

ALZHEIMER'S DISEASE
NEUROIMAGING
INITIATIVE



DEFINING
ALZHEIMER'S
DISEASE

PROCEDURES MANUAL

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Protocol Synopsis

PROTOCOL TITLE	Alzheimer's Disease Neuroimaging Initiative Grand Opportunity (ADNI-GO)
PRIMARY OBJECTIVE	<p>The major goals of ADNI-GO are to:</p> <ol style="list-style-type: none">1. Define and characterize the stage of the AD spectrum that precedes MCI as currently enrolled in ADNI1 (late MCI or LMCI) by enrolling 200 subjects in the mildest symptomatic phase of AD, early amnesic MCI (EMCI, defined more specifically below).2. Perform F18 amyloid imaging (18F-AV-45) on the CN and LMCI subjects from ADNI1 (including those who had C-11 PIB) and the newly enrolled EMCI subjects. FDG PET will also be performed in association with F18 amyloid imaging. This establishes a national network for F18 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, MRI, FDG-PET, CSF and plasma biomarkers from ADNI1.3. Collect 3T MRI on all newly enrolled subjects. MRIs will be collected at Baseline, Month 3, Month 6, and Month 12.4. Continue longitudinal clinical/cognitive and 1.5T MRI studies of approximately 500 LMCI and Cognitively Normal subjects from ADNI1 for an additional 2 years.5. Collect and analyze blood biomarkers from all newly enrolled EMCI and follow-up subjects. Collect and analyze CSF for biomarkers in all newly enrolled EMCI. Follow up subjects will be asked to agree to CSF collection even if they have not had CSF collected for the original ADNI.6. Collect blood samples for DNA and RNA extraction. Newly enrolled subjects will also have samples collected for Cell Immortalization and APOE genotyping.
STUDY DESIGN	This is a non-randomized natural history non-treatment study.
SAMPLE SIZE	<p>200 newly enrolled subjects from approximately 50 sites from the United States and Canada.</p> <p>Approximately 450-500 subjects will be followed from the original ADNI study.</p>



SUMMARY OF KEY ELIGIBILITY CRITERIA

Newly enrolled subjects will be between 55-90 (inclusive) years of age, have a study partner able to provide an independent evaluation of functioning, and will speak either English or Spanish. All subjects must be willing and able to undergo all test procedures including neuroimaging and agree to longitudinal follow up. 100% of the newly recruited EMCI subjects must be willing to undergo at least one lumbar puncture at baseline. Specific psychoactive medications will be excluded.

EMCI Subject Inclusion Criteria:

MMSE scores between 24-30 (inclusive), a memory complaint (reported by subject or informant), must have objective memory loss measured by education adjusted scores on delayed recall of one paragraph from Wechsler Memory Scale Logical Memory II (between approximately 0.5 and 1.5 SD below the mean of Cognitively Normal), a CDR of 0.5, absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia.

Follow-up Subject Inclusion Criteria:

In order to meet inclusion for follow-up these subjects must have been originally diagnosed as either Mild Cognitive Impairment (MCI) or Cognitively Normal (CN), and be willing and able to continue to participate. Subjects will be asked to continue in the trial even if a diagnostic conversion occurs.

Exclusion for amyloid imaging with 18F-AV-45:

Current or recent participation in any procedures involving radioactive agents such that the total radiation dose exposure to the subject 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.

PROCEDURES

All subjects will have clinical/cognitive assessments, biomarker collection, and imaging. A reduced battery of tests can be requested from the project directors if the subject is not able/willing to complete the full battery.

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 process and store biomarker samples. The National Cell Repository for Alzheimer's Disease will process and store genetic samples. All raw and processed image data will be archived at LONI.

Protocol Synopsis



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 18F-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 A β 42, positive amyloid imaging with 18F-AV-45.

SPONSOR

National Institute on Aging, National Institute of Health

Schedule of Events (EMCI Subjects)

Visit Name	Screen	Baseline	Month 3	Month 6	Month 12	Month 18
Visit Type	In-Clinic	In-Clinic	MRI	In-Clinic	In-Clinic	Telephone Check
Explain study	●					
Obtain consent	●					
Demographics, Family History, Inclusion and Exclusion Criteria	●					
Medical History, Physical Exam, Neurological Exam, Hachinski	●					
Vital Signs	●	●		●	●	
Height	●					
Screening Labs	●					
DNA Sample Collection for APOE Genotyping and GWAS		●				
Cell Immortalization Sample Collection		●				
American National Adult Reading Test		●				
Mini Mental State Examination	●			●	●	
Logical Memory I and II	●				●	
Everyday Cognition (ECog)		●		●	●	
Montreal Cognitive Assessment (MoCA)		●		●	●	
Category Fluency (Animals)		●		●	●	
Trails A & B		●		●	●	
Boston Naming Test (30-item)		●		●	●	
Auditory Verbal Learning Test		●		●	●	
Geriatric Depression Scale	●			●	●	
Clock drawing		●		●	●	
Neuropsychiatric Inventory Q		●		●	●	
ADAS-Cog 13 (with Delayed Word Recall and Number Cancellation)		●		●	●	
Clinical Dementia Rating Scale	●			●	●	
Activities of Daily Living (FAQ)		●		●	●	
Plasma and Serum Biomarker Collection		●		●	●	
RNA Sample Collection		●			●	
Concomitant Medications	●	●		●	●	●
Adverse Events	●	●		●	●	●
Diagnostic Summary		●		●	●	
3T MRI Imaging (100%)	●		●*	●	●	
18F-AV-45 Amyloid Imaging (100%)		●				
FDG-PET Imaging (100%)		●				
CSF Collection by Lumbar Puncture (LP) (100%)		●				

*Month 3 MRI is timed from Screening MRI

Schedule Of Events (Follow-Up CN and LMCI Subjects)

Visit name	VISIT 1	VISIT 2	VISIT 3	VISIT 4
Visit Type	In-Clinic	Telephone Check	In-Clinic	Telephone Check
Explain study	•			
Obtain consent	•			
Medical History, Physical Exam, Neurological Exam	•			
Vital Signs	•		•	
Mini Mental State Examination	•		•	
DNA Sample Collection for GWAS	•			
Logical Memory I and II	•		•	
Everyday Cognition (ECog)	•		•	
Montreal Cognitive Assessment (MoCA)	•		•	
Category Fluency (Animals)	•		•	
Trails A & B	•		•	
Boston Naming Test (30-item)	•		•	
Auditory Verbal Learning Test	•		•	
Geriatric Depression Scale	•		•	
Clock drawing	•		•	
Neuropsychiatric Inventory Q	•		•	
ADAS-Cog 13 (with Delayed Word Recall and Word Recognition)	•		•	
Clinical Dementia Rating Scale	•		•	
Activities of Daily Living (FAQ)	•		•	
Plasma and Serum Biomarker Collection	•		•	
RNA Sample Collection	•		•	
Concomitant Medications	•	•	•	•
Adverse Events	•	•	•	•
Diagnostic Summary	•		•	
1.5T MRI Imaging (100%)	•		•	
18F-AV-45 -Amyloid Imaging (100%)	•			
FDG PET Imaging (100%)	•			
CSF Collection by Lumbar Puncture (LP)	•			

NOTE: All Follow-Up participants will be asked if they are willing to consent to at least one LP (even if did not have an LP under ADNI1). Participants who are not able or willing to have LP, MRI, FDG-PET, or 18F-AV-45 Amyloid imaging will still be followed for cognitive and clinical assessments.

Start-Up and General Information

PERSONNEL REQUIREMENTS

The following roles must be assigned, in order to conduct the Alzheimer's Disease Neuroimaging Initiative Grand Opportunity (ADNI-GO) Study.

SITE PROTOCOL PRINCIPAL INVESTIGATOR (PI)

This person is responsible for:

- Ensuring enrollment quotas and protocol adherence under local IRB approval.
- Supervising project personnel and ensuring that raters maintain a high level of skill and accuracy in conducting assessments.

The Site PI may also serve as the study physician

STUDY PHYSICIAN

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.

