to clarify unusual AEs or details of particular importance. Whenever a Fall is reported, the interviewer should comment on the circumstance, (i.e., tripped on rug; stood up, felt faint and fell; worsening gait apraxia; attempted to walk without cane).

Example: Was the left wrist fracture a result of a Fall? If so, why did the subject fall?

Circumstances should be recorded under 'Comments'.

Adverse Events and Hospitalizations

SEVERITY

All adverse events will be graded on a three-point scale (mild, moderate, severe) and severity will be indicated on the online Adverse Event/Hospitalization form.

Definitions of Severity:

Mild: Discomfort noticed, but no disruption of normal daily activity.

Moderate: Discomfort sufficient to reduce or affect the normal daily activity.

Severe: Incapacitating, with inability to work or perform normal daily activity.

To avoid the need for keywords altogether, the diagnosis or symptom should be as specific as possible, with details provided under 'comments'.

RELATIONSHIP TO STUDY PROCEDURE

Every effort must be made by the investigator to explain each clinical adverse event and its relationship to the study procedure. The following guidelines are intended to assist the clinician in determining the relationship of the event to the procedure. The final determination of this relationship is based on the clinician's judgment.

Not Related: This category is applicable to those adverse events which, after careful medical consideration at the time of evaluation, are judged to be clearly, and beyond a reasonable doubt, due to extraneous causes (disease, environment, etc.). Additionally, the event does not meet the criteria for relationship to procedures as listed under Possibly Related or Definitely Related.

Possibly Related: This category applies to those adverse experiences in which the connection with the study procedure appears possible and cannot be ruled out with certainty. To be considered Possibly Related, the adverse experience should meet the following two criteria:

1. It follows a reasonable temporal sequence from initiating the procedure.
2. It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or modes of therapy administered (when applicable).

Definitely Related: This category applies to those adverse experiences which, after careful medical consideration at the time they are evaluated, are considered, beyond a reasonable doubt, to be related to the study procedure.

To be considered Definitely Related, the adverse experience should meet the following criteria:

1. It follows a reasonable temporal sequence from initiating the procedure.
2. It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or modes of therapy administered (when applicable).
3. It follows a known pattern of response to the suspected procedure.

A severe post-lumbar puncture headache is recorded as an Adverse Event, related to study procedures.

Adverse Events and Hospitalizations

Hospitalization

When a subject is hospitalized in an acute care facility, the diagnosis or symptom that prompted hospitalization should be recorded under Event. Visits to the emergency room that do not result in hospital admission should not be recorded as "inpatient."

Serious must always be answered 'Yes' when an event requires or prolongs hospitalization.

Serious Adverse Events

A Serious Adverse Event is one that meets any of the following criteria:

- Death
- A life threatening adverse event
- *Hospitalization or prolongation of existing hospitalization
- Persistent or significant disability or incapacity
- Congenital anomaly or birth defect
- A medically important event
- Suggests any significant hazard, contraindication, side effect or precaution that may be associated with the use of a study procedure

* **When hospitalization is NOT considered serious:** Hospitalization, or prolongation of, in the absence of a medical AE is not in itself a serious adverse event. However, an event may occur during hospitalization that may be considered a serious or non-serious event and will need to be captured according to the protocol.

Examples:

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

DEATH

Death is an ***OUTCOME*** of an event, not an event term or diagnosis. It is necessary to find out the cause of death. When the cause of death is unknown at first reporting, this must be updated once cause is known. When death is the only information available then death can be documented as the event with an additional comment indicating that no qualifying information is available. There should only be one SAE with an outcome of death for each participant.

DEFINITION OF LIFE-THREATENING EVENT

An adverse experience is life threatening if, in the view of the investigator, the subject was at immediate risk of death from the reaction as it occurred.

DEFINITION OF DISABLING/INCAPACITATING EVENT

An adverse event is incapacitating or disabling if the event results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

Serious Adverse Events

DEFINITION OF MEDICALLY IMPORTANT EVENT

An event that may not be immediately life threatening but is clearly of major clinical significance and may require intervention to prevent one of the "Serious" adverse event outcomes. This can be used when seriousness cannot be classified by one of the other "Serious" definitions, but when the event may jeopardize the participant or may require intervention to prevent one of the other "Serious" outcomes.

REPORTING PROCEDURE

1. Report Serious Adverse Events (SAE) by completing the Adverse Events and Hospitalizations eCRF within 24 hours.
2. Complete the form to the best of your ability with the information currently available. If all the information requested on the form is not known, just complete what you can and submit within 24 hours. BE SURE to mark the "Serious" box in the online form.
3. Submit the online form using the "Submit" button. Submission of this online form will trigger an automatic email notification to the Project Director and your clinical monitor, both of whom will immediately review the information you have entered on the Adverse Events and Hospitalizations form.
4. Fulfill the SAE reporting requirements of your IRB as soon as possible (sites should check with their IRB for SAE reporting deadlines).
5. Be sure to update and complete any parts of the Adverse Events and Hospitalizations form that were left blank for the initial submission as soon as the information becomes available.
6. Do not delete text entered in the 'Comments' Field. If updates are made to the comments include date and your initials.

SITES MUST REPORT ANY SERIOUS OR LIFE-THREATENING ADVERSE EVENT WHETHER OR NOT IT IS RELATED TO STUDY PROCEDURES.

Any Serious Adverse Event (including death) due to any cause, which occurs after informed consent has been signed, or within 30 days after the last study procedure, must be reported immediately to Dr. Petersen by completion of the online form.

It is imperative that the Online Form be submitted within 24 hours of a serious adverse experience.

MRI Procedures

SUMMARY

Magnetic Resonance Imaging (MRI) is a principle component of the Alzheimer's Disease Neuroimaging Initiative 2 (ADNI2). All participants newly enrolled into ADNI2 will be scanned using the ADNIGO 3T scanning protocol. These participant will be scanned at Screening, 3 months from the Screening MRI, and then within 2 weeks before or after the Month 6 and subsequent annual visits.

EMCI participants carried forward from ADNI GO will continue with the more modern and expanded 3T scanning protocol initiated in ADNI GO. Imaging for this group will occur annually, within 2 weeks before or 2 weeks after the in-clinic assessments.

CN and MCI participant carried forward from ADNI1 are scanned with the original ADNI protocol on the existing ADNI 1.5T scanner at that site in order to maintain optimum longitudinal consistency unless and until a decision is made by the MRI Core that the site should perform 3T MRI scans on all participants. Imaging for this group will occur annually, within 2 weeks before or 2 weeks after the in-clinic assessments.

The collection of these images is central to meeting the ADNI objective of developing biomarkers to track both the progression of Alzheimer's Disease and change in underlying pathology.

New enrollees in ADNI2 will have a Screening MRI conducted. The Screening MRI is considered a separate visit, and is represented as such in the EDC. The MRI cannot be completed until all other Screening procedures have been completed, and the Screening visit receives both clinician and monitor approval. The Month 3 MRI is to be scheduled 3 months from the date of the screening MRI.

Each site must be qualified for MRI. If the machine being used has already been certified by the ADNI MRI Core under ADNI1 or ADNIGO and has not experienced any software upgrades, re-qualification will ***NOT*** be required.

DATA FLOW

Please refer to the MRI Data Flow chart (next page) for an illustration of this data flow. Every MRI scan completed for ADNI2 will follow this flow of data. Ensure the MRI technician has a copy of the MRI Scan Information form for every scan scheduled (this file can be found in the document repository, and is also included in the worksheet packets). A process should be established for transferring this form back to the study coordinator. The study coordinator will then need to ensure the appropriate data is entered online within 24 hours of the scan.

The MRI center will typically be responsible for uploading each MRI scan to the Laboratory of Neuroimaging (LONI). In some institutions, the study coordinator may be asked to do this uploading. There are instructions for uploading the scans in the MRI Technical Manual (this can be found in the document repository), if you require additional help or training, please email: **adni@loni.ucla.edu**.

After the scan is uploaded into LONI, QC will be completed by the MRI core. For new enrollees in ADNI2 the Screening MRI will determine whether the participant meets eligibility requirements. If the participant requires a rescan, it must be completed within 4 weeks of the original scan.

MRI Procedures

DATA FLOW, CONT'D

Each MRI scan requires a local radiologist interpretation. The clinical read should follow standard practice. The site clinician is responsible to review the local radiological interpretation of the MRI scan, as well as upload the local read to the admin portal (under study file upload).

For new enrollees in ADNI 2, once the MRI scan passes QC by the MRI core and once the site clinician reviews the local read, the site clinician will need to complete the Clinician Verification form in the EDC system indicating if the participant meets eligibility requirements. The monitor will then confirm eligibility by completing the monitor eligibility form in the EDC system, at which time the participant can proceed to baseline.

QUALITY REVIEW OF SCANS

The ADNI MRI QC team at Mayo will review each scan (acquired from LONI). The QC team will check whether the scan meets protocol specifications and identify any clinically significant findings. A phantom must also be scanned each day a participant is scanned. If multiple participants are scanned on a single day, only one phantom scan needs to be acquired.

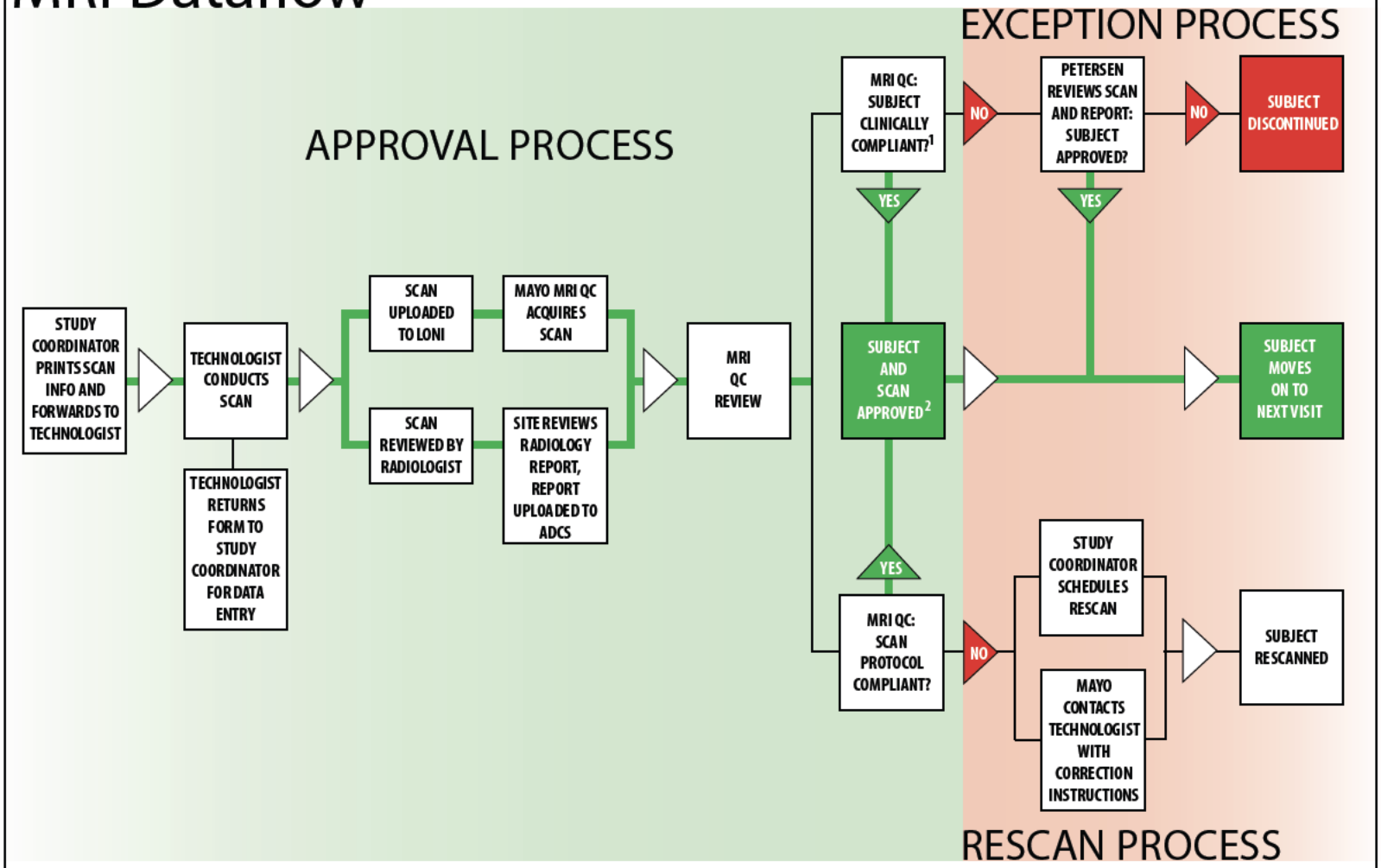
1. **CLINICALLY SIGNIFICANT FINDINGS**
   If a significant abnormality is seen (e.g. hemispheric infarction) on the screening MRI scan, the participant is excluded. In the event that a radiological finding that is not normal for age is identified by MRI QC, the site will be informed of this result by email. If a participant must be screen failed from MRI, please refer to the Screening Visit Procedures section in this manual.

2. **PROTOCOL COMPLIANCE OF SCAN**
   If a problem is found with the way the scan was conducted the MRI QC team will contact the technologist directly to provide further instructions. The study coordinator and site PI will also receive email notification of the scan fail. When requested, a repeat scan will need to be scheduled within four weeks of the original scanning date. If the scan occurs out of window, this protocol deviation must be logged online.

For Technical Questions or Concerns about MRI, please email the MRI technologist help desk: ADNIMRI@mayo.edu

If a scan is not useable (fails MRI QC) due to participant motion or non-compliance with scanning, the reason for the motion and non-compliance should be documented on the MRI Scan Information Form. A rescan should be scheduled if the participant motion is believed to be correctable, and not due to chronic illness or deteriorated cognitive ability. If the rescan also fails due to participant motion or non-compliance the participant may be requested to be excluded from the study due to inadequate Screening MRI scan, or continue in study without any further MRI scans being conducted. In cases where the site believes the failure to be correctable, the site should request an exception to allow the participant to remain in the study. The exception request should sufficiently document the reason for the failed scan and why the site believes the problem to be correctable.

MRI Dataflow



1. The Mayo QC team reviews the scan and the report from the site radiologist side by side. If a significant abnormality is seen (e.g., hemispheric infarction) on the Screening MRI scan, the patient is excluded. If a questionable abnormality is seen, the radiological findings will be reviewed with Dr Petersen and he will make an inclusion/exclusion decision on a case by case basis.
2. Site Clinician completes Clinician Verification only after MRI passes QC and the local read is reviewed.

MRI Procedures

REQUIRED PHANTOM SCANNING AT THE SITE

The radiology center for each site will be required to scan a phantom when scanning ADNI2 participants in order to ensure that the scanners are in compliance with ADNI2 requirements. When the MRI of the participant is uploaded to LONI, the MRI of the phantom should accompany it. Failure to comply with this could prevent the sites from enrolling for ADNI2. Detailed instructions are provided in the MRI technical manual (available in the document repository).

The phantom must be scanned on the same day as the participant. If multiple participants are imaged on the same day, only a single phantom is required.

GUIDELINES FOR SCHEDULING MRI SCANS

Screening 3T MRI

The screening MRI cannot be conducted until both the clinician and monitor indicate that the participant meets inclusion/exclusion criteria for ADNI2. Documentation of approval is done via the ADNI2 EDC system on the clinician verification eCRF and monitor eligibility eCRF. Once both confirm the participant meets eligibility criteria the participant may proceed to have their screening MRI conducted.

PLEASE NOTE: Most sites will need more than 2 weeks in order to obtain an imaging slot at their local MRI center. Please ensure to upload all source document worksheets in a timely manner on the admin website in order for your monitor to review the screening visit. It is recommended that a tentatively scheduled scan date with the MRI center be scheduled 10-14 days after the screening visit. If the participant does not meet clinician and monitor approval to proceed to the screening MRI, the screening MRI must be cancelled.

Follow-Up Participant MRI Scans

EMCI participants carried forward from ADNI GO will continue with the more modern and expanded 3T scanning protocol initiated in ADNI GO. Imaging for this group will occur annually, within 2 weeks before or 2 weeks after the in-clinic assessments.

CN and MCI participants carried forward from ADNI1 are scanned with the original ADNI protocol on the existing ADNI 1.5T scanner at that site in order to maintain optimum longitudinal consistency unless and until a decision is made by the MRI Core that the site should perform 3T MRI scans on all participants. Imaging for this group will occur annually, within 2 weeks before or 2 weeks after the in-clinic assessments.

The MRI can be scheduled with your local MRI center as soon as the participant confirms they are willing to have an MRI scan done. There is no "approval" process when scheduling the MRI scan for ADNI 1 or ADNI GO participants transferring to ADNI2.

GUIDELINES FOR SCHEDULING MRI SCANS, CONT'D

Subsequent Scans

MRI Scans for subsequent visits should be scheduled as far in advance as possible, taking the participant's availability into account. Scans for visits after screening should be scheduled as close to the visit date as possible. Keep in mind that scans must take place within 2 weeks before or 2 weeks after the in-clinic visit, and rescans must be scheduled within 4 weeks of the original scan date. If a scan or rescan is conducted outside of the allotted window a protocol deviation will need to be documented in the EDC system and in the subject's research chart.

NOTE: **The month 3 MRI scan is based 3 months from the screening MRI. The month 6 and month 12 scans will be based 6 and 12 months from the baseline visit.**

Lumbar punctures should be done after any scan for that same time point. If this is not possible, please ensure that there is at least a 3-day window between the lumbar puncture and the MRI appointment.

No sedation medications are allowed for the screening MRI scan. Sedation medications may be allowed at follow up MRI scans. If a potential participant is not comfortable with MRI he/she should not be screened for the ADNI2 study. Record all medications on the Concurrent Medications log.

If you are using a new scanner for ADNI2 we recommend that the ADNI study coordinator attend the first few scan sessions to ensure that he or she understands what is involved in MRI scanning and to create a relationship with technologists.

Checklist for Scheduling MRI Scanning Appointments:

- MRI Screening Form completed/reviewed for changes.
- Participant is given pamphlet with appointment time.
- Participant and Study Partner have Directions and Information for Parking.
- MRI Technologist has copy of MRI data form.
- Scan is uploaded to LONI (by radiologist if possible).
- MRI scan information form received from technologist and data entered within 24 hours.

On the day of each appointment the study coordinator should phone the radiology center, confirm the appointment, and remind the radiologist which ADNI2 MRI protocol should be used in scanning this participant.

Hardware/Software Upgrades: Prior to any software or hardware upgrades the site must inform the ADNI2 MRI Team at Mayo by emailing **ADNIMRI@mayo.edu**. Please provide as much notice as possible. At least 2 months notice is preferred. Depending on the impact of the upgrade the site may be asked to scan a phantom and/or volunteer prior to continued scanning ADNI2 participants.

MRI Procedures

MRI PRE-SCREENING

It is important to know when participants have ferrous (magnetic) metal objects in their body because MRI involves a strong magnetic field that may disrupt or dislodge these objects. The Pre-Screening Form will assess whether or not the participant has any metal in their body and will help to determine whether or not participants are eligible to have an MRI scan.

- **The Pre-Screening Form should be completed *before scheduling the Screening Visit*.**

The participant, the caretaker, or the study partner may fill out either of the screening forms, but anyone completing the form should have a firm understanding of the participant's medical history.

First, write in the Date and the Participant's ADNI2 number at the top of the form.

Then indicate whether or not the participant has any of the items listed in the left hand column of the Pre-Screening Form by placing a check in the appropriate box.

If the participant or study partner answers yes to any of the questions on the Pre-Screening Form under the heading **"Exclusionary Items"** the participant must be excluded from the study. The participant will not be able to participate in MRI scans because the metal object in question is not allowed in MRI scanners.

If the participant answers yes to any of the questions on the Pre-Screening Form under the heading **"Please Inform MRI Center,"** please do not exclude the participant. Instead, please contact your MRI center and let them know about the particular metal item in question. Try to get as much information as possible from the participant regarding the metal object so your radiology site may best assess whether or not a MRI would be safe for the participant.

In addition, if a participant indicates they are claustrophobic please try to discuss the level of discomfort a MRI may pose. Some participants might indicate they are claustrophobic, but are willing to undergo an MRI. Please keep in mind that participants requiring sedation for the screening MRI should not be screened for ADNI2.

If the participant has worked extensively with metal, please ask if he or she is aware of any fragments that have been lodged in the body as a result.

This form is for screening purposes only; it should be kept with the participant's file. Please do not submit the Pre-Screening Form to the ADCS.

Please note this screening form does not substitute for a pre-screen at the radiology site immediately prior to the MRI scan.