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.

Start-Up and General Information



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 ADNIGO. 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. 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 through the ADCS the ADNI training must be completed in full. The training includes one teaching tape and five (5) reliability tapes. To become certified the trainee must agree with four of the five global scores assigned by a Gold Standard to these tapes.

CDR Certified - For those raters who have been previously certified a refresher is required. This refresher includes three (3) reliability tapes. The scores submitted will be compared to the Gold Standard and the site's clinical monitor will contact the trainee if there are any discrepancies.

CDR Certification 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
- ➡ Physical Exam
- ➡ Adverse Events and Hospitalizations
- ➡ MRI/CT Clinical Read
- ➡ 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.

Start-Up and General Information

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 06Jan2010)
- ➔ Protocol Signature Sheet – Amendment 1(dated 10Feb2010)
- ➔ AV45 Protocol Signature Sheet – Amendment 1(dated 16Feb2010)
- ➔ AV45 Investigator Brochure Signature Page (dated 17Nov2009)
- ➔ FDA Form 1572
- ➔ 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).

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: 858-622-2010 | 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
- Electronic Data Capture System Training Module
- 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

All participating sites must complete the certification for 3T MRI. Sites that have been certified previously for ADNI or other ADCS projects must still undergo a MRI certification, as there are study specific sequences used in this trial. Site MRI qualification requires a phantom scan and volunteer scan. Volunteer scanning can be done only after IRB approval. See MRI section for further details.

PET SCAN CERTIFICATION

All sites must complete the PET certification procedures unless previously certified for ADNI on the current scanner and software platform. If your site is using a different PET scanner from ADNI 1 or if your site did not participate in the PET sub-study for ADNI 1, certification of the PET scanner is required. Additionally, if there was a change in software platform from ADNI 1 or during the course of ADNI GO, certification may be required. During start up, a PET questionnaire will be distributed to each site to determine if certification of your PET scanner is required. The certification process includes scanning of a phantom and can be completed prior to regulatory approval. See PET section for further details.

Start-Up and General Information

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 ADNI-GO. Additionally, you will need to identify how many follow-up participants will continue on to ADNI-GO, and whom will have a LP.

Covance will initially provide each site three (3) EMCI Screening Laboratory Kits and one retest kit. There are 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 all other supplies for the ADNI GO Study including:

- DNA, APOE and RNA Collection, Labels and Shipping Supplies.
- Biomarker Collection, Labels and Shipping Supplies.
- CSF Collection and Shipping Supplies (including Sprotte Needles and LP Trays).
- Neuropsychometric Testing Supplies (ADAS Kits, Boston Naming Test Booklets). These are the same supplies as used in ADNI 1. 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 Binders and Screen Fail 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.

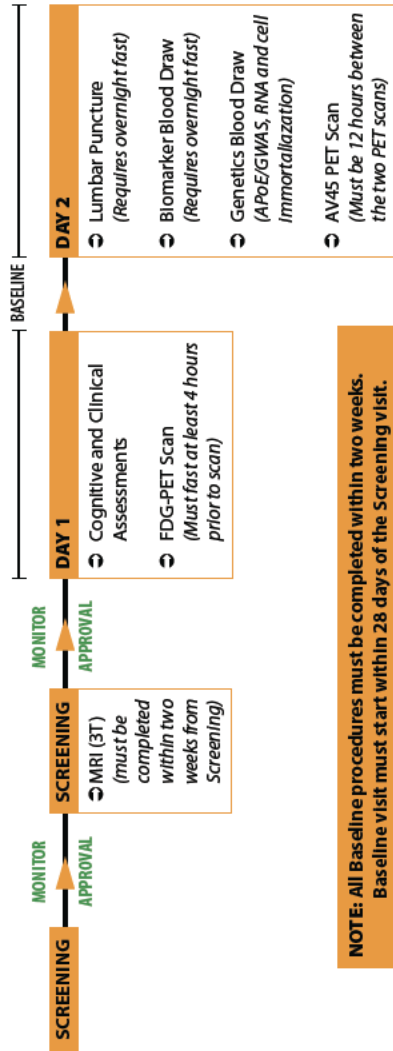
Start-Up and General Information

ADNI GO SAMPLE VISIT SCHEDULE AND GENERAL GUIDELINES FOR SCHEDULING PARTICIPANT VISITS

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

ADNI GO SAMPLE VISIT SCHEDULE

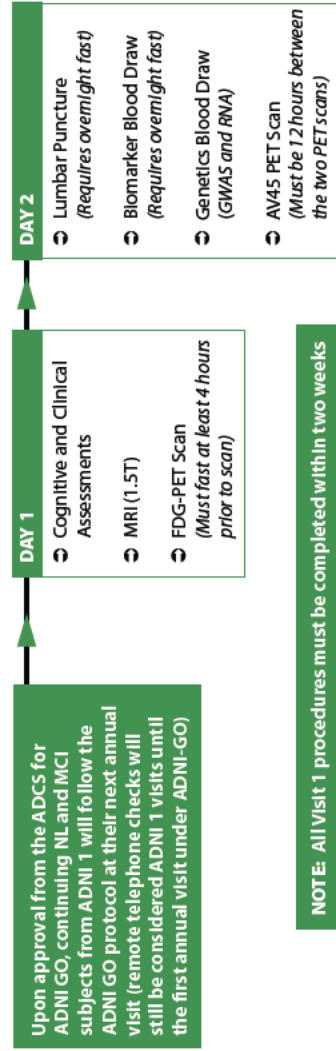
EMCI SUBJECTS SAMPLE VISIT SCHEDULE (SCREENING AND BASELINE)



GENERAL GUIDELINES:

- ➔ LP and Biomarker Blood Draws **require** an overnight 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
- ➔ Cell immortalization blood samples are only necessary for EMCI baselines, unless an ADNI follow-up subject did not contribute a sample previously
- ➔ 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.

ADNI 1 FOLLOW-UP SUBJECTS SAMPLE VISIT 1 (M36, M48, OR M60)



Start-Up and General Information

DATA MANAGEMENT

OVERVIEW

There are three locations for the management of data for the ADNI-GO Study.

1. **ADNI-GO 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 management tools is time and date stamped and is traceable to the user who completed the transaction.

ADNI GO 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 and Access Procedures Manuals
SAE Reports, Study Memorandum, Supply Order Forms.

Navigate to the system using this url: <http://adcs.org/>, select **ADCS Investigators > Study Resources > ADNI GO 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)

Start-Up and General Information



Timeliness Of Data Entry

- Data collected must be entered **promptly** on the ADNI GO Online database (<http://adcs.org/> > **ADCS Investigators** > **Study Resources** > **ADNI GO 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
- Subject Projected Visit Reports
- Regulatory Affairs Documents
- Recruitment Documents

A training powerpoint for the ADCS Administration Website is posted to the document repository under [docs/studydocs/Procedures Manuals](#).

Please note that the ADCS Administration Website is a separate URL from the ADNI GO 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.**

Start-Up and General Information

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.
- 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 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.

Start-Up and General Information

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

ADNI GO 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, Baseline Symptoms and Adverse Events with the study partner, and 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.

Start-Up and General Information

- 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.

Start-Up and General Information

RECRUITMENT AND RETENTION

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

- ➔ Flyer
- ➔ Trifold Brochure
- ➔ Bookmark
- ➔ 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 ADNI GO 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 ADNI GO 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, including a full-page color ad in a special edition of Newsweek for those who are in the 45+ age-range. Additional summer advertising in USA Today being investigated.
- ➔ 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 ADNI GO.
- ➔ Blurb placed in the Alzheimer's Disease Information Network E-Newsletter distributed to over 3,000 subscribers

The advertisement mentioned above is a public service announcement (PSA) featuring Dr. Maya Angelou, who has graciously extended the use of her image from ADNI1 to ADNI GO. In addition to our national outreach, the National Institutes of Aging (NIA) has released a formal announcement of ADNI GO. In summer 2010 the Alzheimer's Association will distribute our Alliance newsletter which will devote all content to ADNI GO. The newsletter is distributed to all Alzheimer's Association chapter heads and will encourage them to advocate for ADNI GO participation by their constituencies.