MRI Screening Form
Alzheimer's Disease Neuroimaging Initiative MRI Study
Alzheimer's Disease Cooperative Study

Date:_____/_____/_____ **Participant ID**_____

Please check Yes/No for each of the following:

☐ Yes ☐ No Previous MRI scan

Exclusionary Items:

☐ Yes	☐ No	Cardiac pacemaker/defibrillator
☐ Yes	☐ No	Aneurysm or aortic clip(s)
☐ Yes	☐ No	Neurostimulator
☐ Yes	☐ No	Cochlear, otologic, or ear implant

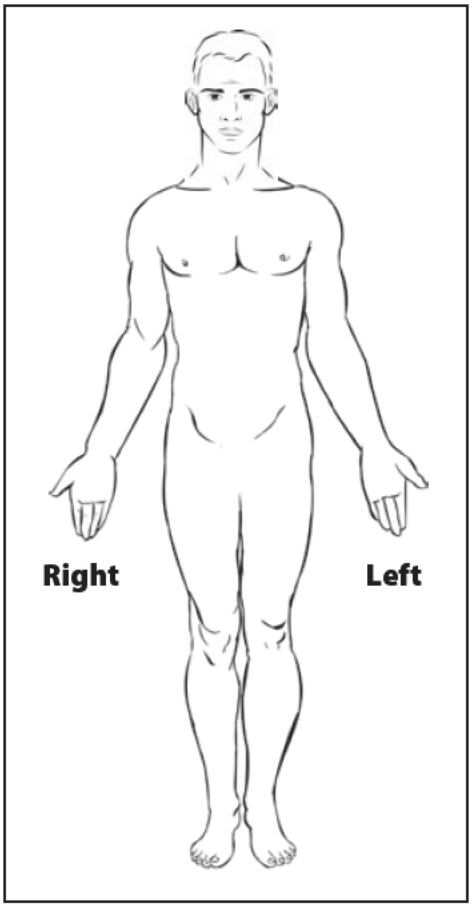
Please Inform MRI Center:

☐ Yes	☐ No	Prosthesis or implant
☐ Yes	☐ No	Artificial limb or joint
☐ Yes	☐ No	Insulin or infusion pump
☐ Yes	☐ No	Bone growth/fusion stimulator
☐ Yes	☐ No	Carotid artery vascular clamp
☐ Yes	☐ No	Electrodes (on body, head, or brain)
☐ Yes	☐ No	Stents, filters or coils (intravascular)
☐ Yes	☐ No	Shunt (spinal or intraventricular)
☐ Yes	☐ No	Vascular access port and/or catheter
☐ Yes	☐ No	Tattooed makeup (eyeliner, lips, etc.)
☐ Yes	☐ No	Body piercing(s)
☐ Yes	☐ No	Any metal fragments or shrapnel (current or removed)
☐ Yes	☐ No	Internal pacing wires
☐ Yes	☐ No	Metal or wire mesh implants
☐ Yes	☐ No	Bone/joint pin, screw, nail, wire, plate
☐ Yes	☐ No	Breathing disorder
☐ Yes	☐ No	Claustrophobia
☐ Yes	☐ No	Hearing aid *(Remove before MRI)*
☐ Yes	☐ No	Dentures *(Remove before MRI)*

If answers below are Yes, please explain below:

☐ Yes	☐ No	Worked extensively with metal (grinding, etc.)
☐ Yes	☐ No	A history of seizures continuing to present

Please mark on the figure below the location of any implant or metal inside your body



Remove all metal objects prior to your MRI examination

Explanation: _____

_____ _____

Signature of participant or participant's representative *Name of representative*

_____ **Date:**_____/_____/_____

Signature of person administering screening form

MRI Procedures

MRI PAMPHLET

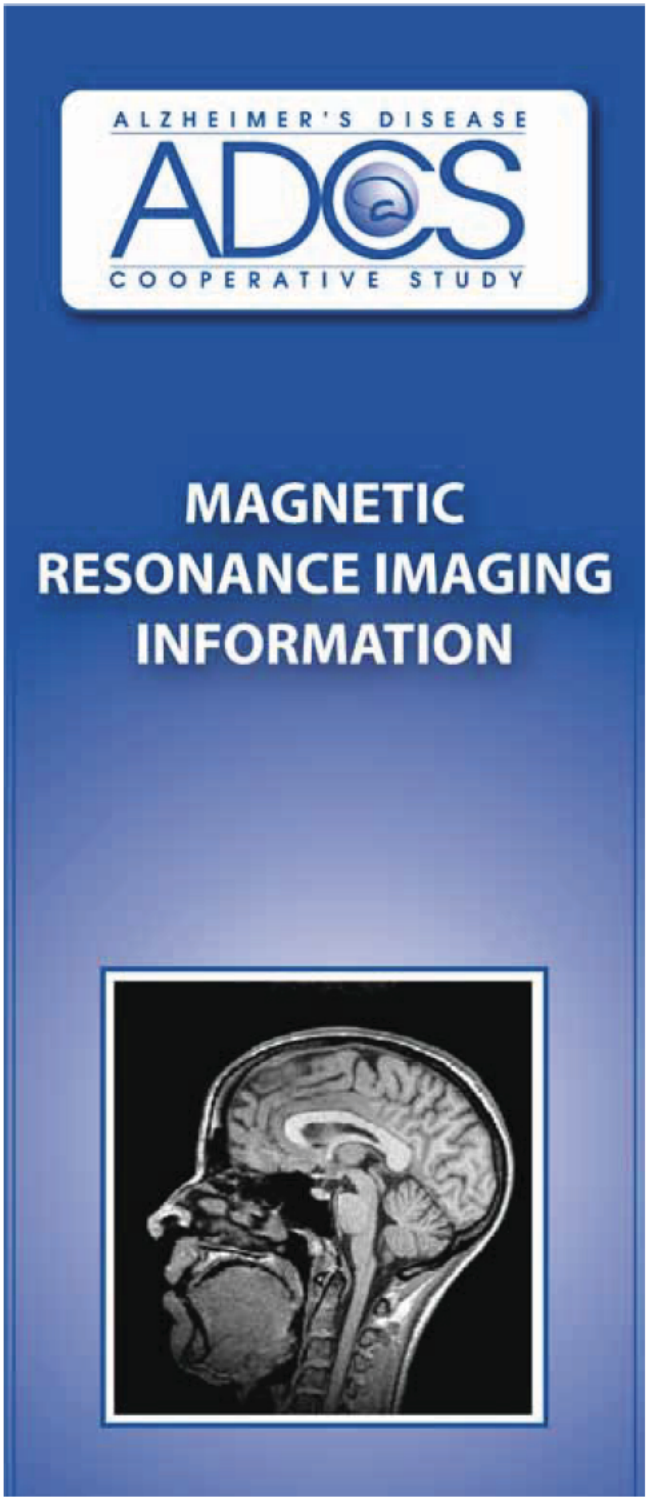
The MRI pamphlet should be distributed to participants in the Alzheimer's Disease Neuroimaging Initiative 2 study (ADNI2).

The MRI pamphlet includes basic information regarding the details of a MRI scan. It briefly describes how participants can best prepare for their MRI and outlines ways participants can reduce anxiety during the procedure.

Participants should have plenty of time to review this information before their MRI appointment so the pamphlet should be distributed to participants when they are scheduled for their MRI scan.

When giving out the pamphlet please be sure to fill out the back page. Use the space provided to write in the specifics of the participant's MRI appointment (date, day of the week, time, and place). If the MRI scan is at a different facility than their clinical appointments, detailed directions to the radiology site should be provided to the participant or the study partner.

In addition, participants should be reminded to bring the pamphlet with them to their MRI appointment and display it when they check in to assure that they are scanned with the appropriate protocol sequence.



IRB approval will be required for the pamphlet.
To request a draft, please email brainlink@ucsd.edu

PET Procedures

SUMMARY

One of the major goals of the Alzheimer's Disease Neuroimaging Initiative is to perform Florbetapir F 18 amyloid imaging (AV-45) and Fluorodeoxyglucose imaging (FDG) on all newly enrolled participants in ADNI2, as well as follow-up participants from ADNI1 and ADNI GO. This establishes a national network for Florbetapir F 18 amyloid imaging, and will test hypotheses concerning the prevalence and severity of brain amyloid accumulation and its relationship to current and previous changes of clinical state.

AV-45 PET and FDG PET imaging will be performed on all newly enrolled participants on 2 separate days (a minimum of 12 hours between scans is required). Scans may be performed in any order but both must be completed within 2 weeks before or 2 weeks after the in-clinic assessments at Baseline and at the 2nd annual visit, 24 months after Baseline.

TIMING OF PET SCANS FOR ADNIGO CONTINUING PARTICIPANTS

Due to funding limitations, EMCI participants carried forward from ADNI GO will have a total of 2 sets of AV-45 PET and FDG PET imagining across ADNI GO and ADNI 2. The timing of the initial AV-45 PET and FDG PET scans under ADNI2 will be based on the date of the last AV-45 and FDG PET scan under ADNI GO. 2 years from that date will be the "initial" AV-45 and FDG PET scan date under ADNI2.

Continuing participants originally enrolled under ADNI GO who had successful PET scans during their ADNI GO baseline visit and continue into ADNI2 at the first annual visit (12 months from ADNI GO baseline) would NOT have an FDG or AV-45 PET scan during their initial ADNI 2 visit, rather the PET scans would occur 24 months after ADNI GO Baseline (which at this time would be their final time point for PET, as this would be a total of 2 sets of scans across ADNI GO and ADNI 2).

TIMING OF PET SCANS FOR ADNI1 CONTINUING PARTICIPANTS

Since the AV-45 scan was not conducted under ADNI 1, continuing participants originally enrolled under ADNI 1 who are going directly into ADNI2 would have the FDG and AV-45 scan at the initial ADNI2 visit and 24 months from the initial visit, as these scans are considered a pair and should occur during the same time point.

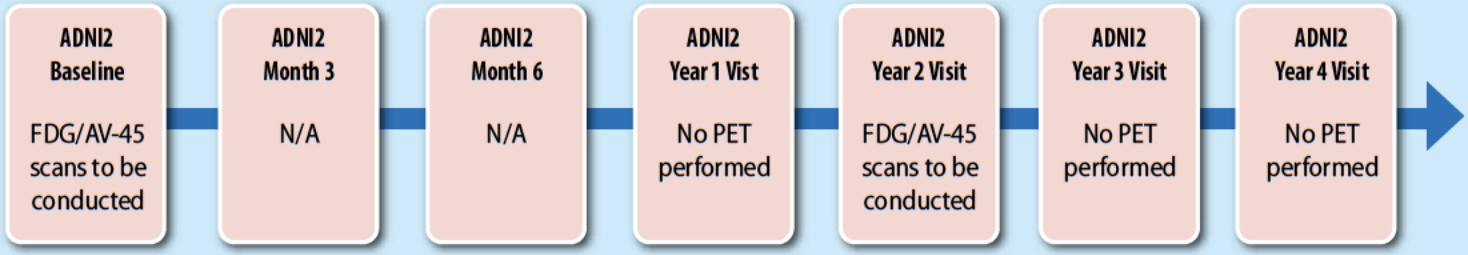
For ADNI1 participants who continued into ADNI GO and then to ADNI2, the timing of their initial PET scan under ADNI2 will be 2 years from that date of the last successful AV-45 and FDG PET scan under ADNI GO.

If a participant agrees to continue from ADNI 1 or ADNI GO into ADNI 2, but is unwilling to consent to 2 PET scans during the initial ADNI 2 visit, please note the AV-45 scan is more valuable than the FDG scan.

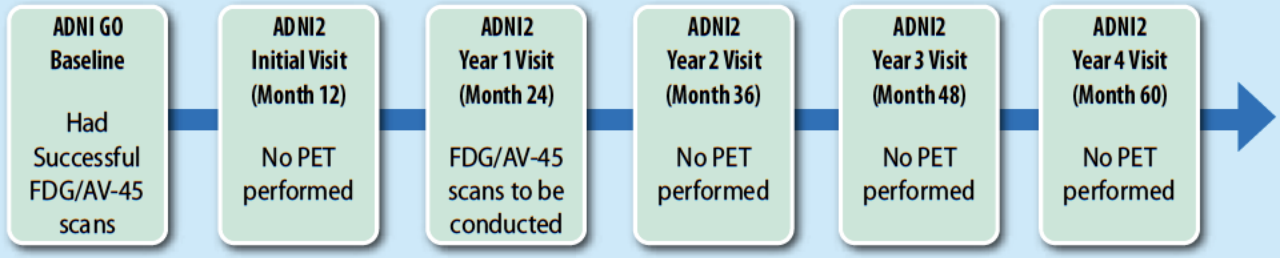
If continuing participant refuses to have both PET scans, he/she should still be followed for all other assessments.

PET SCAN TIMING RULES:

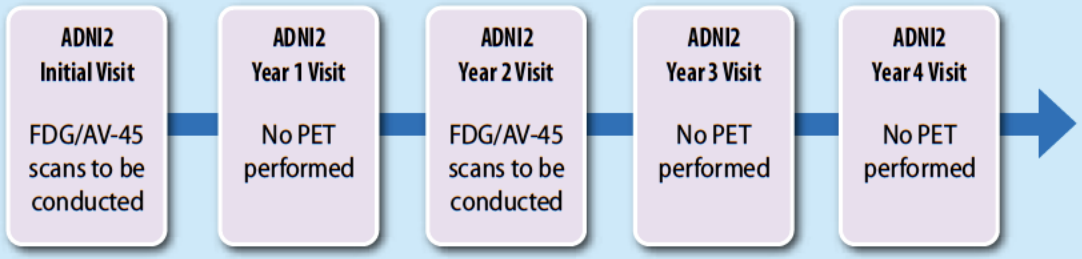
New Enrollee



ADNI GO Continuing Participant



ADNI1 Continuing Participant Directly Into ADNI2



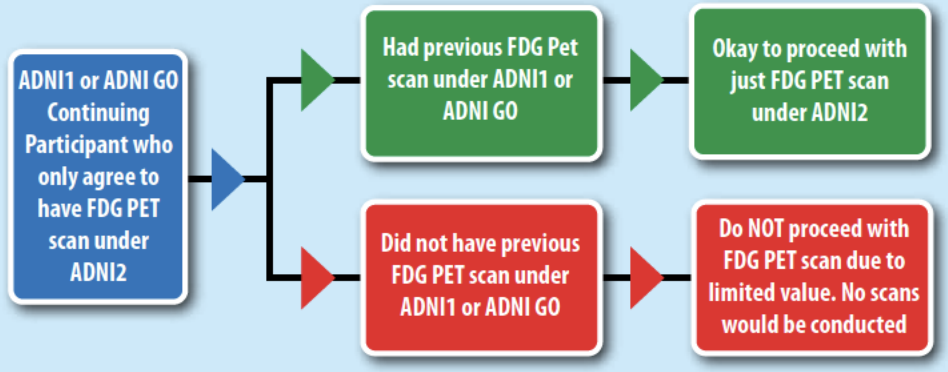
CONTINUING PARTICIPANTS FROM ADNI1 AND ADNI GO TO ADNI2

- If continuing participant from ADNI 1 or ADNI GO only agrees to have one PET scan conducted under ADNI2, the AV-45 PET scan is more valuable. If though, they only agree to have the FDG PET scan conducted, this scan should be conducted ONLY if the participant had a successful FDG scan conducted previously under ADNI 1 or ADNI GO.

- If the participant did not have an FDG scan conducted previously (and is unwilling to have the AV-45 scan conducted) then NEITHER SCAN should be conducted under ADNI2 due to the limited value.

- No continuing participant should be excluded from continuing into ADNI2 if they do not agree to either PET scan. Rather these guidelines are in place for those instances where the participant only agrees to one PET scan.

RULES FOR ADNI1 OR ADNI GO CONTINUING PARTICIPANT WHO ONLY AGREE TO FDG PET SCAN



PET Procedures

PET SCANNER CERTIFICATION

It is preferable for sites to use existing qualified ADNI scanners for both FDG and AV-45 imaging. If a new scanner must be introduced it will need to be qualified using standard ADNI scanner qualification before imaging can be performed.

Ideally, no hardware or software upgrades of the PET imaging system should occur during the duration of the study. In the event of such an upgrade, we ask that you inform the PET core prior to the anticipated upgrade. Depending on the nature of the upgrade the site may be asked to repeat the phantom scans prior to scanning any additional participants.

Contact **adnipet@ucsd.edu** prior to imaging if a new scanner will be used for ADNI2 or if hardware/software upgrades have occurred.

EXCLUSIONARY TO PET SCANS

All participants who consented to receive PET scans must be queried to assure that they do not have specific exclusions to PET. These are pregnancy or risk of pregnancy, a history of radiation therapy within the past year, or a history of receiving radiation for research purposes within the past year. All newly enrolled participants will have had a screening MRI as part of ADNI2 to assure that there are no significant focal lesions before receiving the PET scan.

PET PRE-SCREENING CHECKLIST

This is to be completed by interview if the information is not in clinic records. If the answer to any of these is 'Yes' please consult with a technologist before consenting the participant to PET imaging for ADNI2.

- ☐ Yes ☐ No Is there a history of radiation therapy in the past year?
- ☐ Yes ☐ No Is there a history of having radiation for research in the past year?
- ☐ Yes ☐ No Would there be problems with the participant's ability to cooperate with scan?

AV-45 PET SCAN PROCESS

Prior to imaging, vital signs will be measured. Each participant will receive a single i.v. bolus (370 MBq (10 mCi +/- 10%) of florbetapir F18 prior to AV-45 PET imaging. The injection of the imaging agent will be followed by a saline flush according to the injection procedure in the PET Technical Manual posted in the document repository.

The brain AV-45 PET imaging will be of 20 minutes duration, starting 50 minutes post-dose injection. Vital signs will be obtained again at the completion of the imaging session. Adverse events will be continuously monitored during the imaging session. Participants who experience an adverse event will not be discharged until the event has been resolved or stabilized. A follow-up phone call to the participant (or a person designated to speak for them) will be made approximately 24 to 48 hours after the imaging session to confirm their well-being and to collect information about any new adverse events. For detailed information on the AV-45 scan process please refer to the PET Tech Manual posted in the document repository.

PET Procedures

FDG PET SCAN PROCESS

Participants will need to **fast at least four hours** prior to the scanning session. The participants' blood glucose is checked prior to the scanning and **must be <180 mg/dL**. Each participant will receive a single i.v. bolus (5 mCi +/- 10%) of fluorodeoxyglucose prior to FDG PET imaging. ***The brain FDG PET imaging will be of 30 minutes duration, starting 30 minutes post-dose injection.*** For detailed information on the FDG scan process please refer to the PET Tech Manual posted in the document repository.

DATA FLOW: AV-45 AND FDG PET SCANS

Please refer to the PET Data Flow Charts for an illustration of this process. Study coordinators are responsible for collecting some basic information on each PET scan from the PET center conducting the scan. In general, this will involve interacting with the PET Technologist who will usually be the individual conducting the PET Scans. The study coordinator must ensure the PET Technologist has a copy of the AV-45 and FDG PET Scan Information Forms prior to each scan session. The study coordinator should ensure a process has been worked out with the radiology center on how to transfer this information immediately after the scan is completed. The study coordinator is responsible for entering scan data in the ADNI2 EDC system **within 24 hours of the scan**. All PET scans will be uploaded by your radiology center to the Laboratory of Neuroimaging (LONI). These procedures are outlined in the PET Tech Manual posted in the document repository. If your radiology center is unable to upload scans to LONI, please request training for uploading by emailing: **adni@loni.ucla.edu**.

QUALITY REVIEW OF AV-45 AND FDG PET SCANS

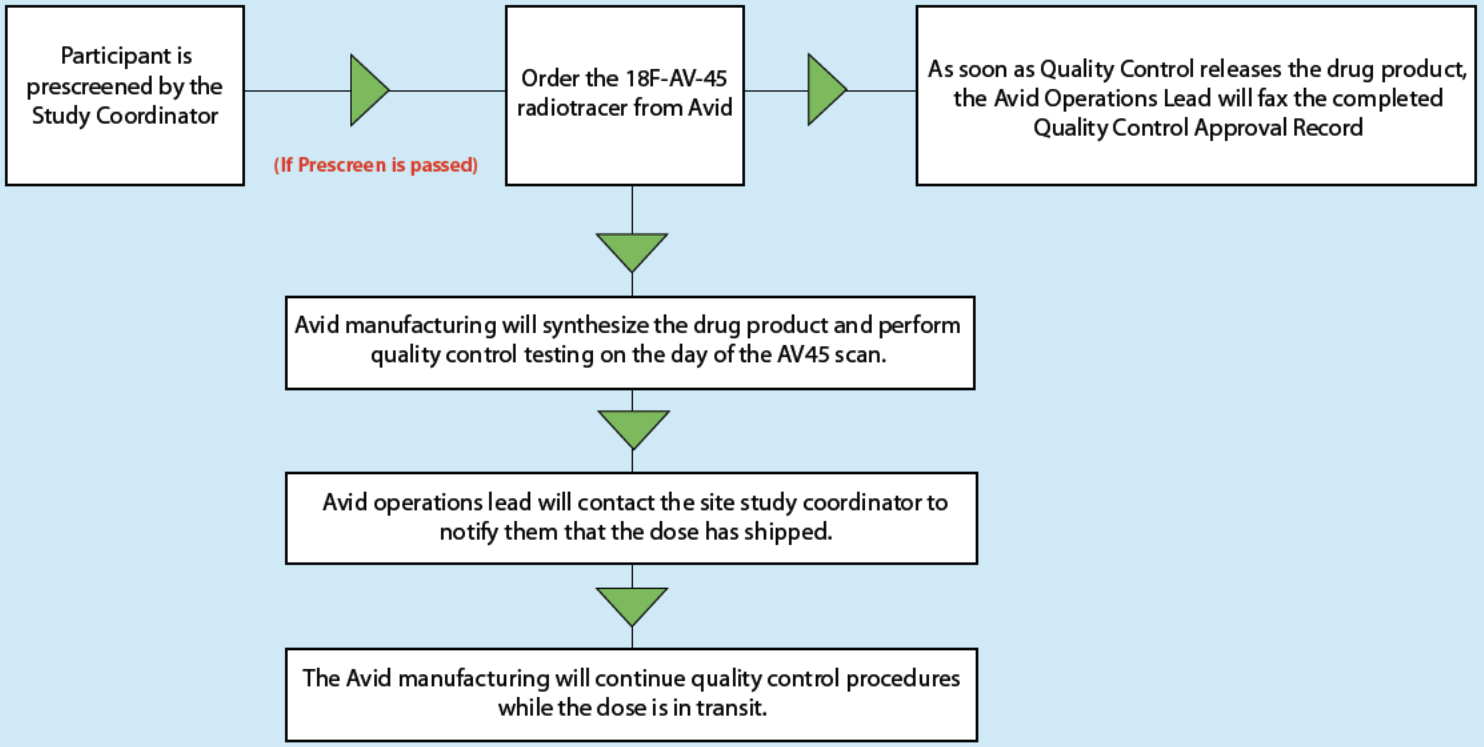
- Every AV-45 and FDG PET scan will be reviewed for protocol compliance by the ADNI PET QC team.
- If a problem is found with the way the scan was done and it can be fixed, the PET QC team will contact the PET technologist directly.
- If the problem with the scan is not fixable, the PET QC team will provide the PET technologist with protocol guidance to apply to future PET scans.

Before requesting the site to schedule a rescan for PET, the participant will be assessed for overall radiation exposure. If an additional scan would not exceed limits on exposure, study coordinators and site PIs will be emailed a request for a repeat scan. When requested, a repeat scan should be scheduled **within two weeks** of the original scanning date. If a scan or rescan is conducted outside of the allotted window document the date of imaging and reason for deviation on the protocol deviation log.

If a scan is not useable (fails PET QC) due to participant motion or non-compliance with scanning, the reason for the motion and non-compliance should be documented on the corresponding PET Scan Information Form. If a rescan is requested, it should only be scheduled if the participant motion is believed to be correctable, and not due to chronic illness or deteriorated cognitive ability.

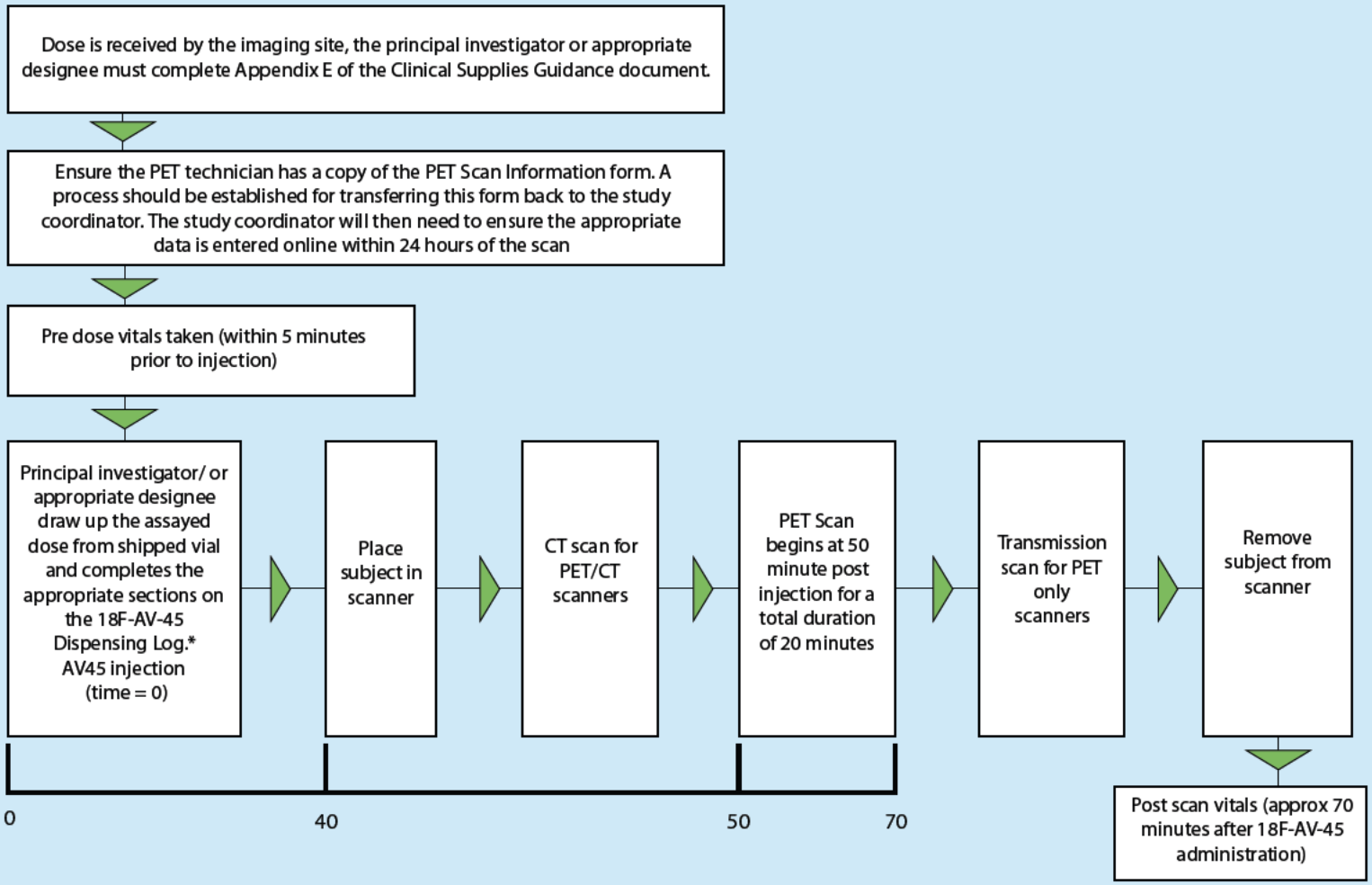
Questions on PET Technical issues:
adnipet@ucsd.edu

Prior to AV45 Scan



NOTE: Complete Appendix A of the Clinical Supplies Guidance Document located in the document repository when ordering the 18F-AV-45 radiotracer.

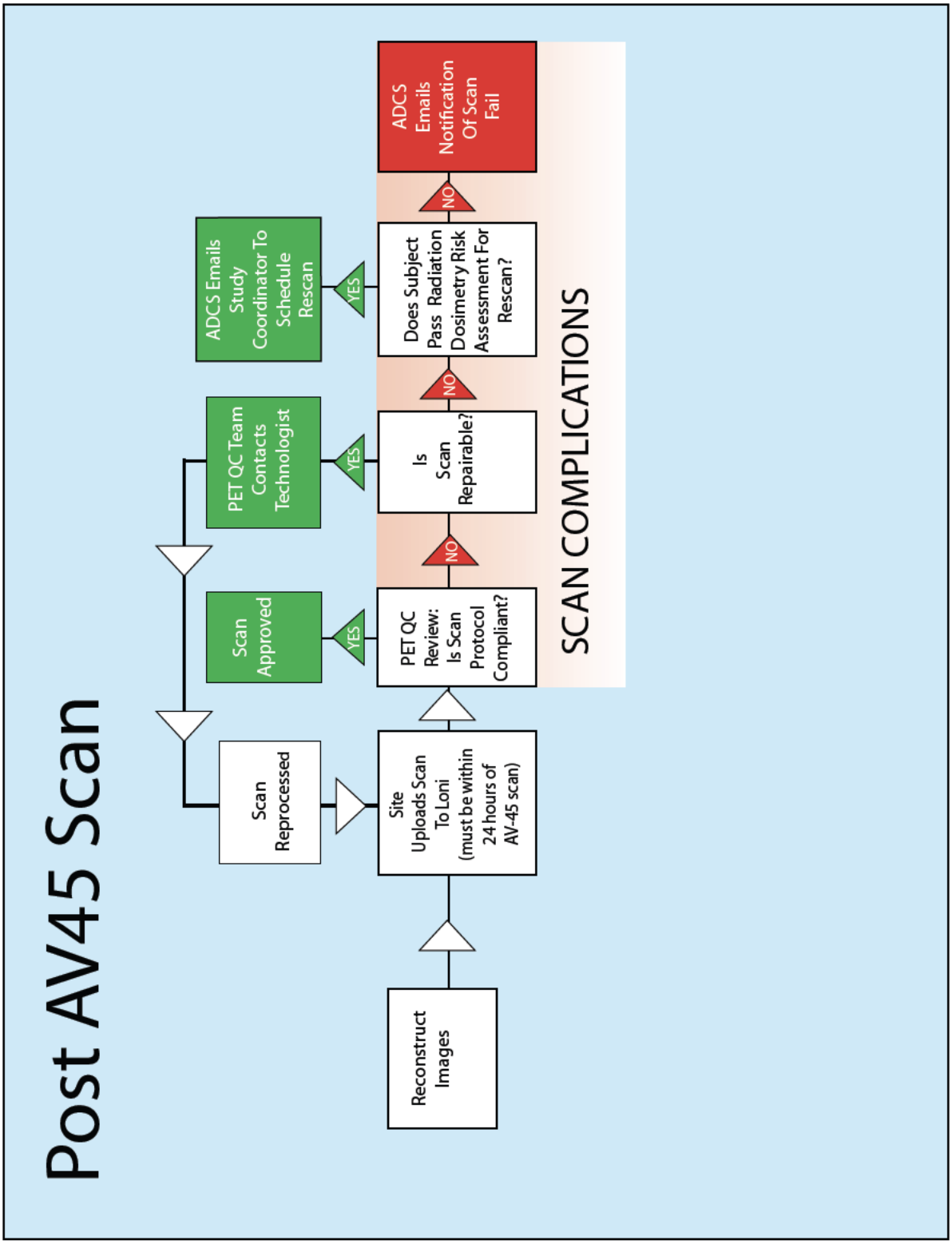
Conducting the AV45 Scan



*** 18F-AV-45 Dispensing Log is Appendix E of the Clinical Supplies Guidance Document**

Modified 7/18/2011

AV-45 PET SCAN POST



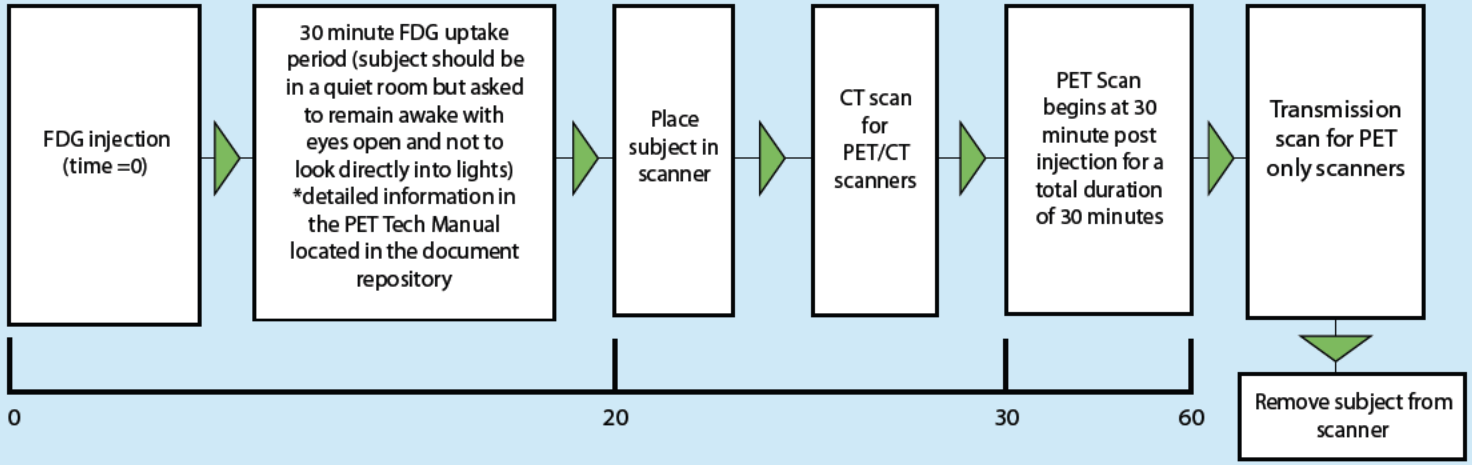
FDG Scan Process

Prior to FDG Scan

Compliance to dietary restrictions should be confirmed (Fasting for at least 4 hours)

→ Check blood glucose level (must be < 180 mg/dl) * If not below 180 subject will need to wait an additional amount of time until blood glucose levels meet this criteria

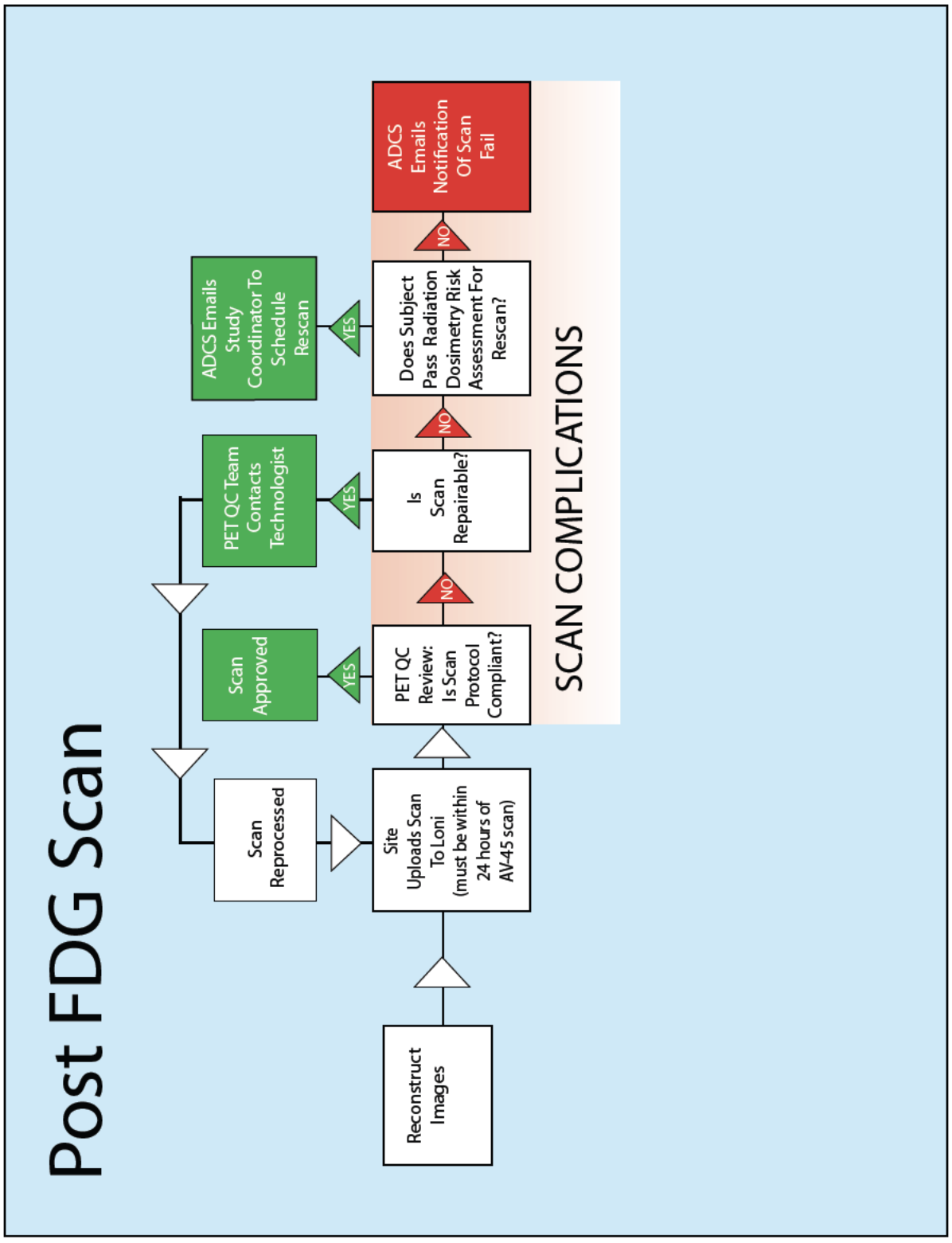
Conducting the FDG Scan



NOTE: Ensure the PET technician has a copy of the PET Scan Information form. A process should be established for transferring this form back to the study coordinator. The study coordinator will then need to ensure the appropriate data is entered online within 24 hours of the scan.

Modified 09/07/2010

FDG SCAN POST



PET Procedures

GUIDELINES FOR SCHEDULING AV-45 and FDG PET SCANS

Most sites will need more than 2 weeks in order to obtain an imaging slot at their local radiology center. The first PET scan for newly enrolled participants in ADNI2 should be scheduled after the Screening MRI scan is reviewed and final approval has been sent to the site PI and study coordinator.

The 2 PET Scans (AV-45 and FDG PET) must occur on 2 separate days. Scans may be performed in any order but both must be completed within a 2-week window before or after the clinic visit to be included in the analysis and reimbursed. If scans take place outside of the allowed window, request a deviation by providing the date of imaging and reason for deviation on the protocol deviation log.

It is recommended that the ADNI study coordinator attend the first few PET scan sessions to ensure that he or she understands what is involved in scanning and to create a relationship with the PET technologists.

NOTE: FDG injection is to be provided by your local radiology center. AV-45 injection is provided by Avid.

AV-45 DELIVERY OF INVESTIGATIONAL PRODUCT

Avid manufacturing will provide AV-45 Injection to all approved imaging facilities. As soon as a participant is scheduled for the AV-45 PET Scan, the study coordinator must notify (by phone and / or email) the Avid Operations Lead of the date and time for imaging.

IMPORTANT: AVID WILL NEED AT LEAST 3 DAYS NOTICE PRIOR TO THE SCHEDULED AV-45 PET SCAN.

Phone: 215-298-9537
Fax: 215-689-4804
Email: kline@avidrp.com

Next the study coordinator will complete the top portion of the **AV-45 Order Form** (located in the visit packet and Avid Clinical Supplies Guidance Document posted in the document repository) and email or fax to Avid Operations Lead to confirm imaging date and time.

Once received, do not inject the AV-45 until the confirmed QA report is received from Avid.

Please refer to the **Avid Clinical Supplies Guidance Document** posted in the document repository for specific details on ordering, shipping and receiving investigational unit doses for AV-45 injection and the process for usage of clinical supplies.

AV-45 DELIVERY OF INVESTIGATIONAL PRODUCT Cont'd

Changes to the scheduling or deviations from the **Avid Clinical Supplies Guidance Document** may be possible (e.g. scheduling a participant with only 24 hours notice), but if they are required, the site should contact Avid as soon as possible to work with the manufacturing team on the logistics.

If lumbar puncture and PET scan are done on the same day, LP should be completed prior to the FDG or AV-45 PET scan; otherwise there should be at least 12 hours between the LP and the scan. Research into whether the binding ligand to Abeta has any effect on CSF Abeta measures or plasma levels is ongoing.

CHECKLIST FOR SCHEDULING PET SCANNING APPOINTMENTS

- ☐ PET pre-screening checklist completed/reviewed for changes.
- ☐ Participant is given pamphlet with appointment information.
- ☐ Participant and Study Partner have Directions and Information for Parking.
- ☐ PET Technologist has copy of appropriate PET Scan Information Form (AV-45 or FDG)
- ☐ Scan uploaded to LONI (by technologist if possible).
- ☐ Appropriate PET Scan Information form (AV-45 or FDG) received and data entered in ADCS data system within 24 hours of scan.

On the day of each appointment the study coordinator should phone the radiology center, confirm the appointment, and remind the radiologist to upload the PET Scan to LONI within 24 hrs of the scan.

PET Procedures

PET PAMPHLET

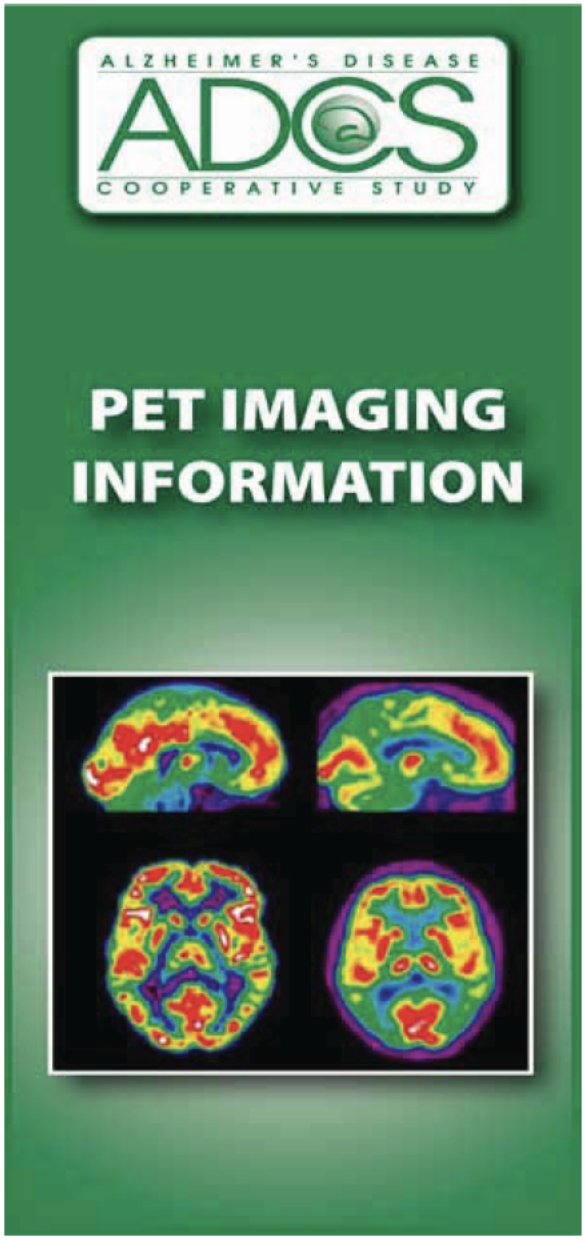
The PET pamphlet should be distributed to any participant undergoing a PET scan for the ADNI2 study.

The PET pamphlet includes basic information regarding the details of the AV-45 and FDG PET scans. It briefly describes how participants can best prepare for their PET scans and outlines ways participants can reduce anxiety during the procedure.

Participants should have plenty of time to review this information before their first PET appointment so the pamphlet should be distributed to participants when they are scheduled for their first PET scan.

When giving out the pamphlet please be sure to fill out the back page. Use the space provided to write in the specifics of the participants PET appointments (date, day of the week, time, and place). If the PET scan is at a different facility than their clinical appointments, detailed directions to the radiology site should be provided to the participant or the caretaker.

In addition, participants should be reminded to bring the pamphlet with them to their PET appointments and display it when they check in to assure that they are scanned with the appropriate PET protocol.



IRB approval is required for the pamphlet.
To request a draft, please email: **brainlink@ucsd.edu**

Biofluids: Collection, Processing And Shipment

SUMMARY

The collection of biofluids is central to the goals of the Alzheimer's Disease Neuroimaging Initiative. The development of valid and reliable biomarkers for AD is needed to:

- Aid in the recognition of the illness at its earliest clinically recognizable stages
- Detect the disease before dementia or other symptoms appear
- Distinguish AD from other causes of dementia

Biomarkers, together with imaging tests, will be especially valuable in the evaluation of disease-modifying therapies.

Promising biomarkers that will be measured in ADNI fluids:

- Tau in CSF
- Amyloid beta in CSF
- CSF BACE levels and enzyme activity
- CSF sAPPβ levels
- Aβ 40 and Aβ 42 in Plasma
- APOE genotyping-blood
- DNA from blood cells
- RNA from blood cells
- Other promising CSF and plasma biomarkers may be added based on ongoing multiplex immunoassay studies and mass spectrometry MRM studies as well

The following topics will be covered in this section:

Biofluids Collection Schedule
Sample Identification and Tracking
Sample Quality Checks
Clinical Laboratory Samples at Screening
DNA Sample Collection for GWAS and ApoE Genotyping
Cells for Immortalization
RNA sample collection
Biomarkers: Blood Samples
Buffy Coat Sample
Cerebral Spinal Fluid Sample Collection

A glossary of terms is at the end of this section.

Biofluids: Collection, Processing And Shipment

BIOFLUID COLLECTION SCHEDULE

NEW ENROLLED CONTROLS/EMCI/LMCI PARTICIPANTS								
	Covance Screening Labs	CSF	Buffy Coat	Plasma	Serum	RNA	APOE/ GWAS	Cell-Immort.
Screening	✓							
Baseline		✓	✓	✓	✓	✓	✓	✓
Month 6			✓	✓	✓			
Ongoing Annual Visits		✓*	✓	✓	✓	✓		

* LP to be performed every two years from Baseline, as funding permits.

NEW ENROLLED AD PARTICIPANTS								
	Covance Screening Labs	CSF	Buffy Coat	Plasma	Serum	RNA	APOE/ GWAS	Cell-Immort.
Screening	✓							
Baseline		✓	✓	✓	✓	✓	✓	✓
Month 6			✓	✓	✓			
Month 12			✓	✓	✓	✓		
Month 24		✓	✓	✓	✓	✓		

Last in-clinic visit for new enrolled AD participants is Month 24. AD participants will have ongoing 6 month phone follow-up visits for 54 months from Baseline.

FOLLOW-UP PARTICIPANTS						
	CSF	Buffy Coat	Plasma	Serum	RNA	GWAS**
Initial Visit	✓*	✓	✓	✓	✓	✓
Ongoing Annual Visits	✓*	✓	✓	✓	✓	

* LP to be performed every two years, as funding permits. Initial LP under ADNI2 for Rollover participants will be based on date of last successful LP under ADNI1/ADNIGO.

** GWAS only if not previously obtained under ADNIGO.

Biofluids: Collection, Processing And Shipment

SAMPLE IDENTIFICATION AND TRACKING

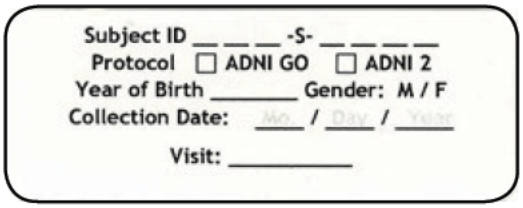
Please confirm you have labels for each visit BEFORE scheduling the visit.

- **Clinical Laboratory Samples at screening** will be done through Screening Kits provided by Covance. Laboratory samples at screen will use Covance's barcode system.

COVANCE BAR CODE

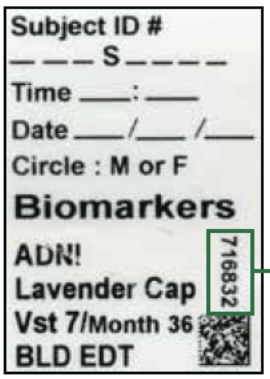
- **All genetic samples** (ApoE, GWAS, RNA, Cell Immortalization, and Buffy Coat) must be identified using the NCRAD Sample Identification label provided by the ADCS.