Start-Up and General Information

Lastly, materials to use in sites' local communities include a localized press release and tailorable Craigslist posting.

RETENTION

To assist retention efforts, the quarterly ADNI Exclusive newsletters for participants in ADNI1 will be distributed to ADNI GO 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 phase of ADNI in addition to briefly touching upon testing procedures involved. Mugs with the ADNI logo will be distributed once enrollment is complete. Lastly, we have various informational materials that sites can utilize on the ADCS Library Tools List.

Contact Us

Most of the materials mentioned above are available on the ADNI GO 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.

Adverse Events and Serious Adverse Events

BASELINE SYMPTOMS CHECKLIST AND LOG

Any condition or symptom present at the ADNI GO screening visit must be noted on the Baseline Symptoms Checklist, with details of the symptoms entered in the Baseline Symptoms Log. Episodic symptoms associated with medical conditions listed on the Medical History form would also be recorded as present on the checklist, with details entered on the log if they have occurred during the three months prior to the initial visit.

EXAMPLE: The participant reports knee pain, which the study partner states is due to osteoarthritis. Record this on the medical history as 'Osteoarthritis' and on the Baseline symptoms log as 'Intermittent knee pain due to chronic osteoarthritis'.

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

- Enter both the symptom number and name.
- 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 'Diagnosis and Symptoms Checklist' with the participant and study partner to ensure any new events are reported. Review the Diagnosis and Symptoms Log to confirm whether any symptoms have ceased or worsened. The eCRF will require confirmation that the log was reviewed.

- If the symptom has ceased, enter the date.
- If the symptom has worsened in chronicity or severity from screening, enter the date the symptom changed in the "Date Ceased" boxes on the log and create a new Adverse Event documenting the change in the symptom.
- If the symptom is still present at the end of the study, check "Yes" for the question, "Is the symptom ongoing?"

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

All new symptoms and Baseline symptoms that have worsened in chronicity or severity **MUST** be recorded as an Adverse Event, and **SHOULD NOT** be added to the Diagnosis and Symptoms Log. If, after the screening visit, a participant and/or study partner reports a symptom(s) that should have been recorded at the screening visit, but was overlooked at the time, then record the symptom as a Baseline symptom, not an Adverse Event. Upon determination that this symptom(s) was/were clearly in existence prior to consent, site personnel should then update the following worksheets:

1.	Baseline Symptoms Checklist: the symptom(s) that was previously recorded as "absent" should be checked as "present".
2.	Baseline Symptoms Log: the 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.

Adverse Events and Serious Adverse Events



ADNI 1 FOLLOW-UP PARTICIPANTS

In general, once an ADNI 1 participant signs the consent for ADNI GO 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 Diagnosis and Symptoms Checklist. Provide details for each existing diagnosis or symptom on the Diagnosis and Symptoms Log.

Medical History: Review the participant's medical history during the initial ADNI GO visit. All significant / relevant medical history will need to be documented in the source worksheets and / or research chart, as well as entered under the ADNI GO EDC. If a subject had an adverse event during ADNI 1 that was associated with a disease or condition, this would now be captured as medical history under ADNI GO.

Adverse Events: Once a subject signs the consent to ADNI GO, any subsequent event that is not a part of medical history or not noted on the Diagnosis and Symptoms Checklist at the 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. AEs that were ongoing during the last visit under ADNI 1 would be considered medical history (since they began prior to consenting to ADNI GO) and if present during the initial GO visit it would be captured as such on the Diagnosis and Symptoms Checklist and Log.

Updating the ADNI 1 EDC system: Anything that occurred while the subject was under consent for ADNI 1 should be reported and updated in the ADNI 1 EDC system. If an adverse event resolved from the time of the last ADNI 1 visit to the time of the initial ADNI GO visit, the end date should be entered in the ADNI 1 EDC system and the condition (if applicable) should be recorded as medical history in the ADNI GO EDC system. Additionally if a concurrent medication for the adverse event was taken during the time of consent to ADNI 1 and has since been discontinued. The date of discontinuation of the concurrent medication should be entered in the ADNI 1 EDC system and the medication would not be reported in the ADNI GO EDC system (unless the medication was taken within three months of the initial ADNI GO visit).

Adverse Events and Serious Adverse Events

SYMPTOMS OF POTENTIAL CONCERN

Some symptoms on the checklist may be particularly difficult to interpret. Other complaints are commonly voiced in vague language. Use the following summary of “Symptoms of Potential Concern” as a guideline to defining and recording symptoms in terminology that is as specific as possible under Description of Symptom.

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

Any change in the chronicity, severity, or action taken, for an adverse event requires a new entry on the Adverse Event/Hospitalizations (AE/H) form, and the previous entry must be closed out. ***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.

At each study visit, review the AE/H online forms with the study partner and make appropriate changes.

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

Adverse Events and Serious Adverse Events



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 arrived at, 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 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.

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 words to be used as a keyword in coding the Adverse Event.

For events that are also behaviors (i.e. "repeatedly washes and combs hair") the word 'behavior' should be added under 'Event' in parenthesis as a keyword. 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:

- ➡ Subject reports 'feeling bloated'.
Event: Bowel Gas, Comments: 'feeling bloated'.
- ➡ Subject reports 'fuzzy feeling'.
Event: Sleepiness, Comments "subject reports 'fuzzy feeling' which is explained as drowsiness in the afternoon".
- ➡ Subject reports "itching back and stomach"
Event: Itching (Skin), Comment: 'back and stomach'
- ➡ Subject is seen at the ER for chest pain and is diagnosed with severe indigestion.
Event: Indigestion, Comment: Seen in ER, reported chest pain.
- ➡ Subject 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). For 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 Serious Adverse Events

Severity

All adverse events will be graded on a three-point scale (mild, moderate, severe) and 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 Serious Adverse Events

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 OR LIFE-THREATENING ADVERSE EVENTS

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

- ➔ Fatal or immediately life-threatening
- ➔ Causes permanent or substantial disability
- ➔ *Requires or prolongs inpatient hospitalization (acute)
- ➔ Congenital anomaly/birth defect
- ➔ Is a cancer
- ➔ Suggests any significant hazard, contraindication, side effect or precaution that may be associated with the use of a study procedure
- ➔ Regarded by the investigator as serious

* **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

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.

Adverse Events and Serious Adverse Events

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 Grand Opportunity (ADNI GO). All newly enrolled EMCI study subjects will have 3.0 Tesla MRI scans completed at Screening, Month 3, Month 6 and Month 12 study visits. ADNI 1 follow-up subjects will complete 1.5 Tesla scanning at their first ADNI GO follow-up visit, and the subsequent annual in clinic visit. The collection of these images is central to meeting the ADNI GO objective of developing biomarkers to track both the progression of Alzheimer's Disease and change in underlying pathology.

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 must be scheduled based on the date of the Screening MRI.

All sites will need to meet 3.0 T MRI certification requirements in order to begin enrolling for ADNI GO. This certification process includes scanning of an MRI phantom and a human volunteer scan. Please refer to the Startup Certification section of this manual for specific instructions on how to become certified for MRI.

CHANGES FROM ADNI 1

The 3T MRI imaging protocol for ADNI GO is quite different from the 3T protocol used in ADNI 1 and is unique for each type of machine (e.g. GE., Phillips). Please ensure that subjects are scanned using the correct protocol. Only newly enrolled EMCI subjects will complete 3T scans. ADNI 1 follow-up subjects will complete 1.5T scanning using the same protocols used in ADNI 1. ADNI 1 follow-up subjects will not be scanned using 3T even if they were previously enrolled in the ADNI 1 3T arm.

DATA FLOW

Please refer to the MRI Data Flow chart (next page) for an illustration of this data flow. Every MRI scan completed for ADNI GO 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. They will indicate whether the subject meets eligibility requirements for newly enrolled EMCI subjects. For all subjects, they will evaluate the quality of the scan, and determine if a rescan is necessary. If the subject requires a rescan, it must be completed within 4 weeks of the original scan.