NCRAD SAMPLE LABEL



- **All biomarker samples** (plasma, serum and CSF) must be identified using the UPENN biomarker Identification label provided by the ADCS.

UPENN BIOMARKER SAMPLE LABEL



License Plate

Please note there are different UPENN labels based on the visit. Please ensure you use the appropriate UPENN label that corresponds to the correct visit.

VISIT NUMBERING

VISIT	NUMBER	ABBREVIATION	LICENSE PLATE
Baseline	2	VST 2	200000 - 299999
Month 6	3	VST 3	300000 - 399999
Month 12	4	VST 4	400000 - 499999
Month 24	6	VST 6	600000 - 699999
Month 36	7	VST 7	700000 - 799999
Month 48	8	VST 8	800000 - 899999
Month 60	9	VST 9	900000 - 999999
Month 72	10	VST 10	1000000 - 1099999
Month 84	11	VST 11	1100000 - 1199999
Month 96	12	VST 12	1200000 - 1299999
Month 108	13	VST 13	1300000 - 1399999
Month 120	14	VST 14	1400000 - 1499999

Biofluids: Collection, Processing And Shipment

SAMPLE TRACKING

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

- Biomarker samples (serum, plasma and CSF) will also be tracked at UPENN using the license plate number listed on the sample label.

The Genetic sample collection worksheet, Biomarker sample collection worksheet, and Buffy Coat sample collection worksheet (located in the Worksheet Packets posted in the Document Repository) 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 ADNI2 web portal must be completed on the day of each visit.

For the APOE/GWAS/RNA/Buffy Coat samples, please email or fax a copy of the sample form to NCRAD before shipping so the lab knows to expect the sample.

NCRAD email: **alzstudy@iupui.edu**

NCRAD fax: **317-278-1100**

For questions regarding biomarker shipping or packaging please contact the UPENN biomarker core help desk: **ADNI@uphs.upenn.edu**

SAMPLE QUALITY CHECKS

In addition to being tracked online in the ADNI2 web portal, the condition and amount 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 form (Sample Collection: Biomarker Samples; Sample Collection: Genetic Samples, and/or Sample Collection: Buffy Coat) in the worksheet packet and eCRF in the ADNI2 web portal. Please ensure the reason why the sample was not obtained is provided.

IMPORTANT: **Please ensure to use the appropriate sample labels for each sample type. NCRAD labels for Cell Immortalization sample, APOE/GWAS sample, RNA sample and Buffy Coat sample. UPENN Label for plasma biomarker sample, serum biomarker sample and CSF.**

There are UPENN Labels specific to the visit (i.e., visit 7/month 36) and sample type (i.e., BLD SER (serum)). It is vital that this match the sample and visit collected.

SAMPLE QUALITY CHECKS (CONT'D)

SAMPLE AMOUNTS OBTAINED AT EACH VISIT (mL)

SAMPLE TYPE	AMOUNT	CN/EMCI/LMCI	AD	FOLLOW-UP
Buffy Coat	1-2 mL	BL, M6, Ongoing Annual	BL, M6, M12, M24	Initial, Ongoing Annual
Plasma from blood	20 mL	BL, M6, Ongoing Annual	BL, M6, M12, M24	Initial, Ongoing Annual
Serum from blood	20 mL	BL, M6, Ongoing Annual	BL, M6, M12, M24	Initial, Ongoing Annual
CSF	20 mL	BL, Ongoing Annual†	BL, M24	Initial††, Ongoing Annual††
Blood for Cell Immortalization	2 x 8.5 mL	BL	BL	Not Applicable
Blood for APOE*/GWAS**	10 mL	BL	BL	Initial
Blood for RNA genotyping	3 x 2.5 mL	BL, Ongoing Annual	BL, M12, M24	Initial, Ongoing Annual

* APOE genotyping will only be done for newly enrolled subjects.
** GWAS only if not previously obtained under ADNIGO.
† LP to be performed every two years from Baseline, as funding permits.
†† LP to be performed every two years, as funding permits. Initial LP under ADNI2 for Rollover participants will be based on date of last successful LP under ADNI1/ADNIGO.

CLINICAL LABORATORY SAMPLES AT SCREENING

CLINICAL LABORATORY KITS

Screening laboratory kits are being provided by Covance, all other laboratory supplies are provided by the ADCS.

Please note that Covance will not handle the management of any labs for ADNI 1 Follow -Up participant visits or ADNI GO Follow-Up participants under the ADNI2 protocol. In addition, Covance will not manage labs for new participants beyond the Screening visit.

To order screening kits please complete the US Resupply Order Form located in the document repository and email to: **resupply.americas@covance.com**.

There is a 7 - 10 day turn around time from the time Covance receives the Supply Order Form to the time screening kits arrive at your site. Please ensure you order screening kits far enough in advance. There are no auto-shipments. You are responsible to order directly from Covance.

Instructions on how to collect, process and package screening laboratory specimens are outlined in the Covance Lab Manual located in the document repository. Instructions are also included on the Laboratory Requisition form included in the screening kits.

Please note the screening kits for ADNI2 do ***NOT*** differ from those provided for ADNIGO.

- If you have any Screening kits left over from ADNIGO that have not expired you can use these for any new Screening visit under ADNI2.
- ***IT IS THE RESPONSIBILITY OF EACH SITE TO MONITOR THE EXPIRATION DATE OF EACH KIT.***

CLINICAL LABORATORY SAMPLES AT SCREENING (Cont'd)

Each 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 Covance
- 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
- Alcohol
- Gauze
- Bandage
- Dry ice
- Urine collection cup

REQUISITIONS

- Use black or blue ink, as Covance 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)

IMPORTANT NOTE: **ALL CLINICAL LABORATORY SPECIMENS MUST BE SHIPPED ON THE DAY OF COLLECTION.**

CLINICAL LABORATORY SAMPLES AT SCREENING (Cont'd)

CLINICAL LABORATORY REPORTS

Covance 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 Covance.
- For all out-of-range results, a clinician at the center must indicate clinical significance (yes or no) by checking the appropriate box on the report.
- 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.

To order additional clinical laboratory kits, or if you have any questions about how to use the clinical laboratory kits, complete the requisition forms, ship supplies, or need to contact covance for any other reason, please call (800) 327-7270.

TO CALL UPS FOR A COVANCE SPECIMEN PICKUP, CALL (866) 961-3790 (US ONLY)	TO CALL FEDEX FOR A COVANCE SPECIMEN PICKUP, CALL (800) 247-4747 (CANADA ONLY)

You can also refer to the Covance Procedures Manual in the Document Repository for specific instructions on sample collection, processing and shipment.

Biofluids: Collection, Processing And Shipment

DNA SAMPLE COLLECTION FOR GWAS AND APOE GENOTYPING

- The single 10 mL EDTA (lavender top) tube of whole blood will be collected at Baseline and will be used for the genome-wide association study across all New Enrolled and Follow-Up participants who didn't have a GWAS sample collected under ADNIGO.
- ApoE genotyping will only be done for the New 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 ball-point pen or permanent marker. Securely place the label onto the EDTA (lavender top) tube ***BEFORE*** the blood draw.

Please note the genetic label has been modified from ADNIGO, to allow for use in both ADNIGO and ADNI2.

- Any remaining ADNIGO genetic labels can be used until complete; all future orders you will receive the new label seen here.
- The participant ID now states ADNI, rather than ADNIGO.
- A field has been included to indicate which protocol the specimen was collected for.
- The visit field should reflect the number of months from ADNI1 Baseline (*i.e.*, Month 48, Month 60, Month 72) or ADNIGO Baseline (*i.e.*, Month 12, Month 24) for continuing subjects into ADNI2. For New Enrolled participants in ADNI2 the visit field should reflect Baseline, Month 6 and so on.

BLOOD COLLECTION:

1 x 10 mL EDTA (lavender top) 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.

COMPLETION OF SAMPLE COLLECTION - GENETIC WORKSHEET:

Ensure all fields on the sample collection worksheet located in the visit packet are complete. Pay particular attention to the questions regarding if the subject consented to DNA testing and sample storage. Ensure 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:

The whole blood sample must be received by the National Cell Repository for AD (NCRAD) within 24 hours of collection. The whole blood sample is maintained at room temperature (20-25 degrees Celsius) and shipped at ambient temperature.

DNA SAMPLE COLLECTION FOR GWAS AND APOE GENOTYPING (cont'd)

SHIPPING:

The whole blood samples must be maintained at room temperature and shipped by Federal Express – **Priority Overnight** (Monday – Thursday) at ambient temperature to NCRAD.

➲ NCRAD will ***NOT*** be able to accept any shipment on Saturday or Sunday.

Pre-Paid Federal Express Air waybills and ambient shippers will be provided by ADCS. If your site needs additional air waybills or ambient shippers please complete the Supply Order Form located in the document repository.

NCRAD Shipping Address:
Kelly Faber
National Cell Repository for AD
980 W Walnut St R3 C158
Indianapolis, IN 46202

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

For those instances in which a Friday study visit is necessary, the EDTA (lavender top) tube 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. (EDTA tubes can be refrigerated from Friday until Monday, if needed. But if whole blood sample is refrigerated it must be shipped with ice packs to NCRAD).

NOTIFYING THE NATIONAL CELL REPOSITORY FOR AD (NCRAD):

The day the blood sample is shipped to NCRAD you must **FIRST** fax a copy of the completed **Sample Collection: Genetic Sample Worksheet** to **(317) 278-1100** or email a copy of the completed worksheet to NCRAD at **alzstudy@iupui.edu. *Also be sure to include a copy of this worksheet with the shipment.***

SAMPLE TRACKING:

Complete the Genetic Sample electronic case report form located in the ADNI2 web portal immediately after sample collection. Remember to include any issues that occurred during the sample collection, with packaging or temperature excursions on the visit comment electronic case report form.

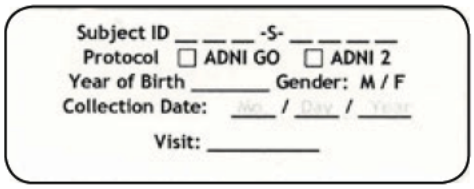
Biofluids: Collection, Processing And Shipment

CELLS FOR IMMORTALIZATION

Blood samples will be collected for Cell Immortalization at Baseline for all **New Enrolled** participants after passing screening criteria for this study. Whole blood will be collected in two 8.5 mL ACD-A (yellow top) tubes.

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 ball-point pen or permanent marker. Securely place the label onto each ACD-A (yellow top) tube before the blood draw.



BLOOD COLLECTION:

2 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.

COMPLETION OF SAMPLE COLLECTION - CELL FOR IMMORTALIZATION WORKSHEET:

Ensure all fields on the sample collection worksheet located in the visit packet are complete. Include the name of the individual who packaged and shipped the blood specimen, along with their phone number and email. 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:

***The whole blood sample must be received by the National Cell Repository for AD (NCRAD) within 24 hours of collection*.** The whole blood sample is maintained at room temperature (20-25 degrees Celsius) and shipped at ambient temperature.

SHIPPING:

The whole blood samples must be maintained at room temperature and shipped by Federal Express – **Priority Overnight** (Monday – Thursday) at ambient temperature to NCRAD.

➲ NCRAD will ***NOT*** be able to accept any shipment on Saturday or Sunday.

Pre-Paid Federal Express Air waybills and Ambient Shippers will be provided by ADCS. If your site needs additional air waybills or ambient shippers please complete the Supply Order Form located in the document repository.

CELLS FOR IMMORTALIZATION (Cont'd)

NCRAD Shipping Address:
Kelly Faber
National Cell Repository for AD
980 W Walnut St R3 C158
Indianapolis, IN 46202

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

For those instances in which a Friday study visit is necessary, the ACD-A (yellow top) tube 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.

It is crucial that the ACD-A tubes are NOT refrigerated, as they must stay at room temperature.

NOTIFYING THE NATIONAL CELL REPOSITORY FOR AD (NCRAD):

The day the blood sample is shipped to NCRAD you must **FIRST** fax a copy of the completed **Sample Collection: Cell for Immortalization Worksheet** to **(317) 278-1100** or email a copy of the completed worksheet to NCRAD at **alzstudy@iupui.edu.** ***Also be sure to include a copy of this worksheet with the shipment.***

SAMPLE TRACKING:

Complete the Cell for Immortalization electronic case report form located in the ADNI2 web portal immediately after sample collection. Remember to include any issues that occurred during the sample collection, with packaging or temperature excursions on the visit comment electronic case report form.

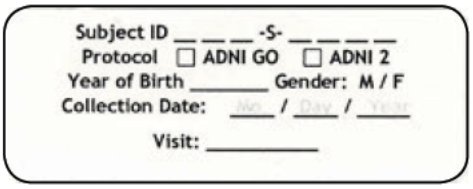
Biofluids: Collection, Processing And Shipment

RNA SAMPLES

In order to measure gene expression across time, an RNA sample will be collected at Baseline and ongoing annual visits across all New Enrolled participants. Participants continuing from ADNI1 or ADNIGO, RNA sample will be collected at initial visit under ADNI2 and annual visits thereafter. 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 ball-point pen or permanent marker. Securely place the label onto each tube before the blood draw.



BLOOD COLLECTION:

3 x 2.5 mL PAXgene Blood RNA tubes will be collected at Baseline and Ongoing Annual visits for New Enrolled participants using the RNA sample collection kit provided by the ADCS. For participants continuing from ADNI1 or ADNIGO, it will be at the initial visit under ADNI2 and annual visits thereafter.

1a. Ensure that the PAXgene Blood RNA tube is at room temperature prior to use.

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" 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 ADCS)

2. 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.

3a. Hold the PAXgene Blood RNA tube vertically, below the blood donor's arm, during blood collection.

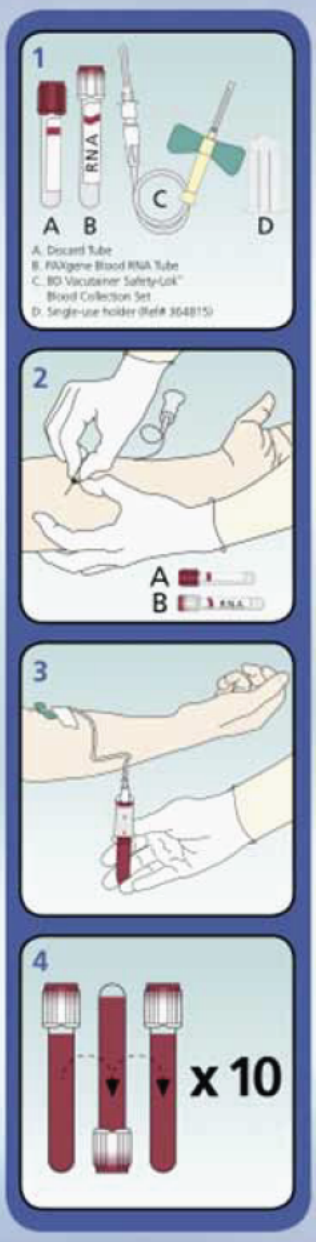
3b. Allow at least 10 seconds for a complete blood draw to take place. Ensure that the blood has stopped flowing into the tube before removing the tube from the holder.

4a. Gently invert the PAXgene Blood RNA tube 8 to 10 times.

4b. 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 (B) is at room temperature (18°C-25°C) prior to use and 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" (A) 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 BD Vacutainer® Safety-Lok™ Blood Collection Set (C), collect blood into the PAXgene Blood RNA Tube using your institution's recommended standard procedure for 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. (See Figure 1)

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) or at 4°C.*

Ref# 762165

BD Vacutainer® Safety-Lok™ Blood Collection Set
Ref# 367281 North America
Ref# 367286 Other Countries

BD Customer Service/Orders:
888.237.2762 (North America)
32.53.720.337 (Europe)

PreAnalytiX
A QIAGEN / BD Company

www.PreAnalytiX.com

CE

*Refer to PAXgene® Blood RNA Tube handbook.

Printed in USA 05/05 VLS933-1

RNA SAMPLES (Cont'd)

COMPLETION OF SAMPLE COLLECTION: GENETICS WORKSHEET:

Ensure all fields on the sample collection worksheet located in the visit packet are complete. Pay particular attention to the questions regarding if the subject consented to RNA testing and sample storage. Ensure 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:

The National Cell Repository must receive the whole blood sample for AD (NCRAD) within 24 hours of collection. The whole blood sample is maintained at room temperature (20-25 degrees Celsius) and shipped at ambient temperature.

SHIPPING:

The whole blood samples must be maintained at room temperature and shipped by Federal Express – **Priority Overnight** (Monday – Thursday) at ambient temperature to NCRAD. NCRAD will not be able to accept any shipment on Saturday or Sunday. Pre-Paid Federal Express Air waybills and Ambient Shippers will be provided by ADCS. If your site needs additional air waybills or ambient shippers please complete the Supply Order Form located in the document repository.

NCRAD Shipping Address:
Kelly Faber
National Cell Repository for AD
980 W Walnut St R3 C158
Indianapolis, IN 46202

NCRAD Helpdesk:
alzstudy@iupui.edu
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Fax: 317-278-1100

For those instances in which a Friday study visit is necessary, the PAXgene Blood RNA tubes **will need to be held at room temperature for 2 hours and then refrigerated until Monday** and then ship to NCRAD with frozen ice packs.

The temperature for RNA sample must stay between 2-8 degrees Celsius.

Please note that since the EDTA (lavender top) tube and ACD-A (yellow top) tubes must stay at room temperature and shipped ambient, two separate shipments would need to occur on Monday for Friday study visits. One shipper would include ice packs and the PAXgene Blood RNA tubes and the second shipper would be shipped ambient with the 10 mL EDTA tube and 2 x 8.5 mL ACD-A tubes.

NOTIFYING THE NATIONAL CELL REPOSITORY FOR AD (NCRAD):

The day the blood sample is shipped to NCRAD you must **FIRST** fax a copy of the completed **Sample Collection: Genetics Worksheet** to **(317) 278-1100** or email a copy of the completed worksheet to NCRAD at **alzstudy@iupui.edu. Also be sure to include a copy of this worksheet with the shipment.**

SAMPLE TRACKING:

Complete the Genetics worksheet electronic case report form located in the ADNI2 web portal immediately after sample collection. Remember to include any issues that occurred during the sample collection, with packaging or temperature excursions on the visit comment electronic case report form.

Biofluids: Collection, Processing And Shipment

GENETICS SAMPLES COLLECTIONS SUPPLIES (GWAS/APOE, RNA, CELL IMMORTALIZATION)

1a. Tube Types

GWAS/
APOE*

Cell Immortalization
(New participants
only at Baseline)

RNA
Tubes

Discharge Tube ***(Only use if RNA is drawn first, then discard)***

*ApoE genotyping will only be done for the newly enrolled participants

1b. Fill out NCRAD label and attach to each tube prior to collecting sample. Please use a ball-point pen or permanent marker.

Subject ID __ __ __ -S- __ __ __ __
Protocol ☐ ADNI GO ☐ ADNI 2
Year of Birth _____ Gender: M / F
Collection Date: ___ / ___ / ____
Visit: _____

2. Genetics samples shipping supplies

INCLUDES:

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

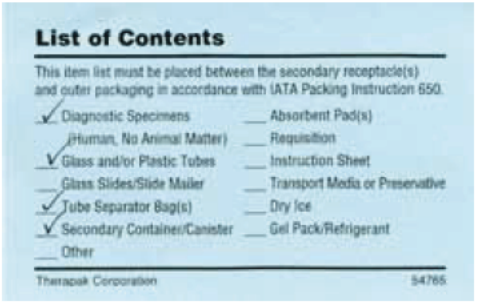
Biofluids: Collection, Processing And Shipment

GENETICS SAMPLES COLLECTIONS SUPPLIES (GWAS/APOE, RNA, CELL IMMORTALIZATION (Cont'd)

3a. Insert all tubes into tube sleeve

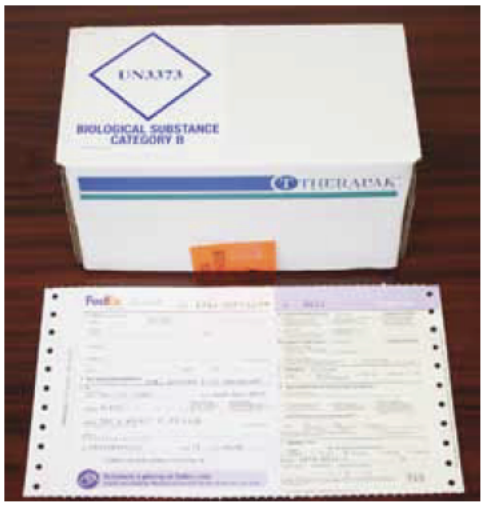
3b. ***NEVER INSERT DISCHARGE TUBE INTO TUBE SLEEVE.*** If used, the discharge tube should be discarded.

4. Carefully roll up sleeve, insert into canister and wrap ***OUTSIDE*** canister in bubble wrap



5. Fill out the list of contents card.

6. Place card and canister into shipping box



7. Please see note below, otherwise affix both biohazard labels to box. Fill out NCRAD FedEx airbill and attach to box.

NOTE: In order to be able to reuse the shipping box, it is recommended to place the shipping box into a FedEx Clinical Pak and affix both biohazard labels/FedEx airbill to Clinical Pak. FedEx Clinical Paks can be ordered directly from FedEx at ***www.fedex.com/us***

Biofluids: Collection, Processing And Shipment

BIOMARKERS: BLOOD SAMPLES

Plasma and serum for biomarkers will be collected at Baseline, Month 6 and Ongoing Annual visits for New Enrolled participants. For ADNI1 and ADNIGO Follow-Up participants plasma and serum for biomarkers will be collected at their initial ADNI2 visit and at annual follow up visits thereafter. (Refer to the ADNI2 protocol Schedule of Events).

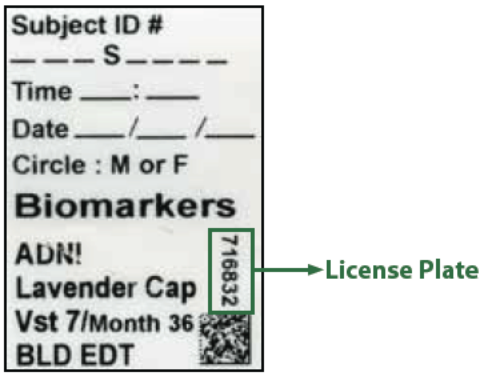
Fasting overnight (minimum 6 hours) is required for plasma, serum, and CSF sample collection.

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



NOTE: Please use a ball-point pen or permanent marker when completing the biomarker label.

BIOMARKERS: BLOOD SAMPLES (Cont'd)

BLOOD COLLECTION:

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.
   - Please remember to use the correct UPENN Label specific to the visit (*i.e.*, visit 7/month 36) and sample type (*i.e.*, BLD SER (serum)). It is vital that this match the sample and visit collected.
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.