DATA FLOW, CONT'D

A local radiological interpretation of the MRI scan is required. The clinical read should follow standard practice. The site clinician should then review the local radiological interpretation of the MRI scan to confirm the subject's eligibility.

If 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 subject meets eligibility requirements. The monitor will then confirm eligibility by completing the monitor eligibility form in the EDC system, at which time the subject can proceed to baseline.

QUALITY REVIEW OF SCANS

The ADNI MRI QC team at Mayo will review the 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 subject is scanned. If multiple subjects are scanned on a single day, only one phantom scan needs to be acquired.

1. CLINICALLY SIGNIFICANT FINDINGS

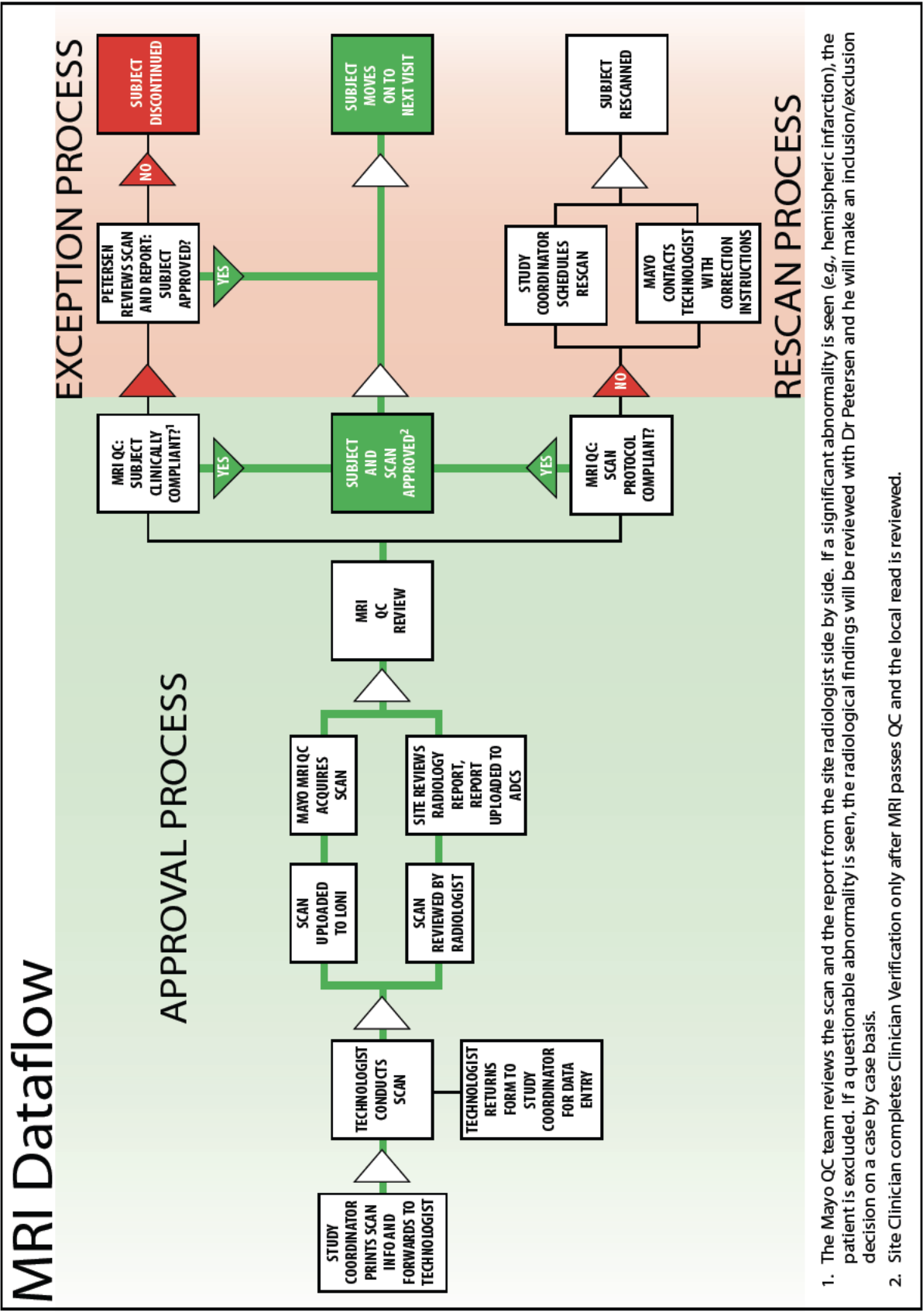
If a significant abnormality is seen (e.g. hemispheric infarction), the patient is excluded. In the event that a radiological finding that is not normal for age is identified by MRI QC, the site will be informed of this result by email. If a subject must be screen failed from MRI, please refer to the 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 subject 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 subject motion is believed to be correctable, and not due to chronic illness or deteriorated cognitive ability. If the rescan also fails due to subject motion or non-compliance the subject should be dropped from the MRI study. In cases where the site believes the failure to be correctable, the site should request an exception to allow the subject to remain in the MRI study. The exception request should sufficiently document the reason for the failed scan and why the site believes the problem to be correctable.



MRI Procedures

REQUIRED PHANTOM SCANNING AT THE SITE

The radiology center for each site will be required to scan a phantom when scanning ADNI GO subjects in order to ensure that the scanners are in compliance with ADNI GO requirements. When the MRI of the subject is uploaded to LONI, the MRI of the phantom should accompany it. Failure to comply with this could prevent the sites from enrolling for ADNI GO. 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

EMCI Screening 3T MRI

The screening MRI cannot be conducted until both the clinician and monitor indicate that the subject meets inclusion/exclusion criteria for ADNI GO. Documentation of approval is done via the ADNI GO EDC system on the clinician review eCRF and monitor eligibility eCRF. Once both confirm the subject meets eligibility criteria the subject 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 subject does not meet clinician and monitor approval to proceed to the screening MRI, the screening MRI must be cancelled.

ADNI 1 Follow-Up Subject Initial 1.5 Scan

For ADNI 1 follow-up subjects, a 1.5T MRI scan will be done during the initial ADNI GO visit. The MRI can be scheduled with your local MRI center as soon as the subject confirms they are willing to have a MRI scan done. There is no “approval” process when scheduling the MRI scan for ADNI 1 subjects transferring to ADNI GO.

MRI Procedures

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 subject'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.

Use of sedative medications prior to imaging is not allowed during the Screening period. If a potential EMCI subject is not comfortable with MRI he/she should not be screened for the ADNI GO study. For scans from Month 3 on, sedatives may be allowed depending on clinician's judgement. Record all medications on the Concurrent Medications log.

If you are using a new scanner for ADNI GO, 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.
- ➔ Subject is given pamphlet with appointment time.
- ➔ Subject 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 ADNI GO MRI protocol should be used in scanning this subject.

Hardware/Software Upgrades: Prior to any software or hardware upgrades the site must inform the ADNI GO 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 ADNI GO subjects.

MRI Procedures

MRI PRE-SCREENING

It is important to know when subjects 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 subject has any metal in their body and will help to determine whether or not subjects are eligible to have an MRI scan.

The Pre-Screening Form should be completed **before scheduling the Screening Visit**. The subject, the caretaker, or the informant may fill out either of the screening forms, but anyone completing the form should have a firm understanding of the subject's medical history.

First, write in the Date and the Subject's ADNI GO number at the top of the form. Then indicate whether or not the subject 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 subject or study partner answers yes to any of the questions on the Pre-Screening Form under the heading **"Exclusionary Items"** the subject must be excluded from the study. The subject will not be able to participate in MRI scans because the metal object in question is not allowed in MRI scanners.

If the subject answers yes to any of the questions on the Pre-Screening Form under the heading **"Please Inform MRI Center,"** please do not exclude the subject. 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 subject regarding the metal object so your radiology site may best assess whether or not a MRI would be safe for the subject.

In addition, if a subject indicates they are claustrophobic please try to discuss the level of discomfort a MRI may pose. Some subjects might indicate they are claustrophobic, but are willing to undergo an MRI.