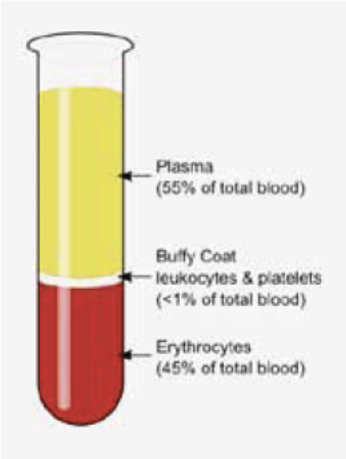
TUBES 3 AND 4: 10 mL LAVENDER-TOP TUBES FOR PLASMA SAMPLES

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.
   - Please remember to use the correct UPENN Label specific to the visit (*i.e.*, visit 7/month 36) and sample type (*i.e.*, BLD EDT PL (plasma)). It is vital that this match the sample and visit collected.
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.

Biofluids: Collection, Processing And Shipment

BIOMARKERS: BUFFY COAT SAMPLE COLLECTION

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 should follow each biomarker lab blood draw. For newly enrolled CN, EMCI, LMCI, and AD participants this means the buffy coat will be extracted at Baseline, Month 6, and Ongoing Annual Visits. For participants continuing from ADNI1 and/or ADNIGO the buffy coat will be extracted at the ADNI2 Initial Visit and Ongoing Annual Visits.

Extract the buffy coat form 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, which will be sent to UPenn. 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, the remaining cells can be discarded.***

- Complete the information on the genetic label. Ensure all fields on the label are complete using a ball-point 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.

Cryogenic Vial 1

Cryogenic Vial 2

COMPLETION OF SAMPLE COLLECTION – BUFFY COAT WORKSHEET:

Ensure all fields on the sample collection worksheet located in the visit packet are complete. A copy of the worksheet should be included with the shipment, original remains onsite.

TEMPERATURE REQUIREMENTS:

- The buffy coat is maintained at room temperature (20-25 degress Celsius) and shipped at ambient temperature.
- ***The buffy coat sample must be received by the National Cell Repository for AD (NCRAD) within 24 hours of collection.***

BIOMARKERS: BUFFY COAT SAMPLE COLLECTION (Cont'd)

SHIPPING:

The buffy coat must be maintained at room temperature and shipped by Federal Express– **Priority Overnight (Monday – Thursday)** at ambient temperature to NCRAD.

NCRAD will NOT be able to accept any shipment on Saturday or Sunday.

Pre-Paid Federal Express Air waybills and ambient shippers will be provided by ADCS. If your site needs additional air waybills or ambient shippers please complete the Supply Order Form located in the document repository.

NCRAD Shipping Address:
Kelly Faber
National Cell Repository for AD
980 W Walnut St R3 C158
Indianapolis, IN 46202

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

For those instances in which a Friday study visit is necessary, the buffy coat should be placed in a -80 or –20 degree Celsius freezer over the weekend and shipped frozen (on dry ice) on Monday to NCRAD.

NOTIFYING THE NATIONAL CELL REPOSITORY FOR AD (NCRAD):

The day the buffy coat is extracted and shipped to NCRAD you must **FIRST** fax a copy of the completed **Sample Collection: Buffy Coat Worksheet** to **(317) 278-1100** or email a copy of the completed worksheet to NCRAD at **alzstudy@iupui.edu**. **Also be sure to include a copy of this worksheet with the shipment.**

SAMPLE TRACKING:

Complete the buffy coat electronic case report form located in the ADNI2 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 on the visit comment electronic case report form.

NOTE: 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.

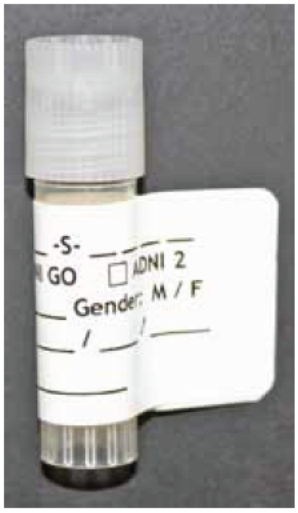
NOTE: Depending on the number of specimen tubes at a given visit being shipped to NCRAD, the buffy coat vials may not fit in the existing ambient shipper used for DNA and RNA (as the shipper holds up to 6 specimen tubes). In such cases a smaller ambient shipper is being provided by the ADCS to ship the buffy coat to NCRAD.

BIOMARKERS: BUFFY COAT SAMPLE COLLECTION (Cont'd)

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

2. Fill out NCRAD label and attach to cryogenic vials. Ensure label is dovetailed to not obscure any information on the label. Please use ball-point pen or permanent marker.

Subject ID __ __ __ -S- __ __ __ __
Protocol ☐ ADNI GO ☐ ADNI 2
Year of Birth _____ Gender: M / F
Collection Date: Mo. / Day / Year
Visit: _____



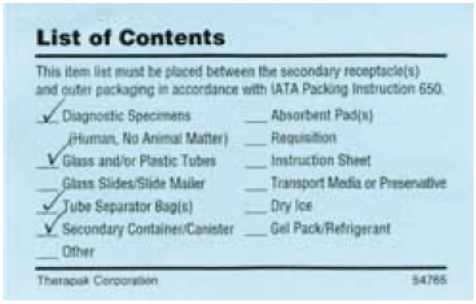
3. Buffy Coat sample shipping supplies

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

BIOMARKERS: BUFFY COAT SAMPLE COLLECTION (Cont'd)

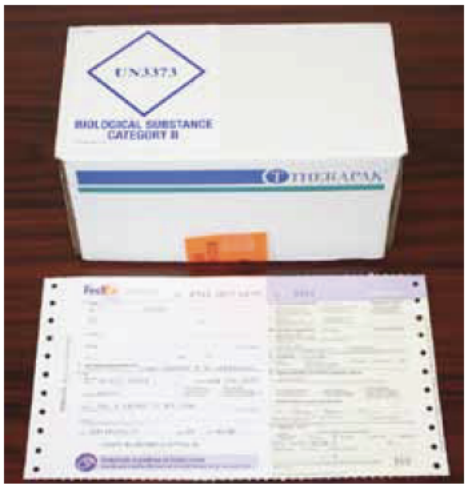
3a. Insert cryogenic vials into tube sleeve

4. Carefully roll up sleeve, insert into canister and wrap ***OUTSIDE*** canister in bubble wrap



5. Fill out the list of contents card.

6. Place card and canister into shipping box



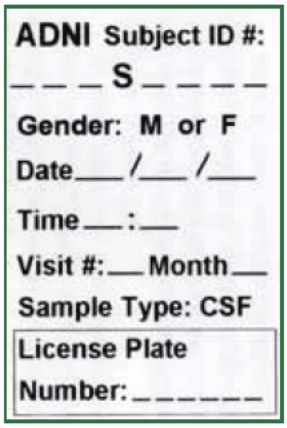
7. Fill out NCRAD FedEx airbill and attach to box

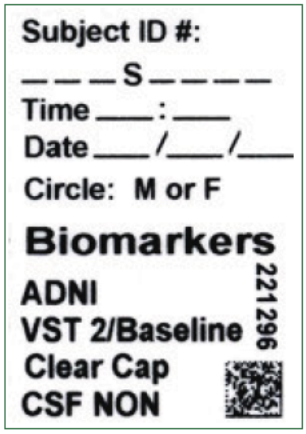
CEREBROSPINAL FLUID COLLECTION:

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

- For all New Enrolled participants, CSF will be collected at Baseline and every two years thereafter, as funding permits.
- For ADNI1 and ADNIGO Follow-Up participants, CSF under ADNI2 will be collected two years from their last successful LP under ADNI1 or ADNIGO.

Next, 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.





PLEASE NOTE: There are 2 different CSF labels. The one on the left above is to be used for ADNI1 or ADNIGO participants continuing into ADNI2. On this label please indicate the visit number and number of months from ADNI1 Baseline or ADNIGO Baseline. Please fill in the license plate number according to the license plate number on the blood and plasma biomarker labels for the subject. The label on the right above is to be used for New Enrolled participants at their Baseline visit.

Follow the detailed procedure as described in the **Instructions for Assisting with the LP Procedure** at the end of this section.

COMPLETION OF SAMPLE COLLECTION: BIOMARKER SAMPLES WORKSHEET:

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.

Biofluids: Collection, Processing And Shipment

CEREBROSPINAL FLUID COLLECTION (Cont'd):

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 waybills and frozen shippers will be provided by ADCS. If your site needs additional UPENN air waybills or frozen shippers please complete the Supply Order Form located in the document repository.

UPENN Shipping Address: **ADNI Biomarker Core Laboratory**
7 Maloney South
University of Pennsylvania Medical Center
3400 Spruce Street
Philadelphia, PA 19104
Email: **ADNI@uphs.upenn.edu**

IMPORTANT	➲ **Complete the Biomarker Samples Online Form before shipping samples.** ➲ **Print a pdf of the completed form and include a copy with the shipment.**

DISCARD APPROPRIATELY ALL GLOVES, TUBES, DISPOSABLE TRANSFER PIPETTES AND WASTE CONTAINING BLOOD OR BLOOD PRODUCTS.

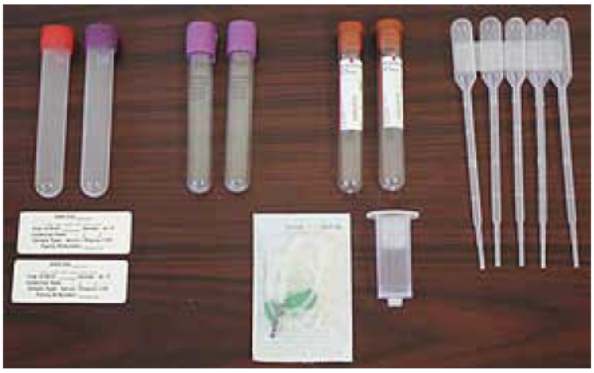
SAMPLE TRACKING:

- Enter the sample collection data on the Biomarker Samples and Method of CSF collection electronic case report forms located in the ADNI2 web portal (**www.adcs.org**) 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.

Biofluids: Collection, Processing And Shipment

SUPPLIES FOR BIOMARKER SAMPLES FROM ADCS:

1. 13-mL polypropylene transfer tubes with colored screw caps (red screw- capped for transfer of serum; lavender screw-capped for transfer of plasma)
2. 10- mL, lavender top plastic Vacutainer blood tubes (for collection of blood for plasma samples)
3. 10-mL, plain red top plastic Vacutainer blood tubes (for collection of blood for serum samples)
4. Disposable **STERILE** transfer pipettes
5. Blood collection set with 21-gauge butterfly needle
6. Vacutainer tube holder
7. Lumbar Puncture supplies (please refer to the lumbar puncture supplies section below where an itemized list of the supplies is outlined)



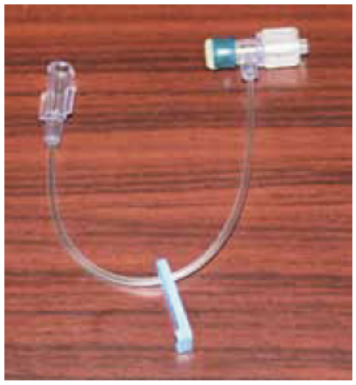
ADDITIONAL LUMBAR PUNCTURE SUPPLIES:

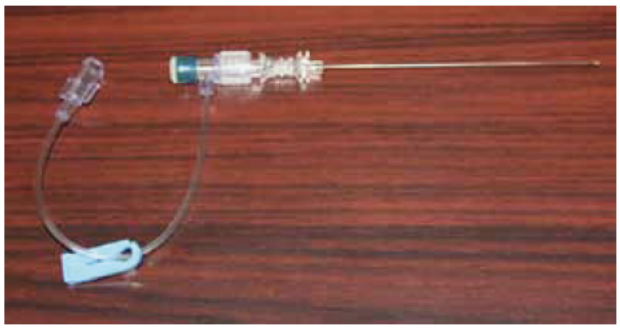
Gravity Collection (recommended)

Suction Collection

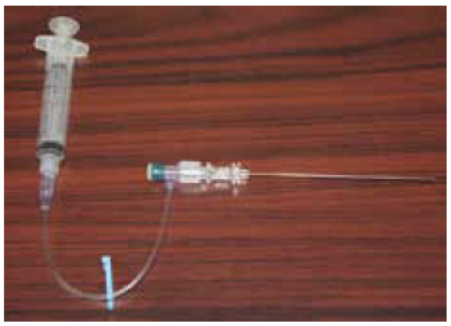
SUPPLIES FOR BIOMARKER SAMPLES FROM ADCS:

USING THE EXTENSION TUBE (suction collection only):





After inserting Sprotte needle, attach extension tube.



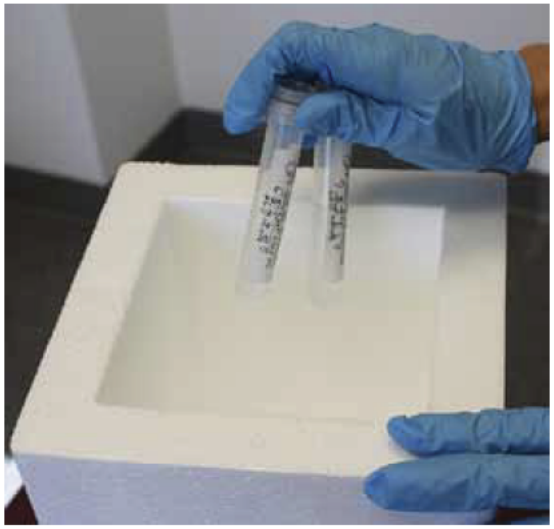
Then attach syringe to other end of tube.

8. Styrofoam inner shipping container
9. Cardboard shipping box
10. Sample bar code labels
11. Shipping labels
12. Bubble-wrap bags
13. Outer ziploc bags

➲ To order additional Biomarker kits, please fill out the Supply order form located in the document repository and send to: **adcs-clinops@ucsd.edu.**

PACKAGING PROCEDURES FOR BIOMARKER SAMPLES:

1. Biomarker samples shipping supplies.



2. Place the 4 transfer tubes (1 red screw-capped for transfer of serum; 1 lavender screw-capped for transfer of plasma; 2 clear screw-capped for transfer of CSF) upright in dry ice and allow to completely freeze.

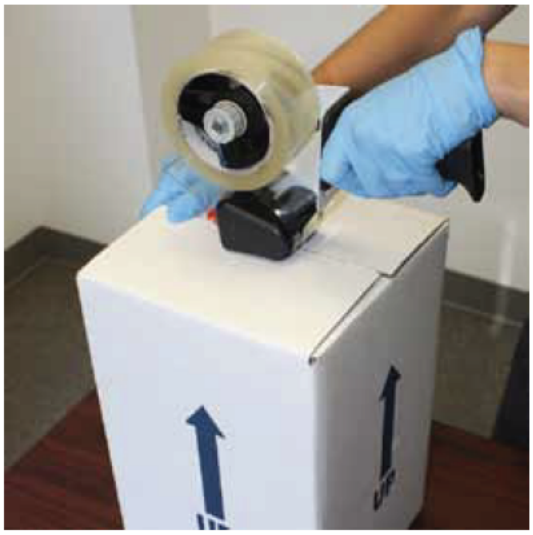
3. Place all 4 transfer tubes into bubble wrap bag.

4. Place bubble wrap bag and copy of collection worksheets into the Ziploc bag.

PACKAGING PROCEDURES FOR BIOMARKER SAMPLES (Cont'd):

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 card board box.



7. Seal cardboard box firmly with packing tape.

8. Affix FedEx label and call for pickup.

Biofluids: Collection, Processing And Shipment

BIOMARKERS: CEREBRAL SPINAL FLUID

CSF samples will be collected from all New Enrolled participants at the Baseline Visit and every two years thereafter. CSF will be collected from ADNI1 and ADNIGO Follow-Up participants every two years from the last successful LP under ADNI1 or ADNIGO. A video describing the LP procedure is available to all sites. To request a copy, please email: **brainlink@ucsd.edu**.

- 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.

NOTE: Lumbar puncture should be done ***after*** any MRI scan for that same timepoint. If this is not possible, please ensure that there is at least a 3-day window between the lumbar puncture and the MRI appointment.

- If LP and PET scan are done on the same day, LP should be completed ***prior*** to the FDG or AV-45 PET scan; otherwise there should be at least 12 hours between the LP and the PET scan.

PREVENTION OF POST-LUMBAR PUNCTURE HEADACHE:

1. Use of a Sprotte 22g atraumatic spinal needle using the gravity drip method and careful technique are optimal for reducing post-LP headache risk.
2. 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.
3. 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. The epidural blood patch is typically performed by an anesthesiologist.

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 who is agreeable to performing an epidural blood patch for any subject who experiences severe post lumbar puncture headache.**

Sites should find out ahead of time who to call to schedule and perform a blood patch at their center, should the need arise, as well as how their study account will be billed.

LUMBAR PUNCTURE SUPPLIES

Gravity drip using a 22g Sprotte needle is the recommended method for CSF collection. However, supplies for collecting and for shipping the CSF are sent according to the on-site clinician's preferred method.

Lumber Puncture Materials (provided by the ADCS) for sites using DRIP:

- Smith's Lumbar Puncture Trays*
- 22g Sprotte Atraumatic Spinal Needles and Introducers
- 25g 1 1/2" needles for deep local anesthesia
- 7 cc sterile polypropylene collection tubes
- 13 mL transfer tubes with clear caps
- 2 mL cryogenic vial (for local laboratory testing)
- Pipette (for transferring CSF from collection to shipping tubes)

Lumber Puncture Materials (provided by the ADCS) for sites using SUCTION:

- Smith's Lumbar Puncture Trays*
- 25g 1 1/2" needles for deep local anesthesia
- 5 cc sterile syringes
- 13 mL transfer tubes with clear caps
- 2 mL cryogenic vial (for local laboratory testing)

Additional Lumbar Puncture kits and needles can be ordered by filling out the Supply order form located in the document repository and send to: **adcs-clinops@ucsd.edu**

The lumbar puncture tray contains the following items which will be used to perform lumbar puncture. ***Please check the expiration date of the lumbar puncture tray before using.***

- Two Medication labels
- One needle stick pad
- Three Sponge Sticks
- Three 2 X 2 Gauze pads
- Two Paper drapes
- Fenestrated Paper Drape
- 3cc syringe ***(attached needle is used for drawing up lidocaine, but NOT for injecting it)***
- 22g 1 1/2" needles for deep local anesthesia
- Prep Well
- Adhesive Bandage (Band-Aid)
- Two 24g Sprotte needles (for sites using suction method)
- Extension tube (for sites using suction method)
- 25g 5/8" needle for local anesthesia
- Two Introducer needles

* *The Smith's LP trays are not approved for use in Canada. Canadian sites will receive LP trays similar to those used in ADNI1. The same recommendation applies (22g Sprotte needle using the gravity method).*

LUMBAR PUNCTURE SUPPLIES (Cont'd)

Please note all Smith's lumbar puncture trays contain the following items:

- **Introducer needle**
- **24g Sprotte needles**
- **Extension tube.**

These items are *NOT* needed when following the ADNI recommended method of CSF collection (gravity drip).

The following "stock" items will also be used:

- 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
- Sterile 25g, 1 1/2"needle for deep infiltration of lidocaine (one, plus extras for backup)
- Sterile 3 cc syringe with 20g needle attached (in case more lidocaine is needed). ***Attached needle is used for drawing up lidocaine, but NOT for injecting it.***
- Bottle of lidocaine
- Sterile 4 by 4 gauze pads (extras)
- Extra adhesive bandages (Band-Aids)
- Clean washcloths and towels
- Sharps container
- Lumbar Puncture Fact Sheet and Post-LP instructions for subjects

INSTRUCTIONS FOR ASSISTING WITH THE LP PROCEDURE

SETTING UP FOR THE LP:

- On the bedside table nearest where the person performing the Lumbar Puncture will sit, place a pair of sterile gloves (in their packaging) and a blue pad. They will need these at the beginning of the Lumbar Puncture.
- Have all other supplies on hand.
- The Lumbar Puncture may be done with the subject either lying down on their side, or sitting. It is critical to try to optimize this positioning, and usually requires an assistant.
- On an over-bed table, remove the contents of the Lumbar Puncture kit from the outer plastic packaging, leaving the contents wrapped in their sterile drape.
- Leave everything wrapped until the person performing the Lumbar Puncture is seated, and begins examining the subject.
- Feel the outside of the Lumbar Puncture kit (still wrapped up) to determine which end contains the spongy swabs. Turn this end toward the person performing the Lumbar Puncture and begin unwrapping the kit.
    - **TOUCH ONLY THE OUTSIDE OF THE PAPER WRAPPER.**
- When you grab an edge to unfold it, touch only the folded under portions of the outside of the wrapper. **Also, don't let the outside of the wrapper touch any part of the inside.**
    - **IF YOU TOUCH ANY PART OF THE INSIDE OF THE PAPER WRAPPER, OR IF ANY NON-STERILE OBJECT OUTSIDE OF THE WRAPPER TOUCHES ANY PART OF THE INSIDE OF THE WRAPPER, *THROW THE KIT AWAY AND START OVER.***
    - **IF YOU ARE IN DOUBT AS TO WHETHER SOMETHING TOUCHED THE INSIDE OF THE PAPER WRAPPER, *THROW THE KIT AWAY AND START OVER.***
- If you reach a point where the kit is pretty much unwrapped but there is a tricky spot that won't unwrap, the person performing the Lumbar Puncture may be able to help, ***once they are gloved up.*** Remember, once they are gloved they can only touch the inside of the paper wrapper, and you can only touch the outside.

ADDING THE BETADINE

Once the kit is successfully unwrapped, very carefully open the bottle of Betadine solution, somewhere away from the kit.

- Use an alcohol wipe to remove any loose chunks of dried Betadine off of the bottle top. You don't want anything to fall onto the open and sterile Lumbar Puncture kit.

Pour enough Betadine into the well to cover the bottom, about 1/4 inch deep. Spend as little time as possible lingering over the kit.

INSTRUCTIONS FOR ASSISTING WITH THE LP PROCEDURE (Cont'd)

MAINTAINING THE STERILE FIELD

Keep in mind that there may be a lot of staff in the room during a Lumbar Puncture, and a big part of assisting with the Lumbar Puncture is keeping the field sterile, keeping people away from it, and reminding people to be careful around it.

- **IF ANYBODY TOUCHES THE INSIDE OF THE PAPER WRAPPER OR ANY PART OF THE CONTENTS OF THE KIT, *THROW THE KIT AWAY AND START OVER*.**
- **IF YOU ARE IN DOUBT AS TO WHETHER SOMEONE TOUCHED THE KIT, *THROW IT AWAY AND START OVER*.**
- **IF A STERILE GLOVED HAND HAS TOUCHED SOMETHING NOT STERILE, *THROW IT AWAY AND START OVER.***

Remember, you are the monitor for whether the person performing the Lumbar Puncture has broken sterility—usually by touching something not sterile with a sterile gloved hand. Feel free to be the boss of people if need be. Be assertive.

SPINAL INTRODUCER, SPINAL NEEDLE, AND SYRINGES

During this time, the person performing the Lumbar Puncture is usually preparing the kit, pulling out sterile drapes, getting out the lidocaine, and familiarizing themselves with the kit. If you need a tube to collect the CSF for labs, ask them to "toss" you one from the kit and carefully pick it up from the end of the kit where they have placed it, being careful not to touch the kit. Do not touch the gloved hand of the person performing the Lumbar Puncture. Hand the tube to the person who will be aliquoting the CSF after the Lumbar Puncture. Label it or have them label it.