If the subject 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 subject'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 Procedures



MRI Screening Form Alzheimer's Disease Neuroimaging Initiative MRI Study Alzheimer's Disease Cooperative Study (ADCS)

Date ____/____/____

Subject 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

Explanation _____

Signature of subject or subject's representative

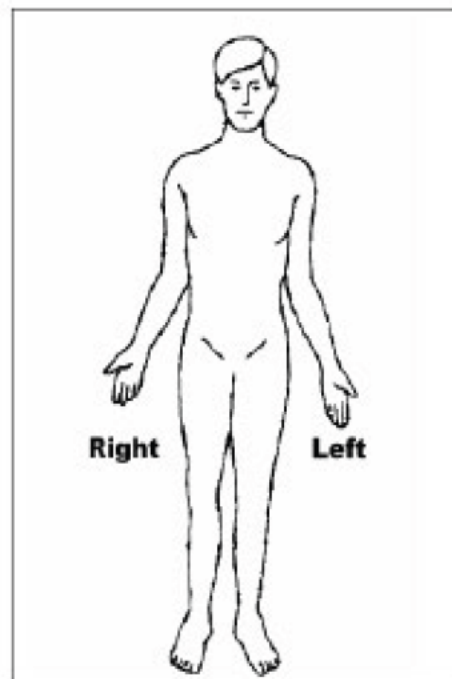
Name of Representative

Signature of person administering screening form

Date ____/____/____

Date ____/____/____

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



Remove all metallic objects prior to your MRI examination

MRI Procedures

MRI PAMPHLET

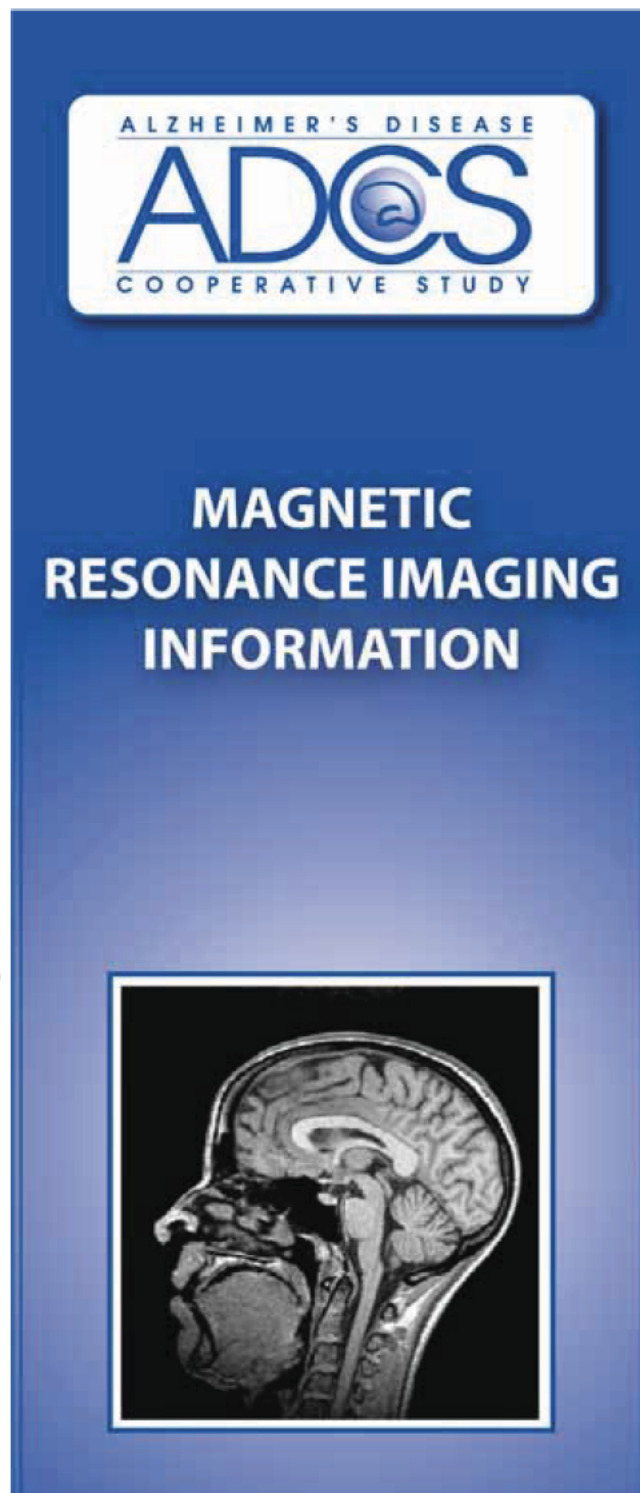
The MRI pamphlet should be distributed to subjects in the Alzheimer's Disease Neuroimaging Initiative Grand Opportunity (ADNI GO) study.

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

Subjects should have plenty of time to review this information before their MRI appointment so the pamphlet should be distributed to subjects 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 subject'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 subject or the study partner.

In addition, subjects 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 Alzheimer's Disease Neuroimaging Initiative Grand Opportunity (ADNI GO) protocol.



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 Grand Opportunity (ADNI GO) is to perform F18 amyloid imaging (AV-45) and fluorodeoxyglucose imaging (FDG) on the ADNI 1 follow-up subjects and the newly enrolled EMCI subjects. This establishes a national network for F18 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.

The AV-45 and FDG PET scans will occur during the initial ADNI GO in clinic visit for ADNI 1 follow up subjects switching into GO and during the baseline visit for the newly enrolled EMCI subjects. 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 to be included in the analysis and reimbursed.

PET SCANNER CERTIFICATION

If your site is using a different PET scanner from ADNI 1 or if your site did not participate in the PET sub-study for ADNI 1, your site may need to meet PET certification requirements in order to begin AV-45 and FDG PET scans on EMCI and ADNI 1 follow-up subjects. A PET questionnaire will be distributed to each site to determine if certification of your PET scanner is required. This certification process includes scanning of a phantom and can be completed prior to regulatory approval. The ADCS will contact you if your site's PET scanner requires certification. Details regarding the certification process will be reviewed with your site at that time.

EXCLUSIONARY TO PET SCANS

All subjects 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 EMCI subjects will have had a screening MRI as part of ADNI GO 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 subject to PET imaging for ADNI GO.

- | | | |
|------------------------------|-----------------------------|--|
| <input type="checkbox"/> Yes | <input type="checkbox"/> No | Is there a history of radiation therapy in the past year? |
| <input type="checkbox"/> Yes | <input type="checkbox"/> No | Is there a history of having radiation for research in the past year? |
| <input type="checkbox"/> Yes | <input type="checkbox"/> No | Would there be problems with the subject's ability to cooperate with scan? |

PET Procedures

AV-45 PET SCAN PROCESS

Prior to imaging, vital signs will be measured. Each subject will receive a single i.v. bolus (370 MBq (9 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. Subjects who experience an adverse event will not be discharged until the event has been resolved or stabilized. A follow-up phone call to the patient (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.

FDG PET SCAN PROCESS

Subjects will need to **fast at least four hours** prior to the scanning session. The subjects' blood glucose is checked prior to the scanning and **must be <180 mg/dL**. Each subject 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 ADNI GO 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.

PET Procedures

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 no problems are found with the scan, the subject will be approved to continue in ADNI GO.

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.

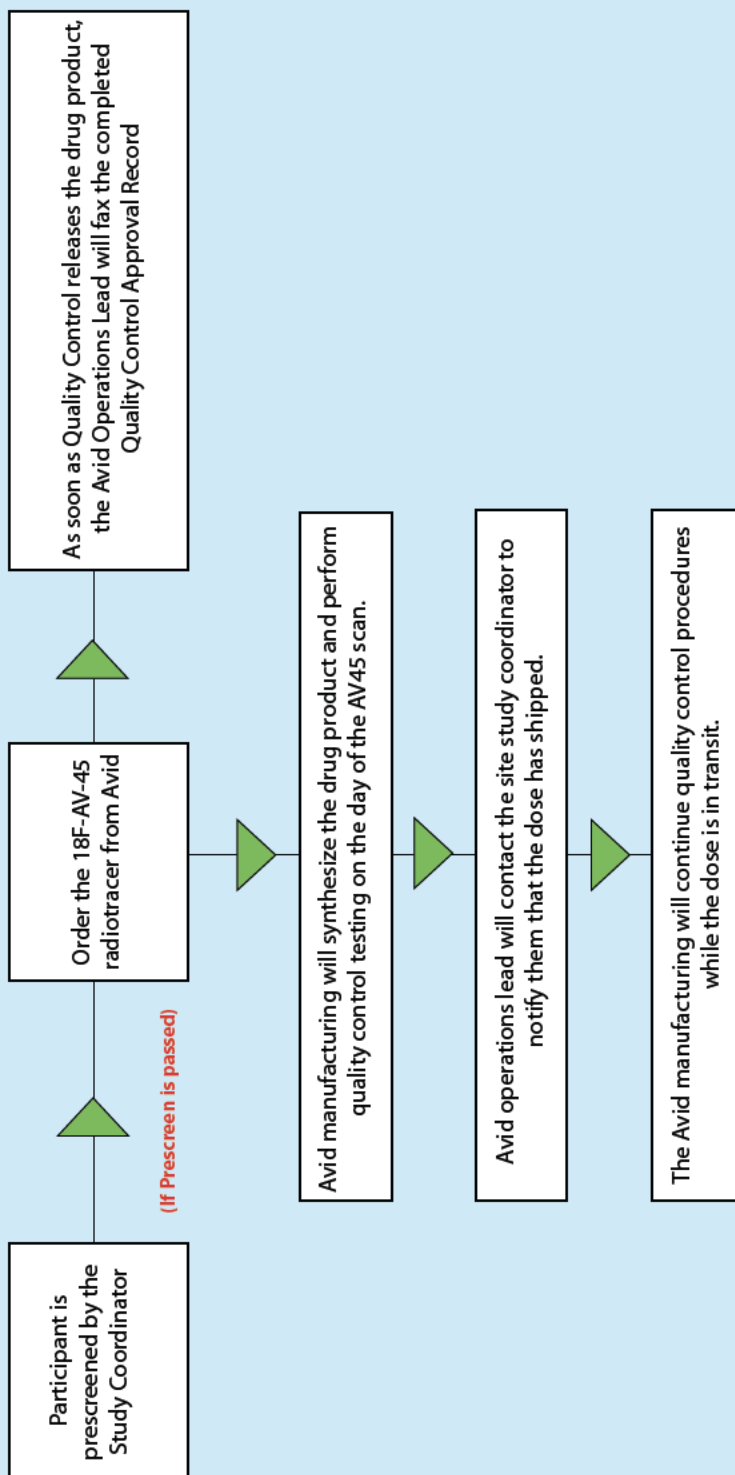
Before requesting the site to schedule a rescan for PET, the subject will be assessed for overall radiation exposure. If an additional scan would not exceed limits on exposure, study coordinators and site PIs will be emailed a request for a repeat scan. When requested, a repeat scan should be scheduled **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 subject 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 subject motion is believed to be correctable, and not due to chronic illness or deteriorated cognitive ability.