Wait until the person performing the Lumbar Puncture is finished preparing the kit and has started administering the lidocaine to the subject before you begin dropping items on the tray. This makes it easier for them to get the items they need first before you add more items to the tray, and they won't accidentally fling a syringe into the Betadine or something else.

After they start numbing up the subject, carefully, and maintaining sterility, unwrap and drop the 25g 1 1/2" deep infiltration needle, spinal introducer and the Sprotte spinal needle onto the Lumbar Puncture tray. Everyone has their own special technique to accomplish this. With the spinal needle and introducer, it often works best to pinch the item through the clear plastic portion of the package firmly, while removing the paper strip from the other side. Then drop the item onto the tray while holding onto the packaging.

- Do not drop any packaging onto the tray.
- Do not let the item touch the outside of the packaging on its way to the tray.

INSTRUCTIONS FOR ASSISTING WITH THE LP PROCEDURE (Cont'd)

The 25g 1 1/2" needle and sterile syringes are a little different. The packaging is more flexible. One way is to take hold of the two sides of the packaging with the thumb and forefinger of each hand and pull them apart making sure the opening is facing down toward the tray. Again remember, do not drop any packaging onto the tray, do not touch the tray with your hand, and do not let the item touch the outside of the packaging on its way to the tray. Start with 3 syringes, but be ready to add more if the person performing the Lumbar Puncture needs them.

- Occasionally, the person performing the Lumbar Puncture will need to use more lidocaine to numb up a particular spot a little more or if they need to move to another spot entirely. In either case, they will need another 3 cc syringe and needle (packaged together and sterile).

  Open the package as you would a sterile syringe by pulling open the two sides of the packaging without touching the inside or the syringe, but hold it upright instead, so that the person performing the Lumbar Puncture can grab the syringe without touching the outside of the packaging. There's no need to do this over the tray. Then, you will need to take a bottle of lidocaine (check the expiration date) and swab the top of it with an alcohol wipe. Show the bottle label to the person performing the Lumbar Puncture.

  Next, hold the bottle upside down and at a slight angle toward the person performing the Lumbar Puncture so that they can plunge the needle into the bottle and extract some lidocaine without touching you or the bottle. Use two hands to stabilize the bottle.

- **If the person performing the Lumbar Puncture needs to change the site of the Lumbar Puncture (a different lumbar interspace), they will also need a *NEW* 25g needle for injecting lidocaine, a *NEW* introducer, and a *NEW* spinal needle.**

  They will let you know if they do. Open them the same way as before, by dropping them onto the tray.

  Often they will need an extra sterile 4 x 4 gauze pad. Again, they'll let you know. Open it the same way as the syringe and needle example above, by holding open the package so the person performing the Lumbar Puncture can grab the gauze without touching you or the package.

INSTRUCTIONS FOR ASSISTING WITH THE LP PROCEDURE (Cont'd)

ALIQUOTTING THE CSF

At this point, you will need to glove up. One usually waits until this time because it is easier to supply all of the sterile items without gloves on.

As the person performing the Lumbar Puncture fills the 7 cc collection tubes (or 5 cc syringes if using suction method), they will place them at the far end of the Lumbar Puncture kit, far from them, near to you. Pick each one up carefully, avoiding touching the kit. This is a gray area as far as sterility goes; however, we try to keep it as sterile as possible.

- To clear any blood from minor trauma associated with needle insertion, the first 1-2 mL of CSF should be discarded (or more if needed) to eliminate blood.
- 20 mL of CSF should then be collected from each participant for use and treatment in the following manner:
  - The first 2 mL will be used for standard tests done at your local laboratory
  - The remaining CSF (18 mL) will be collected in polypropylene collection tubes and transferred to polypropylene shipping tubes and sent to UPENN.

Hand the first full tube to the aliquoter; have them aliquot 1 mL for red and white cell count into the 2 mL cryogenic vial and 1 mL for total glucose and protein into another 2 mL cryogenic vial. The two 2 mL cryogenic vials will then need to be shipped to your local laboratory for testing.

Transfer each 7 cc of CSF from the collection tube into the barcode-labeled transfer tubes using the provided **STERILE** pipettes (if performing gravity drip CSF collection). Each transfer tube can hold the volume from approximately two 7 cc tubes so the first two collection tubes are transferred into one transfer tube, labeled with a CSF bar code, and the subsequent collection tubes are transferred into the second CSF bar code-labeled tube, for a total of ~18 mL of CSF collected.

- It is important to get them on dry ice as soon as possible, and in the upright position, so that the CSF freezes at the bottom of the tube. Please refer to the Cerebrospinal Fluid Collection section for full details for the labeling, freezing on dry ice, packaging and shipment of CSF samples.

WASHCLOTHS, BAND-AID, CLEAN UP

After the person performing the Lumbar Puncture collects the last of the CSF, they will remove the needle and introducer and wash the Betadine off the subject. They can use two warm, wet washcloths and a dry washcloth or towel. Have these ready for them, or appoint someone to retrieve them for them. All visible traces of iodine should be cleaned from the skin (use 2 wet washcloths), the skin dried, and the Band-Aid applied over the puncture site. The Band-Aid is in the lumbar puncture kit. After they have made the subject more comfortable, they will remove the sharps from the kit. They do this because they are more familiar with the kit and where they put all the sharps and how many there are, etc. Acquire a sharps container in which to dispose of them all.

Next, throw all the rest of the kit away and toss the washcloths/towel (you should wear gloves for this - there may be some blood or CSF on the washcloths) into the laundry. After the study ends and the subject has left, wash the over-bed table down with a bleach wipe.

Please enter results for red and white cell count, protein and glucose on the CSF-local lab results eCRF in the ADNI2 web portal (www.adcs.org) as soon as they are received.

INSTRUCTIONS FOR ASSISTING WITH THE LP PROCEDURE (Cont'd)

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 1/2" 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.**

PROCESSING CSF

- Ensure that all necessary equipment and supplies are available ahead of time.
- When gravity drip method is used for lumbar puncture, the CSF is draw 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 upright on dry ice for at least 20 minutes before being packaged.

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: brainlink@ucsd.edu.

BIOFLUIDS GLOSSARY

ADNI	Alzheimer's Disease Neuroimaging Initiative
ADNI1 FU	ADNI 1 Follow-Up Subjects
AD	Alzheimer's disease subject
NC	Normal Control subject
EMCI	Early Mildly Cognitively Impaired subject
LMCI	Late Mildly Cognitively Impaired subject (classic MCI)
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 Immortalization Sample
GWAS	Genome Wide Association Study
NCRAD	National Cell Repository for Alzheimer's Disease
LP	Lumbar Puncture

Neuropathology

ADNI-NPC PURPOSE AND AIMS

The aim of the ADNI Neuropathology Core is to provide the "gold standard" validation of the clinical diagnoses and imaging surrogates through neuropathological examination of ADNI1, ADNIGO and ADNI2 participants who come to autopsy. Neuropathologic diagnosis remains essential to validate clinical diagnoses; otherwise, the data generated by the different clinical assessments, imaging modalities, and biomarkers obtained from ADNI participants believed to have Alzheimer's disease (AD) may be contaminated by individuals who in fact do not have AD. Given the importance of the data that can be obtained from the neuropathologic examination of ADNI participants, it is essential that autopsy and brain donation be offered to every ADNI participant. In order to facilitate the autopsy discussion, the ADNI-NPC has developed the following guidelines for obtaining provisional autopsy consent as well as some educational materials to provide to ADNI participants.

DISCUSSING AUTOPSY AND OBTAINING PROVISIONAL CONSENT

An ADNI clinician will lead a discussion about autopsy with all participants (cognitively normal, MCI and AD) at their initial assessment (study partners and families are welcomed in the discussion and required for AD participants). There are 3 objectives of the discussion:

1. To convey information about the value of brain autopsy in confirming the clinical diagnosis and advancing knowledge regarding MCI and AD;
2. To initiate consideration of the individual's wishes concerning an autopsy.
3. To answer questions, misconceptions, or concerns about autopsy.

The involvement of the physician in these discussions emphasizes the importance of autopsy.

- The discussions are repeated at each ADNI visit (unless the participant has provided consent or has clearly refused autopsy), both to ensure the participant's wishes regarding brain donation are carried out and that family members and/or participant's Durable Power of Attorney (DPOA) are aware of the participant's wishes.
- There is no pressure on an individual to decide; they are encouraged to involve family members, clergy, physicians, or other appropriate persons in their decision-making.
- Participants are assured that a decision not to have autopsy in no way jeopardizes their research participation or any other patient rights.
- It is important to note that autopsy will not interfere with funerary arrangements nor will it be a financial burden to the participant's family.

As a supplement to this discussion, the ADNI-NPC has developed an Autopsy Brochure which dispels some of the common myths and concerns regarding autopsy and a Brain Donation letter which explains the importance of autopsy and brain donation in lay language. We encourage clinicians to use these tools when discussing autopsy with ADNI participants.

AFTER OBTAINING PROVISIONAL CONSENT

When voluntary consent is granted, more detailed information should be provided to the participant about procedures to follow at time of death, including telephone numbers to call and other guidelines. The ADNI-NPC has developed autopsy notification materials including wallet cards and letters to primary care physicians and nursing homes to communicate the participant's wishes regarding autopsy.

Neuropathology

AFTER OBTAINING PROVISIONAL CONSENT (Cont'd)

Participants are strongly encouraged to share this information with next-of-kin, legally authorized representatives (*e.g.*, Durable Power of Attorney or DPOA), and private physicians. In many states, final legal authorization by the DPOA or next-of-kin must be obtained at the time of death. As ADNI is a multi-center study involving sites in the US and Canada, please be sure to follow state and local laws regarding autopsy consent procedures.

It is important to emphasize to ADNI participants and caregivers the procedure for notifying the ADNI site at the time of death so that the autopsy protocol may be initiated. Wallet cards should be given to all participants that list contact information for the person they should notify at the time of death.

AT THE TIME OF EXPIRATION

Once your site has been notified of the death of an ADNI participant, please follow the autopsy procedures as outlined in the ADNI-NPC manual or the specific autopsy procedures developed for your site (see manual procedure below):

Autopsy Procedures *(to be carried out by site ADNI coordinator at time of death)*:

1. Notify the ADNI-NPC Coordinator (Lisa Taylor-Reinwald) of the death of the ADNI participant by calling **314.362.8079** or sending an email to **ltaylor@pathology.wustl.edu**. If you have questions or need urgent assistance, please page **314.841.4738**.
2. Contact the participant's family or informant/collateral source to clarify autopsy procedure. Obtain information about the funeral home they plan to use.
3. Contact the participant's funeral home and make arrangements for transportation to and from the autopsy location. Obtain a preliminary cost for these procedures. Discuss any atypical costs with the ADNI-NPC Coordinator.
4. Contact the pathologist or technician who has agreed to perform the brain removal. These arrangements should be made in advance with the assistance of the ADNI-NPC Coordinator. If arrangements have not been made in advance or you are unaware of the arrangements, contact the ADNI-NPC Coordinator.
5. Ensure that the pathologist or person performing the brain removal has a copy of the ADNI-NPC Brain Removal Protocol. This should also be supplied in advance; however, copies are available in the document repository on the ADNI2 website **www.adcs.org/Resource/studyResources.aspx** for download.
6. Schedule the brain removal in accordance with the pathologist's schedule. While it is important that the brain removal take place as soon as possible after death, participants who expire outside of normal business hours (i.e. overnight) can have the brain removed the following morning.
7. After brain removal, the pathologist should ship the fixed and frozen brain tissue to the ADNI-NPC following the Brain Removal Protocol (see below).
8. The ADNI-NPC Coordinator will follow up with the pathologist to ensure that the tissue is shipped and received at the ADNI-NPC lab.
9. Final Neuropathology reports will be available from the Neuropathology Core approximately 6 months after the brain removal. It is left to the ADNI Clinician's discretion to obtain the Neuropathology reports and share the findings with the participant's family/DPOA.

Neuropathology

ADNI-NPC NEUROPATHOLOGY PROTOCOLS

Where possible, each center will undertake its own brain assessment and forward a standard set of fixed tissue blocks or sections and frozen tissue to ADNI-NPC (see below). For sites that do not routinely undertake neuropathologic studies, a separate brain removal protocol is listed in the Appendix.

FINANCIAL ASSISTANCE WITH BLOCK SAMPLING, PRESERVATION, AND SHIPPING COSTS

The ADNI-NPC will fund all costs in shipping frozen and fixed tissue samples to St. Louis. To assist participating centers and neuropathologists with the costs of obtaining frozen tissue blocks and/or formalin-fixed paraffin wax-embedded tissue the followingcosts will be reimbursed, if requested:

1. Harvesting of frozen tissue and/or formalin-fixed paraffin wax-embedded tissue blocks (*see list of brain regions below) $300.
2. Harvesting formalin-fixed paraffin wax-embedded tissue sections or frozen sections (*see list of brain regions below) $100.

*ADNI-NPC BLOCK SAMPLING

Resources to defray the costs of sampling, tissue, processing, administration, and transport will be made available to each center already undertaking neuropathology. These resources are to facilitate the provision of the standard set of blocks for ADNI-NPC.

To minimize the burden on participating centers, formalin-fixed, paraffin wax embedded tissue blocks from the following 16 areas from the left cerebrum will be forwarded to ADNI-NPC:

1. Middle frontal gyrus
2. Superior and middle temporal gyri
3. Inferior parietal lobe (angular gyrus)
4. Occipital lobe to include the calcarine sulcus and peristriate cortex
5. Anterior cingulate gyrus at the level of the genu of the corpus callosum
6. Posterior cingulate gyrus and precuneus at the level of the splenium
7. Amygdala and entorhinal cortex
8. Hippocampus and parahippocampal gyrus at the level of the lateral geniculate nucleus
9. Striatum (caudate nucleus and putamen) at the level of the anterior commissure
10. Lentiform nuclei (globus pallidus and putamen)
11. Thalamus and subthalamic nucleus
12. Midbrain
13. Pons
14. Medulla oblongata
15. Cerebellum with dentate nucleus
16. Spinal cord

In the unusual situation where it is impractical to forward a tissue block (e.g., if the block is used for stereology), 10 paraffin wax sections (4-8µm) from each block will be provided to ADNI-NPC for systematic neuropathology and diagnosis.

Neuropathology

FROZEN TISSUE

To provide tissue for biochemical studies and to advance the aims of the Biomarkers Study, snap frozen tissue will be dissected, frozen, and sent to ADNI-NPC. The following coronal hemibrain slices (0.5 to 1cm thick), where possible, will be taken:

1. Frontal lobe to include striatum;
2. Frontal and temporal lobe at the level of the mamillary body;
3. Temporal and parietal lobes at the level of the lateral geniculate nucleus;
4. Occipital lobe to include the calcarine sulcus.

SHIPPING INSTRUCTIONS

- Please package and ship frozen tissue and paraffin blocks separately.
- Please contact Lisa Taylor-Reinwald, ADNI Neuropathology Core Coordinator, for FedEx account and shipping materials (if needed).
- Please ship materials to the address below:

Lisa Taylor-Reinwald, BA, HTL(ASCP)
ADNI Neuropathology Core Coordinator
Department of Pathology and Immunology
Washington University School of Medicine
Campus Box 8118
660 South Euclid Ave.
St. Louis, MO 63110 USA
Tel: +1-314-362-8079
Lab Tel: +1-314-362-7420
Fax: +1-314-362-4096
After office hours pager: +1-314-841-4738
Email: ltaylor@pathology.wustl.edu

Shipments should be sent via FedEx Monday-Thursday. No one is available to receive weekend shipments.

Neuropathology

REIMBURSEMENTS FOR AUTOPSY COSTS AND TISSUE SHARING

The ADNI-Neuropathology Core (ADNI-NPC) will cover brain autopsy costs, with the following limitations:

1. ADNI sites with existing ADRC/ADC neuropathology arrangements in place for handling ADNI Participant brain donations will continue to make their own arrangements for brain autopsies.
2. ADNI sites with no arrangements in place for handling ADNI Participant brain donations:
    a. Local transportation costs will be paid by ADNI-NPC if arrangements are set-up by ADNI-NPC (see the Out-of-Town Arrangements list); if not, ADNI-NPC will pay up to $500 for these costs. Charges above $500 require approval from the ADNI-NPC Leader.
    b. Brain removal performed out-of-state or out of local area: Transportation costs will be paid by ADNI-NPC if arrangements are set-up by ADNI-NPC.

PAYMENT OF FEES AND REIMBURSEMENTS BY ADNI

To receive reimbursement funds from ADNI when submitting paraffin blocks and frozen tissue to the ADNI-NPC, please submit an invoice to:

Lisa Taylor-Reinwald
ADNI-NPC Coordinator
Box 8118
660 South Euclid Avenue
Saint Louis, MO 63110
ltaylor@pathology.wustl.edu

Phone: (314)362-8079
Fax: (314)362-4096
Pager: (314)841-4738

For Transportation, Brain Removal and other Fees:

Service providers should be directed to send an invoice to the ADNI-NPC Coordinator (see above).

Cognitive Assessments
General Guidelines

The goal of ADNI2 neuropsychological testing is to use standardized procedures to objectively and reliably assess a participant's cognitive abilities. However, neuropsychological testing is not a mechanical process. The examiner encounters a wide range of emotional and physical problems that can interfere with testing, and the skill and judgment of the examiner often affect the participant's willingness to be tested and the effort he/she invests. Thus, during an actual test session the psychometrist must simultaneously administer tests, observe and assess participant behavior, and make necessary adjustments. The following guidelines are provided to maintain inter-rater reliability and ensure standard administration of cognitive tests for the ADNI2 protocol. Following these guidelines at your site will help generate valid and accurate measurements with a minimum of stress and discomfort for participants.

SCHEDULING TESTING

When possible, do not schedule Cognitive Testing after blood draws or Lumbar Punctures, as this might affect results. Every effort should be made to conduct testing at the same time of day in order to reduce variability due to circadian (i.e., time of day) effects. If Cognitive Testing cannot be done prior to any other assessment that day, ensure the participant is given an adequate break including food or drink. Please refer to the Sample Visit Schedule (Start-up and General Information section) for more information.

CREATING A PRODUCTIVE TESTING ENVIRONMENT

Because the examiner can influence testing to some degree even when standardized procedures are used, it is desirable to have the same psychometrist conduct all assessments during the course of this protocol. As with any neuropsychological testing, it is important that the testing takes place at a desk or table, in a quiet room, free of distractions. Before testing, question both the participant and the study partner about the participant's ability to hear and see and make sure the participant is wearing needed corrective eyeglasses or hearing aids.

INTRODUCING THE 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

Administer the battery in the order indicated in the source doc worksheet packets, with adherence to time limits and standardized instructions. This may be challenging with participants who interrupt testing or digress into excessive conversation. In these cases, the examiner must regain control and "reorient" the participant back to the task at hand.

Cognitive Assessments
General Guidelines

KEEPING PARTICIPANTS FOCUSED

If the participant is exhibiting signs of frustration or requests to terminate the test, the examiner should acknowledge the participant's concerns, and take note of any reported or expressed physical symptoms (e.g., pain, fatigue) that could be interfering with test performance. It may become necessary to differentiate the participant who refuses to continue a task from the participant who cannot continue a task due to physical or severe cognitive impairment. (This is made more difficult by the fact that a participant may refuse testing due to frustration over their inability to perform a task.) Whether a participant is fatigued, frustrated or merely distracted, there is no one approach that will work with all participants, but the examiner should have a flexible style that acknowledges the participant's concerns, while gently diverting their attention back to the task.

ASSESSING PARTICIPANT COMPREHENSION

It is the examiner's responsibility to see that the participant understands the instructions before each test is started and that this understanding is maintained throughout the test. Instructions may be repeated or simplified according to the instructions for each task during the test session, taking care not to provide any new information, hints or answers.

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.

Please remember that the participant's name should NOT be written on the worksheet.

Cognitive Assessments

Order of Neuropsychological Assessments

Please note that this order of assessments was designed to preserve delay intervals for the Logical Memory, or the Rey Auditory Verbal Learning Test, and to separate list-learning tasks from each other. If testing goes too quickly or takes more time than anticipated, you may need to administer delayed testing in a different order. Document any deviations on the protocol deviations form. Spanish language testing worksheets are available on the Document Repository.

If you have questions about the order of assessments, please contact your clinical monitor.

NEW PARTICIPANTS (CN, EMCI, LMCI, AD)

SCREENING:

MMSE

Logical Memory I - *[Please conduct other assessments that would take AT LEAST 30 AND NO MORE THAN 40 MINUTES before you proceed with the Logical Memory II assessment (delayed recall). Do not administer the MMSE or CDR during the period of delay; other activities including the depression questionnaire (GDS) and patient demographics are permissible*

Logical Memory II (30-40 minute delay)

BASELINE:

ANART
ADAS-Cog
Everyday Cognition - Participant Self-Report
Everyday Cognition - Study Partner Report
Rey Auditory Verbal Learning Test (Trials 1-6)
Montreal Cognitive Assessment (MoCA)
Clock Drawing
Category Fluency (animals)
Trails A & B
Boston Naming Test (30 items)
Rey Auditory Verbal Learning Test (30 minute Delay)

MONTH 6 VISIT:

ADAS-Cog
MMSE
Rey Auditory Verbal Learning Test (Trials 1-6)
Montreal Cognitive Assessment (MoCA)
Clock Drawing
Category Fluency (animals)
Trails A & B
Boston Naming Test (30 items)
Rey Auditory Verbal Learning Test (30 minute Delay)
Everyday Cognition - Participant Self-Report
Everyday Cognition - Study Partner Report

Cognitive Assessments
Order of Neuropsychological Assessments

ADNI1/ADNIGO FOLLOW-UP PARTICIPANTS

INITIAL VISIT:

ADAS-Cog
MMSE
Logical Memory IA
Rey Auditory Verbal Learning Test (Trials 1-6)
Montreal Cognitive Assessment (MoCA)
Clock Drawing
Category Fluency (animals)
Trails A & B
Boston Naming Test (30 items)
Logical Memory IIA (30-40 minute delay)
Rey Auditory Verbal Learning Test (30 minute Delay)

ALL PARTICIPANTS

ANNUAL VISIT:

ADAS-Cog
MMSE
Logical Memory IA
Rey Auditory Verbal Learning Test (Trials 1-6)
Montreal Cognitive Assessment (MoCA)
Clock Drawing
Category Fluency (animals)
Trails A & B
Boston Naming Test (30 items)
Logical Memory IIA
Rey Auditory Verbal Learning Test (30 minute Delay)

Alzheimer's Disease Assessment Scale - Cognitive (ADAS-COG)

INTRODUCTION TO THE ADAS-COG

The ADAS is a brief cognitive test battery that assesses learning and memory, language production, language comprehension, constructional praxis, ideational praxis, and orientation.

The test items on the cognitive part of the ADAS should be given in the order indicated.

The *word recall* test is given first and the *word recognition* task is given last with the other cognitive tests given in between.

Separating the two word memory tasks in this way minimizes the chance that a Participant will confuse the words from the two tasks. Following the objective testing, subjective clinical ratings of language ability and the ability to remember test instructions are performed by the examiner.