Questions on PET Technical issues:
adnipet@ucsd.edu

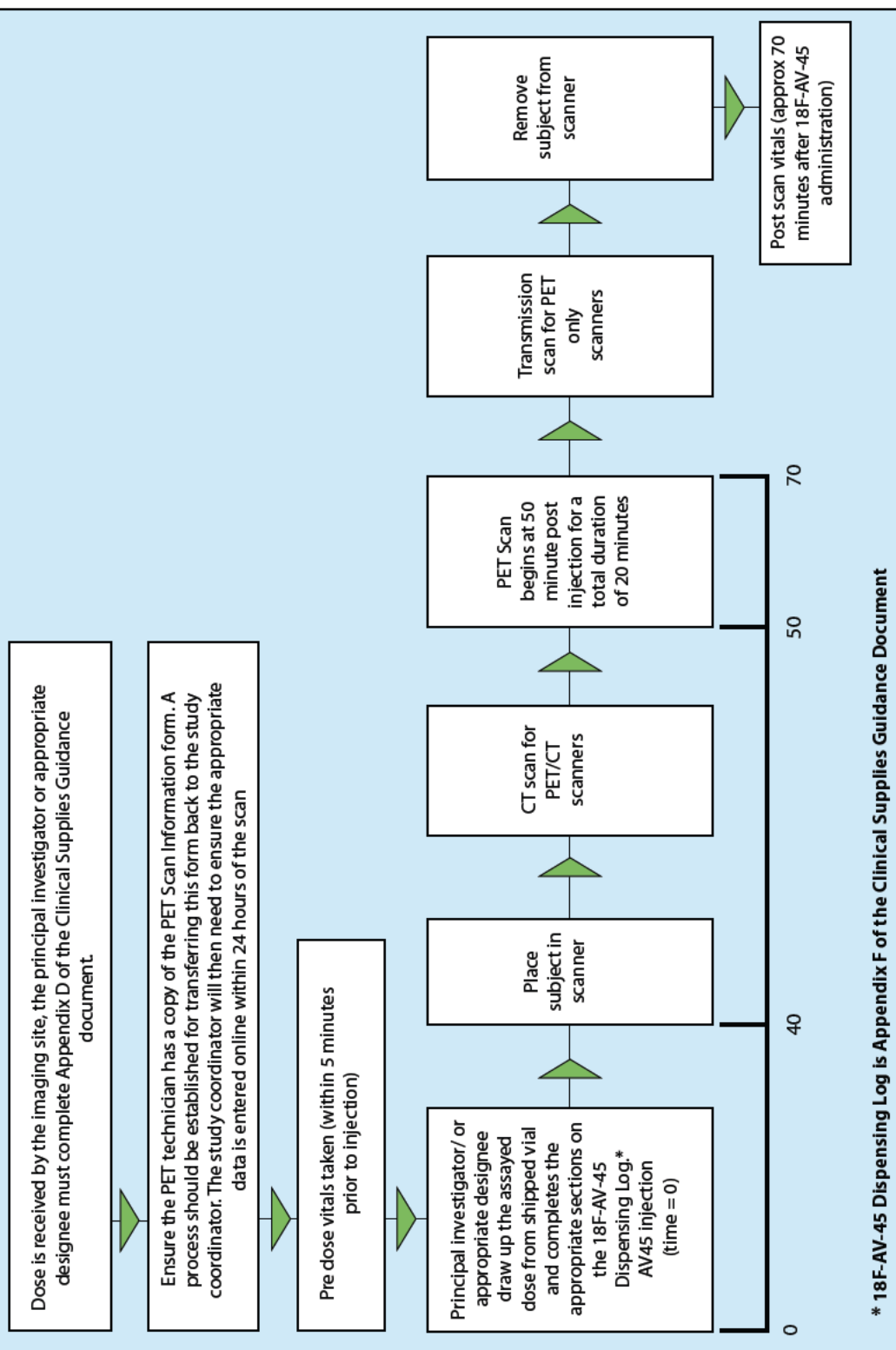


Prior to AV45 Scan

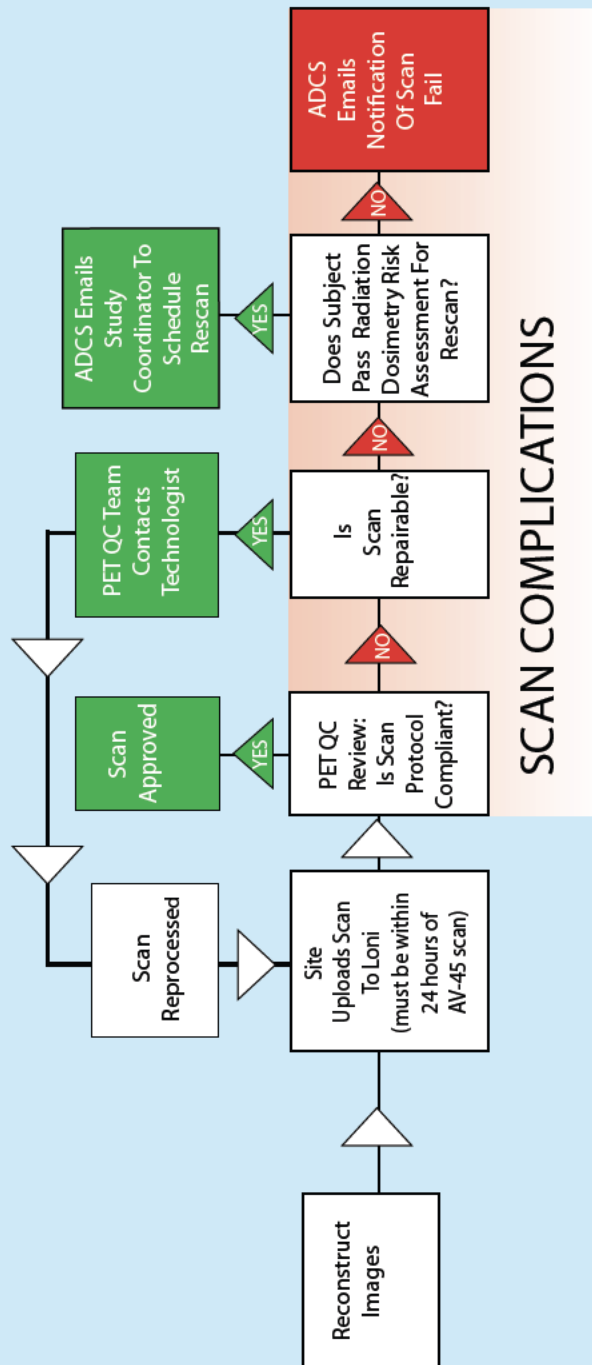


NOTE: Complete Appendix A of the Clinical Supplies Guidance Document located in the document repository when ordering the 18F-AV-45 radiotracer.

Conducting the AV45 Scan

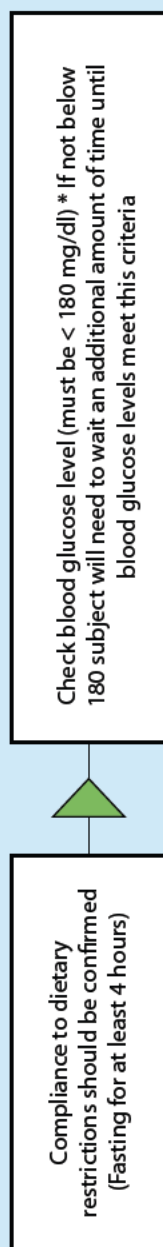


Post AV45 Scan

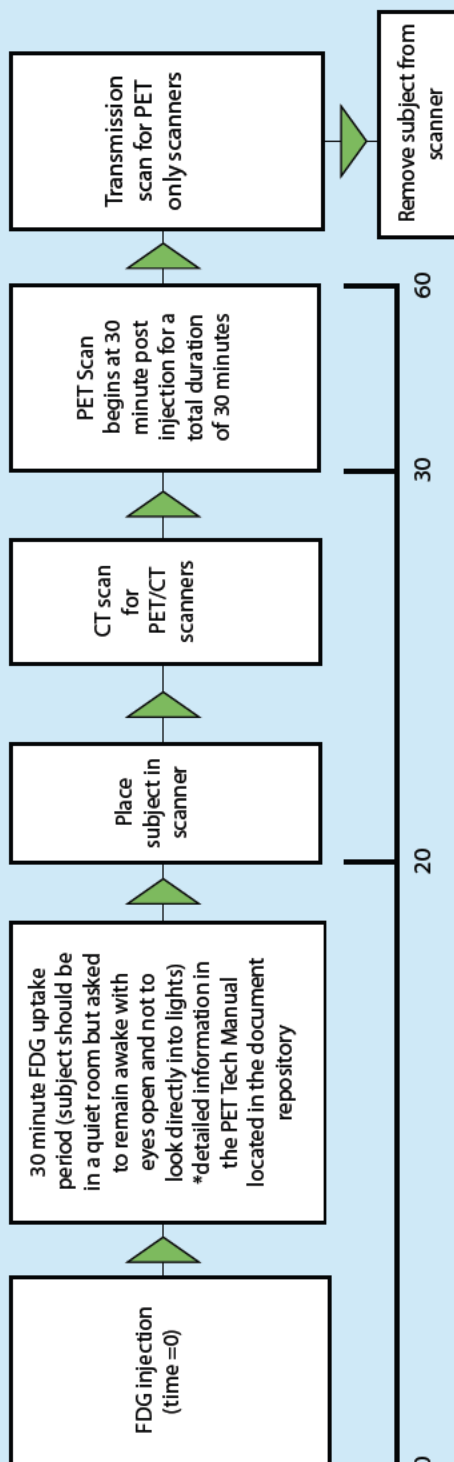


FDG Scan Process

Prior to FDG Scan

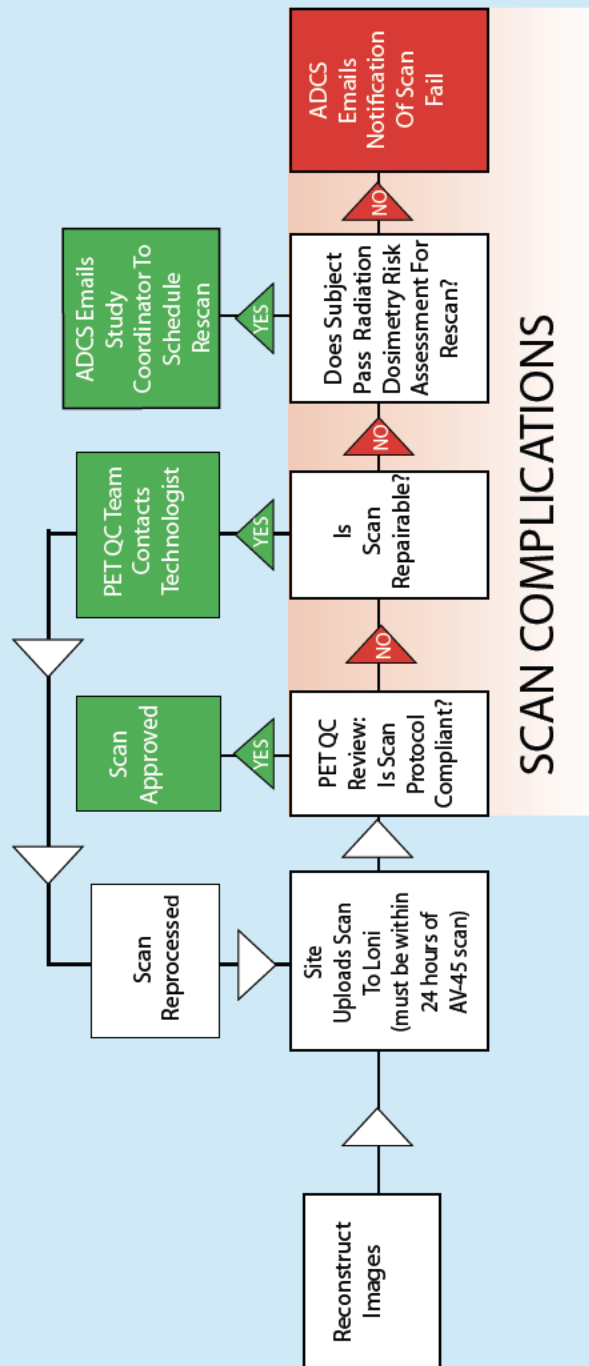


Conducting the FDG Scan



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.

Post FDG Scan



SCAN COMPLICATIONS

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 EMCI subjects 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 subject 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.