The ADAS is not a timed test and the Participant's score does not depend upon how rapidly the test is completed. The cognitive items should be given so that the session moves smoothly and quickly, but so that the Participant does not feel pressured to respond rapidly.

Feedback to the Participant should be neutral and, usually, should not indicate whether or not the response was correct. Comments such as **"That's fine"** or **"You're doing well"** are appropriate as long as the Participant is trying. If the Participant specifically asks whether or not they were correct, feedback can be given.

BEGINNING THE TESTING SESSION

At the start of the test session, before giving the **Word Recall** test, engage the Participant in a short conversation about neutral topics (i.e., weather, hobbies). This conversation will help to put the Participant at ease before the testing begins and will give the tester an opportunity to observe how well the Participant can use and understand language. It is recommended not to use conversation topics that rely heavily on memory as that could start the testing session with anxiety.

The rating of the Participant's language ability (*i.e.*, spoken language, word finding difficulty and comprehension) will be based on this introductory conversation as well as the Participant's speech throughout the ADAS testing session.

Administer the test using the ADNI worksheets and stimuli, provided on the document repository. You are not required to calculate the scoring of the ADAS.

Cognitive Assessments
ADAS-Cog: Word Recall Task

On this task, the Participant is given three trials to learn a list of 10 high-frequency, high-imagery nouns. The 10 words are printed in block letters on white cards.

At the start of the first trial, the tester gives the following instructions:	**"I am going to show you some words printed on these white cards. Please read each word out loud and try to remember it, because later I will ask you to try to remember all of the words I have shown you. Ready, read the word and try to remember it."**
The examiner can prompt, as necessary, with:	**"Read it out loud and try to remember it"**

If the Participant cannot read the word or is slow, the examiner can say the word out loud and have the Participant repeat it. In some cases (*e.g.*, anopsia), the examiner may have to say all of the words and have the Participant repeat them. Regardless, make sure the Participant looks at each word while repeating it.

- The presentation of each word is not timed.

After presentation of the 10 words, the tester asks the Participant to try to recall as many of the words as possible by saying:	**"Good, now tell me all the words you remember that were on the list."**
Once the Participant appears to have recalled as many words as possible, prompt with:	**"Any others?"**

- Encouragement can also be given if the Participant is nervous or giving up.

For trials 2 and 3, say to the Participant:	**"Now I'm going to show you that same list of words again. Read each word out loud and try to remember it."**
Again, say:	**"Good, now tell me all the words you remember that were on the list."**

- Encouragement can be given if the Participant is nervous or giving up.

SCORING

Check each word recalled correctly and record total number of words recalled for each trial.

NEW PARTICIPANTS (CN, EMCI, LMCI, AD)	VISIT	LIST
	Baseline	**LIST 1**
	Month 6	**LIST 2**
	Annual	**LIST 1**
ADNI1/ADNIGO FOLLOW-UP	**VISIT**	**LIST**
	Initial Visit	**LIST 1**
	Annual Follow-Up	**LIST 1**

Cognitive Assessments
ADAS-Cog: Commands/Instructions

This task is designed to assess receptive speech. The Participant is asked to carry out five separate commands with 1 to 5 steps per command.

Each command should be read once. Speak in a clear voice with adequate volume. If the Participant does not respond or looks confused or asks for a repetition, the examiner should give the ***ENTIRE*** command one more time. Then go on to the next command.

To begin testing, say:	**"Now I am going to ask you to do a few things. First…"**

- All commands should be given to every Participant. Each command should be read once; however, if the subject does not respond or looks confused or asks for a repetition, the examiner can give the command one (and only one) additional time.

If the Participant demonstrates hearing or attentional difficulties, orient them by saying:	**"Ready?"** or **"Now, I want you to…"** prior to giving the command.

Do **not** give the command more than twice.

Commands three and four require the use of stimulus materials (a pencil, a watch, and a card) that are placed on the table directly in front of the subject

- There should be no other materials near the pencil, watch and card (pens, paper, etc.).
- Each underlined element represents a single step.
- Remove all materials before giving last command ("tap each shoulder…").

SCORING

- Each command is scored as a whole (no partial credit). All components must be correct for the response to be scored as correct.
- Check each command performed correctly.

Cognitive Assessments

ADAS-Cog: Constructional Praxis

This test assesses the Participant's ability to copy 4 geometric forms ranging from a very simple one (circle) to a fairly difficult one (cube).

- The forms should be presented one at a time.
- The tester should give the Participant a lead pencil with an eraser along with the figure.

The instructions to the Participant should be similar to the following:	**"On this piece of paper is a shape. Try to draw another one that looks just like this, somewhere on the page."** (Examiner may point to shape)
If the Participant's response is quick or sloppy, prompt with:	**"Take your time and try to draw it just like this one."**

The Participant may be allowed **two attempts** for each shape (make sure that attempts are clearly numbered). Allow a second attempt if the Participant asks or indicates a problem with his/her drawing. **The Participant may erase if they need to.** If the Participant draws on top of the printed design, count this as one attempt and indicate that they should try on an empty part of the page. If Participant indicates the reproduction is poor, query if Participant wants another try. When two attempts are made, ask the Participant to indicate which one is best, and then score that attempt.

- If the Participant cannot reproduce the figure in two attempts, the tester should go on to the next item.

NOTE : We permit the tester to write brief explanations or comments on the stimuli regarding the Participant's efforts on the drawings.

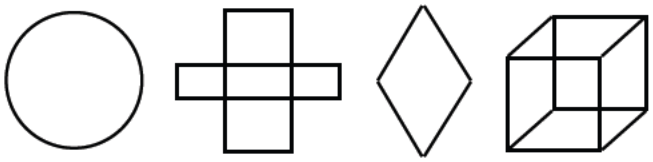
The stimuli should be presented in the following order:

Circle

Two overlapping rectangles

Diamond

Cube



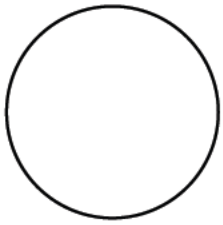
SCORING

A drawing should be scored correct if the Participant has reproduced all of the essential geometric features of the original.

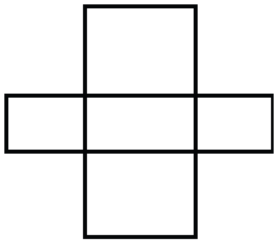
- Changes in size do not count as errors.
- Small gaps between lines do not indicate an error, as long as the shape has been reproduced.
- A "recognizable attempt", is an attempt that shows at least one line that might represent a side or portion of the shape.

ADAS-Cog: Constructional Praxis

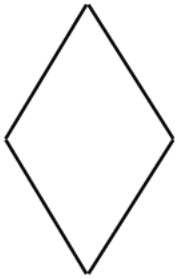
CIRCLE: A closed curved shape



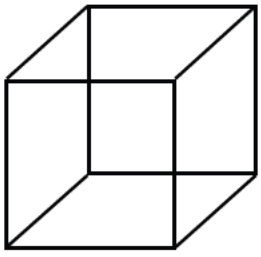
TWO OVERLAPPING RECTANGLES: Each shape must be four-sided and overlap must be similar to presented diagram.



DIAMOND: Shape must be four-sided, oriented so that the points are at the top and bottom, and the sides approximately equal length (*e.g.*, longest side is not >1.5 times the length of the shortest side).



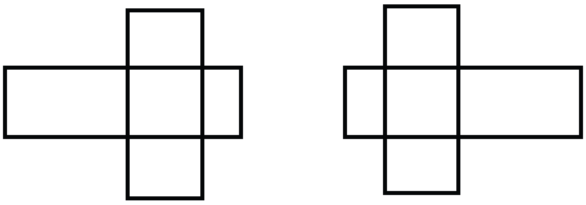
CUBE: The shape is 3-dimensional, with front face in the correct orientation, internal lines drawn correctly between corners. Opposite sides of faces should be approximately parallel.



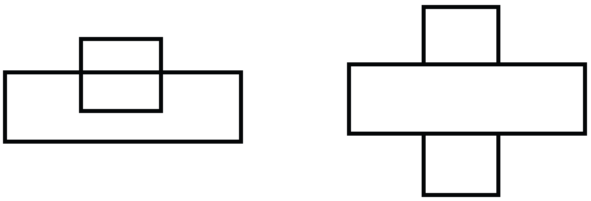
Examples of Correct and Incorrect Drawings:

OVERLAPPING RECTANGLES

Correct

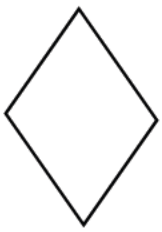


Incorrect



DIAMOND

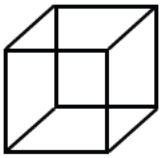
Correct



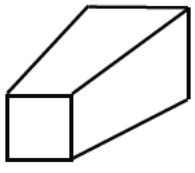
Incorrect

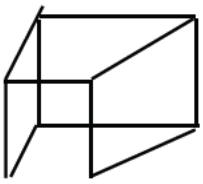
CUBE

Correct



Incorrect





➲ On the online CRF, indicate if each shape was drawn correctly, shape drawn incorrectly or no recognizable attempt at drawing any side/section of shape.

ADAS-Cog: Delayed Word Recall

Delayed free recall of the word list should be attempted approximately 5 minutes after trial 3 of the Word Recall Task. The interval should be filled by the ADAS Commands and Constructional Praxis items. If these tasks are completed in less than 5 minutes, the delay interval should be filled with the continuation of the interview to assess language, concentration, etc. before beginning delayed word recall.

To begin the Delayed Word Recall task say:	**"A few minutes ago I had you read some words printed on these cards (point to wordlist). Tell me all of the words you can remember that were on the cards."**
Prompt with:	**"Any others?"** as necessary.

- Discontinue when there is no further response or if the Participant indicates that he/she cannot recall any more words after prompting.

SCORING

On the online CRF, click the checkbox for every word recalled ***correctly***.

Cognitive Assessments
ADAS-Cog: Naming Task

For this task, the Participant is asked to name the 12 randomly presented real objects, with :

high (Flower, Bed, Whistle, Pencil),
medium (Rattle, Mask, Scissors, Comb), and
low (Wallet, Harmonica, Stethoscope, Tongs) **frequency values.**

The Participant is also asked to name the fingers on his/her dominant hand.

➲ Objects should be presented in random order. Do not allow the Participant to touch the objects.

Give the Participant instructions similar to the following:	**"Now I am going to show you some objects. I want you to tell me what their names are. What is this called?"** (present object)
Continue to present objects in random order. The first question about each object should be:	**"What is this called?"** or **" What is the name of this thing?"**
If the Participant responds with the object's function say:	**"Yes, that's what it does, but what is its name?"**

➲ If the Participant does not respond, the examiner should give the clue for that item provided below. If the Participant still does not respond or makes an error, go on to the next object.

ITEM	CLUES
Flower	grows in a garden
Rattle	a baby's toy
Wallet	holds your money
Bed	used for sleeping in
Mask	hides your face
Harmonica	a musical instrument
Whistle	makes a sound when you blow on it
Scissors	cuts paper
Stethoscope	doctor uses it to listen to your heart
Pencil	used for writing
Comb	used on hair
Tongs	picks up food

ADAS-Cog: Naming Task

➲ The Participant is also asked to name the fingers of his/her dominant hand (*e.g.*, thumb, index finger [pointer/forefinger], middle finger, ring finger, and pinky/little finger).

Give the Participant instructions similar to the following:	**"Place your right (or left) hand on the table. Now I am going to point to a part of your hand and I want you to tell me what it's called. What is this finger called?"**
For the 4 fingers, if a query is necessary, say:	**"What is another name for this finger?"**

SCORING

ITEM
Thumb
Index/forefinger/pointer
Middle
Ring
Pinky

NOTE: ***"Little"*** is an acceptable response for ***"pinky"*** finger

The hardest part of scoring the naming task is determination of the range of correct responses based on the Participant's cultural and geographical background. A response other than the name given on the response form should be scored as correct if it is a name that would be used by a non-demented person with the same cultural background as the Participant.

FOR EXAMPLE: the **Mask** might be called a **"false face"** in some parts of the U.S.; the **Wallet** might be called a **"billfold"** or the **Harmonica** might be called a **"mouth organ"**.

➲ Descriptions of the object, semantic or phonemic paraphasias should not be scored as correct.

EXAMPLES OF INCORRECT RESPONSES ARE: **"listening thing"** for **Stethoscope,** **"cutter"** for **Scissors,** and **"prongs"** for **Tongs.**

➲ On the online CRF, check each object and finger named correctly.

Cognitive Assessments
ADAS-Cog: Ideational Praxis

This task is designed to determine whether the Participant can perform a familiar but complex sequence of actions.

- A long envelope, an 8.5" x 11" sheet of paper and a pencil are placed in front of the Participant. (Do not permit the Participant to handle any of the materials yet.)

Give the Participant instructions similar to the following:	**"I want you to pretend you have written yourself a letter. Take this piece of paper, fold it so that it will fit into the envelope, and then put it into the envelope. Then, seal the envelope, address the envelope to yourself, and show me where the stamp goes."**

- There are 5 components to this task.

- If the Participant forgets part of the task, or is having difficulty, the tester should repeat the instruction for the component of the task where the Participant is having difficulty.

For example:

If the Participant stops after folding the paper and putting it into the envelope, the tester should give one reminder on the next component:	**"Now seal the envelope."**
If the Participant cannot do this part, move on and give one reminder on the next component:	**"Now address the letter to yourself."**

After the first complete instruction only one additional reminder should be given for each component.

- Have Participant place an "X" on the envelope to indicate where the stamp goes. If the Participant merely points to where the stamp goes, the rater should write the "X" on the envelope.

- Any address which would enable a postal worker to deliver the envelope is counted as correct, even though it might not contain the Participant's current address.

The address should contain: **name**
street
city
state
Zip code is *not* required

SCORING: Check each component of the task correctly completed.

NOTE: To maintain Participant anonymity, do ***NOT*** upload the envelope to the study file upload tool on the admin portal. The clinical monitor will review the envelope on site.

Cognitive Assessments
ADAS-Cog: Orientation

This task is designed to determine how well-oriented the Participant is with regard to time and place.

The components of orientation are:
- Person
- Month
- Year
- Time of Day
- Day of Week
- Date
- Season
- Place

- Ask the Participant for each of these pieces of information ***one at a time***.
- One restatement of each question is allowed (*e.g.*, if Participant confuses day and date).
- Make sure no watches, clocks, calendars, etc. are visible to the Participant.

Preface the **clock/time** question with:	**"Without looking at your watch, tell me approximately what time it is."**
Prompt the **place** question with:	**"Where are we now?,"** or **"What is the name of this place?"**

DO NOT give any clues about your location with questions such as:

"What's the name of this hospital?"

SCORING: Check each item answered correctly. Guidelines regarding the range of appropriate correct responses and information about the seasons are provided here:

SCORING	
Full Name:	Must be exact
Month:	Must be exact
Date:	± 1 day.
Year:	Must be exact
Day of week:	Must be exact
Season:	Within 1 week of upcoming season or within 2 weeks of previous season.
Time:	± 1 hour.
Place:	Partial names are acceptable (*e.g.*, the name of hospital, the clinic, or the professional building), but generic terms are not acceptable (*e.g.*, "hospital", or "doctor's office").

SEASONS		
2011	**Winter =**	**12/22/10 – 3/19/11**
	Spring =	**3/20 – 6/20**
	Summer =	**6/21 – 9/22**
	Fall =	**9/23 – 12/21**
2012	**Winter =**	**12/22/11– 3/19/12**
	Spring =	**3/20 – 6/19**
	Summer =	**6/20 – 9/21**
	Fall =	**9/22 – 12/21**
2013	**Winter =**	**12/21/12 – 3/19/13**
	Spring =	**3/20 – 6/20**
	Summer =	**6/21 – 9/22**
	Fall =	**9/23 – 12/20**
2014	**Winter =**	**12/21/13– 3/19/14**
	Spring =	**3/20 – 6/20**
	Summer =	**6/21 – 9/22**
	Fall =	**9/23 – 12/20**
2015	**Winter =**	**12/21/14– 3/19/14**
	Spring =	**3/20 – 6/20**
	Summer =	**6/21 – 9/22**
	Fall =	**9/23 – 12/20**
2016	**Winter =**	**12/21/15– 3/19/16**
	Spring =	**3/20 – 6/19**
	Summer =	**6/20 – 9/22**
	Fall =	**9/23 – 12/20**

Cognitive Assessments
ADAS-Cog: Word Recognition

On this task the Participant is given one trial to learn a list of 12 words, presented one at a time, that are printed in block letters on white cards.

Start the learning trial by saying:	**"I am going to show you some words printed on these white cards. I want you to read each word out loud and try to remember it, because later I will ask you to remember all of the words I have shown you. Ready? Read the word and try to remember it."**

The examiner can prompt, as necessary, with: **"Read it out loud and try to remember it".**

➲ If the Participant cannot read a word or is slow, the examiner can say the word out loud and have the Participant repeat it. In some cases, (e.g., anopsia), the examiner may have to say all of the words and have the participant repeat them. Regardless, make sure the participant looks at each word while repeating it.

NOTE: The presentation of each word is not timed.

RECOGNITION TRIAL	
Immediately after the last word is read aloud, the examiner says:	**"Now I'm going to show you another set of words. Some of the words were on the list I just showed you and others are new. For each word I want you to tell me whether it is one of the words I just showed you."**
The tester shows the first word and says either:	**"Is this one of the words I showed you before, yes or no?",** or **"Did I show you this word before?"**

The same instruction is given before the second test word.

For the remaining test words the tester should say:	**"How about this one?"**
The Participant may be encouraged with:	**"Just take your best guess".**

If the Participant does not remember the task (e.g., reads the word rather than responding yes or no) then the tester should repeat or rephrase the entire question and make a check in the "Reminder" column that the Participant had to be reminded of the task instructions. The Participant's ability to stay on task will be reflected in Question 9 of the ADAS (Remembering Test Instructions), which is automatically calculated on the ECRF).

Please note that the Participant is prompted for the first two words as part of standard instructions. The rating reflected in Question 9 (Remembering Test Instructions) will not include the prompts given for the first two words.

WORD RECOGNITION TASK SCORING: Check the **"yes"** or **"no"** response made by the participant for each of the target and distractor items.

ADAS-Cog: Remembering Test Instructions & Comprehension

REMEMBERING TEST INSTRUCTIONS

This item is based **ONLY** on observations during the Word Recognition task (Question 8) and evaluates the Participant's ability to remember the requirements of the Word Recognition task. This is automatically calculated in the EDC for ADNI. If the Participant fails to respond (e.g., yes/no) in the recognition trials, this signifies that the instructions have been forgotten and the instruction is repeated. Each instance of memory failure for the test instructions after the first two items is noted. The ECRF will automatically score this item. Ensure the paper source document matchs the ECRF.

Check level of impairment:

None	-	Participant never needs extra reminders of instructions
Very mild	-	forgets once
Mild	-	must be reminded 2 times
Moderate	-	must be reminded 3 or 4 times
Moderately severe	-	must be reminded 5 or 6 times
Severe	-	must be reminded 7 or more times

COMPREHENSION

This item evaluates the Participant's ability to understand speech. To rate this item the tester should consider how well the Participant was able to understand the tester's speech during the opening discussion and during the test session. Do not include responses to commands.

Check level of impairment.

None	-	no evidence of poor comprehension
Very mild	-	one or two instances of misunderstanding
Mild	-	3-5 instances of misunderstanding
Moderate	-	requires several repetitions and rephrasing
Moderately severe	-	Participant only occasionally responds correctly; i.e., yes/no questions
Severe	-	Participant rarely responds to questions appropriately, not due to poverty of speech

ADAS-Cog: Word-Finding Difficulty & Spoken Language Ability

WORD FINDING DIFFICULTY

This item rates impairment in expressive speech. The examiner rates the level of difficulty the participant had in finding the desired word in spontaneous speech during the interview and test session.

NOTE: The participant may attempt to mask word finding difficulty by circumlocution (i.e., giving explanatory phrases or nearly satisfactory synonyms). **DO NOT** include the participant's responses on the formal object and finger naming tasks in this rating.

Check the best response:

None	-	no evidence of word-finding difficulty in spontaneous speech
Very mild	-	1 or 2 instances, not clinically significant
Mild	-	noticeable circumlocution or synonym substitution
Moderate	-	loss of words without compensation on occasion
Moderately severe	-	frequent loss of words without compensation
Severe	-	nearly total loss of content of words; speech sounds empty; 1-2 word utterances

SPOKEN LANGUAGE ABILITY

This item is a global rating of the quality of speech, i.e., clarity, difficulty in making oneself understood. In rating this item the tester should consider all of the speech produced by the Participant. Quantity of speech and word-finding difficulty, i.e., circumlocutions, are not rated on this item. It should be noted that moderately severe and severe rating for this item are reserved for Participants whose expressive language abilities are impaired to such an extent that they seldom communicate without difficulty.

Check level of impairment:

None	-	no instances where it is difficult to understand the Participant
Very mild	-	one instance of lack of understandability
Mild	-	Participant has difficulty less than 25% of the time
Moderate	-	Participant has difficulty 25-50% of the time
Moderately severe	-	Participant has difficulty 50% of the time
Severe	-	one or two word utterance; fluent, but empty speech; mute

Cognitive Assessments
ADAS-Cog: Number Cancellation

EXAMPLE INSTRUCTIONS

Place the practice form in front of the participant and say:	**"On the top of this page are two numbers. Throughout this page you will find these numbers mixed in with other numbers. I'd like you to begin here..."** (point to the beginning of the first line), **"...and going across (line by line), cross off each number that matches either of the two numbers at the top of the page. Please work as quickly as you can."**

Discontinue the example after 30 seconds.

TASK INSTRUCTIONS

Place the form in front of the participant and say:	**"On the top of this page are two numbers. Throughout this page you will find these numbers mixed in with other numbers. I'd like you to begin here..."** (point to the beginning of the first line), **"...and going across (line by line), cross off each number that matches either of the two numbers at the top of the page. Please work as quickly as you can."**
If the first cancellation done by the participant is incorrect, say:	**"These are the correct numbers to cross out,"** and point to the numbers at the top of the page in the heading.

If the participant becomes confused or stops while doing the test, repeat the standard instructions as needed. **Discontinue the test after 45 seconds.**

SCORING

Enter the following:

1) The number of correct targets crossed out .
2) The number of total errors of commission (i.e., crossing out a non-target number) .
3) The number of times the participant needed to be reminded of the task or re-directed back to the task.

THERE ARE TWO VERSIONS OF THE NUMBER CANCELLATION:

- ADNI1/ADNIGO Follow-Up participants will complete Version A annually.
- New participants will complete version A at Baseline, B at Month 6, and A annually.

ADAS Certification Instructions

ADAS raters must meet ADCS certification requirements prior to administering the ADAS in this trial.

Certification may only be accomplished by completion of the ADAS Standardization/ Certification Questionnaire. Raters who have previously completed the Questionnaire and received a letter of certification from the ADCS in the last five (5) years are certified and do not need to repeat the certification process.

Raters who have not been certified for previous ADCS studies or has been over 5 years since you have been certified as an ADAS rater, you must complete the Standardization/Certification Questionnaire.

To request an ADAS Certification Package:
Email the ADCS Helpdesk: adcs-clinops@ucsd.edu

Completed questionnaires should be faxed to Clinical Operations: (858) 246-1415

American National Adult Reading Test (ANART)

AMERICAN NATIONAL ADULT READING TEST (ANART)

Grober, E. & Sliwinski, M. (1991). Development and validation of a model for estimating premorbid verbal intelligence in the elderly. Journal of Clinical and Experimental Neuropsychology, 13, 933-949.

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.

Cognitive Assessments
Boston Naming Test

Kaplan, E., Goodglass, H., Weintraub, S. The Boston Naming Test. Philadelphia: Lea and Febiger, 1983.

DESCRIPTION

This reduced version of the Boston Naming Test is a measure of the ability to orally label (name) 30 line drawings of objects. The objects are presented in order of frequency, from most frequent (i.e., bed) to least frequent (i.e., protractor). This test is sensitive to aphasia and also to object recognition deficits. Boston Naming Test cards used at the in-person visits contain a short form and standard form. Use the standard form where card 1 is bed, 3 is pencil and 5 is whistle.For the purposes of this study, only the odd-numbered items from the full test will be administered.

ADMINISTRATION

Begin at item 1 and present all 30 items (i.e., odd #s 1 – 59) in order.

Place the test booklet in front of the participant and say:	**"I am going to show you some pictures in this book, one at a time. I would like you to tell me the name of the object that you see."**
Expose the first item and say:	**"Tell me what this is called."**

Allow 20 seconds for each response, unless the participant says they do not know the word before 20 seconds has elapsed. If the answer is correct, check the first column on the Worksheet for Boston Naming Test –30 (Odd-numbered items). Record any response other than the correct one.

If the participant has given a response that indicates misperception of the picture, she or he is supplied with the semantic cue, which is printed in brackets under the response line for each item.

The participant is allowed up to 20 seconds to name the picture after the stimulus cue is given. If the item is named correctly within that time, check the column "correct with semantic cue". Otherwise check "incorrect with semantic cue" and again record the response verbatim.

The semantic cue is presented only when the participant's response reflects misperception. If the response following the stimulus cue is incorrect, move on to the phonemic cue. The phonemic cue is also given after every failure to respond or after any incorrect response. Provide the first sound in the name of the item (indicated on the test form in bold). If the participant succeeds with a phonemic cue, place a check mark in the column "correct with phonemic cue". If the participant fails, place a check mark in the column "incorrect with phonemic cue." The number correct following phonemic cues is of clinical interest but is not included in the total score.

Discontinue testing after 6 consecutive failures (i.e., failure to name correctly either without assistance or with a stimulus cue).

Boston Naming Test (Cont'd)

SCORING

There are 6 scores:

1. Total correct without a cue
2. Total semantic cues given
3. Total correct with a semantic cue
4. Total phonemic cues given
5. Total correct with phonemic cues
6. Total correct = sum of 1 + 3 above

The total score (i.e., #6) is the number of items that are named correctly without assistance **PLUS** the number of items named correctly following a stimulus cue if one had to be given (maximum total score = 30). Enter the total score on the online form.

- Record the participant's responses verbatim if incorrect or circumlocutory, and write in 'DK' only if the participant actually says she or he doesn't know.
- Mispronunciations are treated as incorrect unless they clearly reflect a regional or dialect specific pronunciation (e.g. someone from the Boston area may omit the 'r' sound in 'dart').
- If a mispronunciation does not reflect such a regionalism (e.g. 'esculator'), the answer is incorrect and cueing proceeds as appropriate.
- If the participant gives a more general or circumlocutory response (e.g. 'boat' or 'it floats on water' for the word 'canoe'), say "Can you think of a more specific name for it?"
- If the participant gives a more specific response (e.g. 'daisy' for 'flower'), say "Can you think of a more general name for it?"
- If the participant gives the correct name, but says it is not that object (e.g. "Well it's not a canoe"), the response is considered incorrect and cueing proceeds if appropriate.

Category Fluency Test

Adapted from the CERAD administration and scoring procedures for Verbal Fluency (Morris et al., 1989).

CATEGORY FLUENCY TEST

DESCRIPTION

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 for 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 any more"***). It is also permissible to repeat the instruction or category if the participant specifically requests it.

Category Fluency Test

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. Any word repeated, even if an intrusion, is counted as a perseveration. It 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.

Cognitive Assessments
Clock Drawing Test

Goodglass, H., & Kaplan, E. (1983). The assessment of aphasia and related disorders. Philadelphia: Lea & Febiger.

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.

Clock Drawing Test (Cont'd)

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.

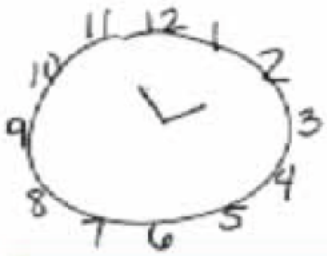
5. Presence of two hands set to ten after eleven. To receive credit for this item, the two hands must be set to the numbers eleven and two and of the appropriate relative lengths (i.e., shorter hand to eleven, longer hand to two).

See the examples of scored clock drawings on the next page.

Clock Drawing Test (Cont'd)

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

Cognitive Assessments
Logical Memory

Modified from Wechsler D. Wechsler Memory Scale-Revised. San Antonio, Texas: Psychological Corporation; 1987.

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

DESCRIPTION

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.

Logical Memory (Cont'd)

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:

TEXT FOR STORY A	GENERAL RULE	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	NONE	Thompkins; Thomas
of South	"South" (in any context)	from South; who lived in South; who came from the South	NONE
Boston,	"Boston" (in any context)	who worked in Boston; on a trip to Boston	NONE
employed[1]	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[1]	"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	NONE	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	NONE
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

Logical Memory (Cont'd)

SCORING (Cont'd)

TEXT FOR STORY A	GENERAL RULE	EXAMPLES OF ALTERNATIVE 1-POINT RESPONSES	EXAMPLES OF 0-POINT RESPONSES
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 not 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 collected was 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

[1] "Anna Thompson, a cook in a..." gets credit for "employed" and "as a cook".

Logical Memory (Cont'd)

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."**

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 Greg Fortune story was used, please see the worksheet posted on the document repository under supplemental worksheets for directions on how to administer and score.

Mini Mental State Exam

[redacted]

ORIENTATION

[redacted]

SCORING

[redacted]

IMMEDIATE RECALL

[redacted]

SCORING

[redacted]

ATTENTION

[redacted]

SCORING

[redacted]

DELAYED RECALL

[redacted]

SCORING

[redacted]

Mini Mental State Exam (Cont'd)

LANGUAGE NAMING

[redacted]

SCORING

[redacted]

COMMAND

[redacted]

SCORING

[redacted]

REPETITION

[redacted]

SCORING

[redacted]

READING

[redacted]

SCORING

[redacted]

WRITING

[redacted]

SCORING

[redacted]

CONSTRUCTION

[redacted]

SCORING

[redacted]

Cognitive Assessments

Montreal Cognitive Assessment (MoCA)

Adapted from the official MoCA Instruction Guide, Version November 12, 2004 © Z Nasreddine

The Montreal Cognitive Assessment (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.**

IMPORTANT

Use the ADNI-adapted worksheet and ADNI administration and scoring procedures provided here rather than instructions provided by the instrument author. ADNI 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.

1. ALTERNATING TRAIL MAKING:

Administration: 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.

NOTE: Any error that is not immediately self-corrected would result in this task being scored as incorrect.

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.)

Administration: 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.

Montreal Cognitive Assessment (MoCA) - (Cont'd)

3. VISUOCONSTRUCTIONAL SKILLS (CLOCK):

Administration: 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.

4. NAMING:

Administration: 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:

(1) camel or dromedary, (2) lion, (3) rhinoceros or rhino.

5. MEMORY:

Administration: 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 (s)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.

Montreal Cognitive Assessment (MoCA) - (Cont'd)

6. 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.**

Scoring: 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

Administration: 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.

Scoring: ***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.

7. SENTENCE REPETITION

Administration: 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).

Montreal Cognitive Assessment (MoCA) - (Cont'd)

8. VERBAL FLUENCY:

Administration:

- ***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).

9. ABSTRACTION

Administration: 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)

10. DELAYED RECALL

Administration: 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.

11. ORIENTATION

Administration: 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.

Cognitive Assessments
Rey Auditory Verbal Learning Test (AVLT)

Rey, A. (1964). L'examen clinique en psychologie. Paris: Presses Universitaires de France.

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 all trials, record verbatim responses and intrusions. These are totaled for each trial. Pluralized words are counted as correct. Any word repeated, even if an intrusion, is counted as a perseveration. It is counted as an intrusion the first time, then a perseveration the second time. But to be clear, the second intrusion is not given an additional count added to the intrusions.

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 and total intrusions.

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."***

Cognitive Assessments
Trail Making Test

Partington JE, Leiter RG. Partington's Pathway Test. The Psychological Service Center Bulletin. 1949;1:9-20. Reitan RM. Validity of the Trail-Making Test as an indication of organic brain damage. Perceptual Motor Skills. 1958;8:271-276. ; Reitan R, Wolfson D. The Halstead-Reitan Neuropsychological Test Battery. Tucson: Neuropsychology Press; 1985.; Spreen O, Strauss E. A compendium of neuropsychological tests. New York: Oxford University Press; 1998.

DESCRIPTION

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.

Trail Making 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.

Global, Functional, and Behavioral Assessments

Annual Telephone Visit Option

Please note that there is an annual telephone visit option that should be presented to participants who are unwilling or unable to come into the clinic for their annual in-clinic visit. This telephone visit would replace the annual in-clinic visit and is separate from the interim phone checks.

The following participants are eligible for telephone visits:

1. MCI or Control originally enrolled in ADNI1 and /or EMCI originally enrolled in ADNIGO who is not willing to return for annual in-clinic visits.
2. ADNI2 new enrollees who have completed all baseline assessments under ADNI2 but then after this visit are only available by phone.

The Global, Functional, and Behavioral Assessments that can be done over the phone include:

- **Clinical Dementia Rating (CDR)**
- **Geriatric Depression Scale (GDS)**
- **Neuropsychiatric Inventory (NPI)**
- **Activities of Daily Living (FAQ)**

The Everyday Cognition is also part of the annual telephone visit; however, it must be mailed to the participant and study partner ***PRIOR*** to the scheduled visit. The participant and study partner then have to mail the assessment back to the site for data entry.

If either the participant or study partner are unable to return the assessment by mail, the interview may be done over the phone as long as the participant and/or study partner are looking at the worksheet.

CLINICAL DEMENTIA RATING (CDR) VERSIONS

CDR Version 1- Full interview with informant and participant

- Should be used at every in clinic visit where a CDR interview is conducted with both the participant and informant.

CDR Version 2- Full interview with only informant

- Used in cases where an annual telephone visit is being conducted in replace of the in person clinic visit, as CDR version 1 should NOT be used for telephone visits.
- Or in cases when a standard in clinic study visit is being conducted but the participant is unable to participate in the interview.

CDR Version 3- Abbreviated interview with only informant

- Limited interview that should only be used when the study participant is unable to participate in the interview and the informant is not willing to complete CDR version 2 interview. This version is a very brief questionnaire and can be used when the informant has limited time available.

All three versions of the CDR interview are able to determine a global CDR score. The version to be used is based on visit type and availability of participant and informant.

Should you have any questions on what version to use, please contact your assigned monitor.

Global, Functional, and Behavioral Assessments

Clinical Dementia Rating (CDR)

Morris, JC "Clinical Dementia Rating" 1993 Neurology 43: 2412-2414

The scores acquired from the CDR are key Inclusion Criteria and are critical for detecting conversion to another diagnosis. For new particiipants the CDR is conducted at Screening, Month 6 and then annually. For ADNI1 and/or ADNIGO follow-up participants, the CDR is conducted at ongoing annual visits.

CDR RATER

CDR certification is required prior to administering the CDR for ADNI2. It would be preferable for the CDR rater to conduct only the CDR on a given visit. If this is not possible due to staffing, the CDR should be conducted prior to other assessments. If possible, the same person should administer the CDR at each participant's visit throughout the study.

Anyone administering the CDR must be certified. Certification is required every five years and can be done online through the Washington University website: **http://alzheimer.wustl.edu/cdr/Application/Step1.htm**. A certificate is sent to the rater upon completion. Please ensure to email a copy of the certificate to **adcs-clinops@ucsd.edu** or fax to **(858) 246-1415**.

THE SAME PERSON CANNOT ADMINISTER BOTH THE CDR AND ADAS DURING A SINGLE CLINIC VISIT.

INSTRUCTIONS

Worksheets have been created with a semi-structured interview for the informant and participant. A certified CDR Rater must conduct the interviews and complete the provided worksheets. Supplementary information may be added to the existing questions on the worksheet to support the assigned box scores.

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 study coordinator 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.

In the CDR – Judgment and Problem Solving Section for participants, question 8 states ***"upon arriving in a strange city, how would you locate a friend that you wished to see?"*** If a participant states **"through the Internet,"** this should be considered correct and ADCS will be revising this field to allow this response.

Global, Functional, and Behavioral Assessments
Clinical Dementia Rating (CDR)

DETERMINING GLOBAL CDR SCORE

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

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

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

CDR = Global Box Score

M = Memory Box Score

CDR = M if at least three secondary categories are given the same score as memory.

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

Whenever three or more secondary categories are given a score greater or less than the memory score, CDR = score of majority of secondary categories on whichever side of M has the greater number of secondary categories. In the unusual circumstance in which three secondary categories are scored on one side of M and two secondary categories are scored on the other side of M, CDR = M.

The above rules do not cover all possible scoring combinations. Unusual circumstances are scored as follows:

(1) With ties in the secondary categories on one side of M, choose the tied scores closest to M for CDR (e.g. M and another secondary category = 3, two secondary categories = 2, and two secondary categories = 1; CDR =2).

(2) When only one or two secondary categories are given the same score as M, CDR = M as long as no more than two secondary categories are on either side of M.

(3) When M = 1 or greater, CDR cannot be 0; in this circumstance, CDR = 0.5 when the majority of secondary categories are 0.

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

To verify the global CDR, you may also access the Washington University CDR web page:

http://www.biostat.wustl.edu/adrc/

Global, Functional, and Behavioral Assessments
Everyday Cognition (ECOG)

Farias ST, Mungas D, Reed BR, Cahn-Weiner D, Jagust W, Baynes K, Decarli C. The measurement of everyday cognition (ECog): scale development and psychometric properties. Neuropsychology. 2008 Jul;22(4):531-44.

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-2 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.

Global, Functional, and Behavioral Assessments
Geriatric Depression Scale (GDS)

Sheikh JI, Yesavage JA, Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. Clinical Gerontology: a Guide to Assessment and Intervention 165-173, NY: The Haworth Press, 1986.

The Geriatric Depression Scale is a brief questionnaire that consists of 15 questions and is designed to identify symptoms of depression in the elderly. For new participants the GDS is conducted at Screening, Month 6 and annual ongoing visits. For ADNI1 and/or ADNIGO follow-up participants, the GDS is conducted at the initial ADNI-2 visit and ongoing annual visits. Site staff should administer the GDS as a direct interview with the participant only, ***NOT*** the study partner.

INSTRUCTIONS

Say, ***"In the next part of this interview, I will ask you questions about your feelings. Some of the questions I will ask you may not apply, and some may make you feel uncomfortable. For each question, please answer 'yes' or 'no', depending on how you have been feeling in the past week, including today."***

- Answers in **BOLD CAPS** suggest depression. Although differing sensitivities and specificities have been obtained across studies, for clinical purposes a score >5 points is suggestive of depression and should warrant a follow-up interview. Scores >10 are almost always depression.
- 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 answer.
- If the Participant does not comprehend the first 5 questions adequately enough to give answers, then check the box that states "Participant is unable to complete the GDS based on the clinician's best judgement."

NOTE: If a participant being screened for the study is unable to complete the GDS (and has no history of depression), the participant may be able to continue in the study. An exception will need to be requested.

Choose the best answer for how you have felt over the past week:

yes or **NO**	1. Are you basically satisfied with your life?
YES or no	2. Have you dropped many of your activities and interests?
YES or no	3. Do you feel that your life is empty?
YES or no	4. Do you often get bored?
yes or **NO**	5. Are you in good spirits most of the time?
YES or no	6. Are you afraid that something bad is going to happen to you?
yes or **NO**	7. Do you feel happy most of the time?
YES or no	8. Do you often feel helpless?
YES or no	9. Do you prefer to stay at home, rather than going out and doing new things?
YES or no	10. Do you feel you have more problems with memory than most?
yes or **NO**	11. Do you think it is wonderful to be alive now?
YES or no	12. Do you feel pretty worthless the way you are now?
yes or **NO**	13. Do you feel full of energy?
YES or no	14. Do you feel that your situation is hopeless?
YES or no	15. Do you think that most people are better off than you are?

NOTE: If the Participant says he/she cannot choose an answer, ask him/her to select the best response.

Functional Assessment Questionnaire (FAQ)

FUNCTIONAL ASSESSMENT QUESTIONNAIRE (FAQ)

Pfeffer, RI, Kurosaki TT, Harrah CH, et al. Measurement of functional activities of older adults in the community. J Gerontol 37:323-9, 1982.

The FAQ measures activities of daily living and is administered at Baseline, Month 6 and at ongoing annual visits for new participants. For ADNI1 and/or ADNIGO follow-up participants, the FAQ is administered at all annual visits.

INSTRUCTIONS

The study partner should be queried based on the participant's level of difficulty on each item in the past four weeks.

Global, Functional, and Behavioral Assessments

Modified Hachinski

Rosen, Modification of Hachinski Ischemic Score (Ann Neurol 7: 486-488, 1980)

The Modified Hachinski is administered as a part of the screening process for new participants. The form should be completed by a clinician familiar with the participant.

INSTRUCTIONS

Complete the Modified Hachinski 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.

- **The participant must have a total score of 4 or less at the Screening Visit to be included in the study**
- **If "history of stroke" is checked, participant is excluded from the study unless an exception is granted by the Project Director**

Global, Functional, and Behavioral Assessments

Neuropsychiatric Inventory (NPI)

THE PURPOSE of the Neuropsychiatric Inventory (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 to be administered by a site clinician. Certification is not required.

Twelve behavioral areas are included in the NPI:

- Delusions
- Apathy
- Hallucinations
- Disinhibition
- Agitation / Aggression
- Irritability
- Depression
- Aberrant motor behavior
- Anxiety
- Night-time behavior
- Euphoria
- Appetite and eating changes

The NPI is based on responses from a study partner, preferably one living with the participant.

The interview is best conducted with the study partner in the absence of the participant to facilitate an open discussion of behaviors that may be difficult to describe with the participant present.

Several points should be made when you introduce the NPI interview to the study partner:

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

Questions should be asked exactly as written.

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

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

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

Neuropsychiatric Inventory (NPI)

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). Emphasize to the study partner that the questions pertain to behaviors that have appeared or changed since the onset of illness. For example: The questions might be phrased, "Since he/she began treatment with the new medications..." or "Since the dosage of _____ was increased..."

For all visits, ask the study partner to indicate whether the participant behaviors occurred during the previous 4 weeks. If so, use the following scales to rate the frequency, severity, and amount of distress the behaviors caused the caregiver.

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

If the answer to the screening question is negative, mark NO and proceed to the next screening question without asking the subquestions.

- If the answer to the screening question is positive or if there are any uncertainties in the study partner's response or inconsistencies between the response and other information known by the clinician (e.g., the study partner responds negatively to the euphoria screening question but the participant appears euphoric to the clinician), the category is marked YES and is explored in more depth with the subquestions.
- If the subquestions confirm the screening question, the severity and frequency of the behavior are determined according to the criteria provided with each behavior. When determining frequency and severity, use the behaviors identified by the subquestions as most aberrant.

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

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

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

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

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

Neuropsychiatric Inventory (NPI)

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.

When determining **FREQUENCY,** say to the study partner:	"Now I want to find out how often these things [define using the description of the behaviors they noted as most problematic on the subquestions] occur." "Would you say that they occur less than once per week, about once per week, several times per week but not every day, or every day?"

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

When 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:
Less than once per week
About once per week
Several times per week
Daily or continuous

Severity Descriptions:
Mild
Moderate
Severe

This also saves the examiner from reiterating the alternatives with each question.

Neuropsychiatric Inventory (NPI)

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 NA (upper right corner of each section), 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), NA 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 if your protocol includes the distress assessment.

- To do this, ask the study partner how much, if any, "emotional or psychological" distress the behavior he or she just discussed causes him or her (the study partner).

The study partner must rate their own distress on a five point scale:

0	no distress
1	minimal
2	mild
3	moderate
4	severe
5	very severe or extreme

The distress scale of this instrument was developed by Daniel Kaufer, M.D.

Neuropsychiatric Inventory (NPI)

SCORING THE NPI

FREQUENCY is rated as:

1.	Occasionally	less than once per week
2.	Often	about once per week
3.	Frequently	several times per week but less than every day
4.	Very frequently	daily or essentially continuously present

SEVERITY is rated as:

1.	Mild	produces little distress in the participant
2.	Moderate	more disturbing to the participant but can be redirected by the study partner
3.	Severe	very disturbing to the participant and difficult to redirect

DISTRESS is scored as:

0	no distress
1	minimal
2	mild
3	moderate
4	severe
5	very severe or extreme

THUS, FOR EACH BEHAVIORAL DOMAIN THERE ARE FOUR SCORES:

1.	Frequency
2.	Severity
3.	Total (frequency x severity)
4.	Caregiver distress

THE SCORE FOR EACH DOMAIN IS:
DOMAIN SCORE = FREQUENCY X SEVERITY

- A **TOTAL NPI SCORE** can be calculated by adding all domain scores together
- The distress score is not included in the total NPI score.
- Individual and total distress scores can be generated from the NPI.

Neuropsychiatric Inventory (NPI)

NPI REFERENCES

Instructional Videotape

An instructional videotape demonstrating the use of the NPI is available through:

UCLA Alzheimer's Disease Center
Neuropsychiatric Institute
710 Westwood Plaza
Los Angeles, California 90095-1769

The cost of the videotape is $25.00 (subject to change).

Translations of the NPI

The NPI is available in many languages.

References

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994; 44: 2308-2314.

Mega MS, Cummings JL, Fiorello T, Gornbein J. The spectrum of behavioral changes in Alzheimer's disease. Neurology 1996; 46: 130-135.

Acknowledgments

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NEUROPSYCHIATRIC INVENTORY QUESTIONNAIRE (NPI-Q)

Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillian A, Sheeley T, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neuroscience 12:233-9, 2000.

The NPI-Q is an abbreviated version of the Neuropsychiatric Inventory. The NPI-Q is conducted for both new participants and continuing participants at every interim phone check visit.

CERTIFICATION

ADNI personnel conducting the NPI-Q are recommended to complete the online training certification developed by the University of California Los Angeles and The National Alzheimer's Coordinating Center (NACC). The NPI-Q Interviewer Certification may be accessed through the NACC website at **https://www.alz.washington.edu/npiq/Signin.html**.

INSTRUCTIONS

Please ask each question to the study partner based upon changes from the participant's usual behavior. Indicate 'yes' only if the symptom has been present in the past month; otherwise, indicate 'no'. If the study partner answers 'yes' to any of the initial questions, ask the sub-question evaluating Severity.