PET Procedures

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 subject 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 a subject consents to lumbar puncture, it is preferable for the Lumbar Puncture to be done PRIOR to PET scans (AV-45 and FDG 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.
- ☐ Subject is given pamphlet with appointment information.
- ☐ Subject 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

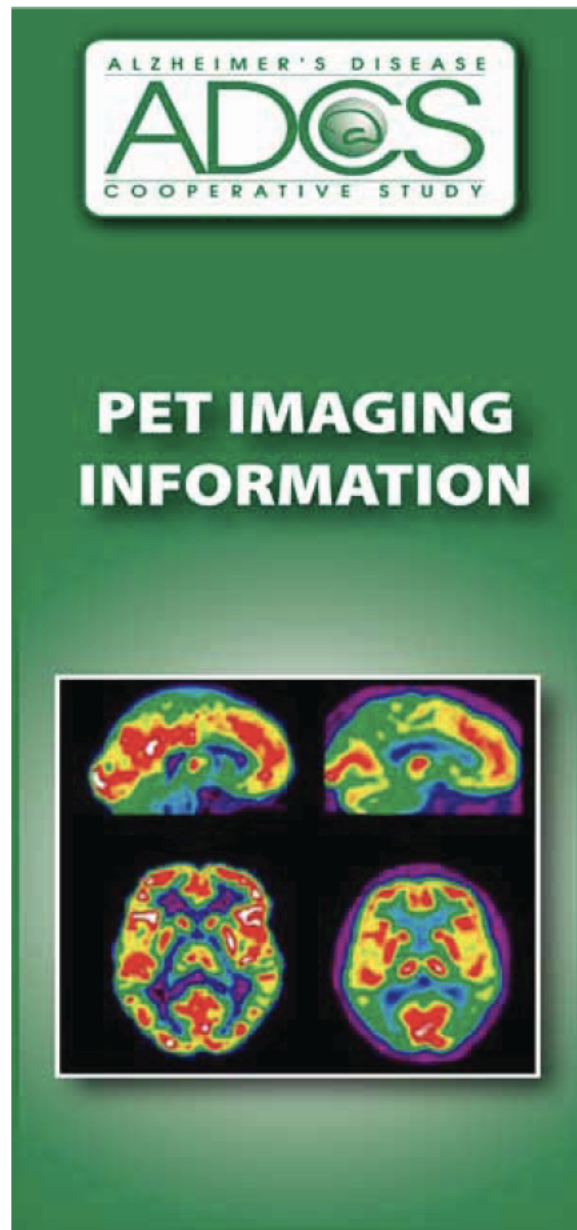
The PET pamphlet should be distributed to any subject undergoing a PET scan for the ADNI GO study.

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

Subjects should have plenty of time to review this information before their first PET appointment so the pamphlet should be distributed to subjects 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 subjects 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 subject or the caretaker.

In addition, subjects 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 Alzheimer's Disease Neuroimaging Initiative Grand Opportunity (ADNI GO) 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
- Aβ 40 and Aβ 42 in Plasma
- Amyloid beta in CSF
- APOE genotyping-blood
- Isoprostanes in CSF, plasma, urine
- DNA from blood cells
- Homocysteine in plasma, CSF
- RNA from blood cells

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

Cerebral Spinal Fluid Sample Collection

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

B I O F L U I D C O L L E C T I O N S C H E D U L E

EMCI SUBJECTS							
	Covance Screening Labs	CSF	Plasma	Serum	RNA	APOE/GWAS	Cell-Immort.
Screening	✓						
Baseline		✓	✓	✓	✓	✓	✓
Month 6			✓	✓			
Month 12			✓	✓	✓		

FOLLOW-UP LMCI AND CN SUBJECTS						
	CSF	Plasma	Serum	RNA	APOE*/GWAS	Cell-Immort.
Initial Visit (Baseline)	✓	✓	✓	✓	✓	
Annual Visit (Month 12)		✓	✓	✓		

*APOE genotyping will only be done for newly enrolled EMCI subjects

Biofluids: Collection, Processing And Shipment

SAMPLE IDENTIFICATION AND TRACKING

- ➔ Clinical Laboratory Samples for **EMCI subjects** 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) must be identified using the NCRAD Sample Identification label provided by the ADCS.

NCRAD SAMPLE LABEL

ADNI-GO ____ -S- ____
Year of Birth ____ Gender: M / F
Collection Date: ____ / ____ / ____
Subject Type: ☐ EMCI ☐ Follow-Up ADNI Subject
Visit: ☐ Baseline ☐ Month 12

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

UPENN BIOMARKER SAMPLE LABEL

Subject ID #
____ S ____
Time ____: ____
Date ____/____/____
Circle : M or F
Biomarkers
ADNI!
Lavender Cap
Vst 7/Month 36
BLD EDT

Please note there are different UPENN labels based on the visit for EMCI and ADNI 1 follow up subjects. Please ensure you use the appropriate UPENN label that corresponds to the correct visit.

→ License Plate

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

V I S I T N U M B E R I N G

VISIT	NUMBER	ABBREVIATION
EMCI Baseline	2	VST 2
EMCI Month 6	3	VST 3
EMCI Month 12	4	VST 4
ADNI 1Month 36	7	VST 7
ADNI 1Month 48	8	VST 8
ADNI 1Month 60	9	VST 9
ADNI 1Month 72	10	VST 10

Biofluids: Collection, Processing And Shipment

SAMPLE TRACKING

All samples (except for EMCI 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 APOE/GWAS/RNA genotyping collection eCRF and Biomarker collection eCRF must be completed **on the date of each visit**. Additionally the APOE/GWAS/RNA genotyping form and Biomarker collection form included in the worksheet packet located 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.

For the APOE/GWAS/RNA Genotyping 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 ADNI GO 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 and/or Sample Collection: ApoE/GWAS/RNA Genotyping) in the worksheet packet and eCRF in the ADNI GO EDC system. Please ensure the reason why the sample was not obtained is provided.

SAMPLE AMOUNTS OBTAINED AT EACH VISIT (mL)

SAMPLE TYPE	AMOUNT	EMCI VISIT	ADNI 1 FOLLOW UP VISIT
Plasma from blood	20 mL	BL, M6, M12	Initial Visit (BL), Annual Visit (M12)
Serum from blood	20 mL	BL, M6, M12	Initial Visit (BL), Annual Visit (M12)
CSF	20 mL	BL	Initial Visit (BL)
Blood for Cell Immortalization	2 x 8.5 mL	BL	
Blood for APOE*/GWAS	10 mL	BL	Initial Visit (BL)
Blood for RNA genotyping	3 x 2.5 mL	BL, M12	Initial Visit (BL), Annual Visit (M12)

*APOE genotyping will only be done for newly enrolled EMCI subjects.

IMPORTANT: Please ensure to use the appropriate sample labels for each sample type. NCRAD labels for Cell Immortalization sample, APOE/GWAS sample, and RNA 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.

Biofluids: Collection, Processing And Shipment

CLINICAL LABORATORY SAMPLES AT SCREENING

CLINICAL LABORATORY KITS

Screening laboratory kits for EMCI subjects are being provided by Covance, all other laboratory supplies are provided by ADCS.

Please note that Covance will not handle the management of any labs for ADNI 1 follow up subject visits under the ADNI GO protocol. In addition, Covance will not manage labs for EMCI subjects 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.

Instructions on how to collect, process and package screening laboratory specimens for EMCI subjects 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 ADNI GO differs from those provided for ADNI

- The Rapid Plasma Reagin (RPR) test is not conducted during Screening. For this reason, the yellow-topped tube contained in the Covance screening kit will be smaller, 3.5 mL as opposed to the 5 mL tube used in ADNI 1
- **IT IS THE RESPONSIBILITY OF EACH SITE TO MONITOR THE EXPIRATION DATE OF EACH KIT.**

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.
- 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)

Biofluids: Collection, Processing And Shipment

CLINICAL LABORATORY SAMPLES AT SCREENING (Cont'd)

You Will Need To Provide:

- Tourniquet
- Alcohol
- Gauze
- Bandage
- Dry ice

Provided by Covance at the Start of ADNI:

- Shipping boxes: ambient, frozen, and combination
- Airbill labels

Please note the initial shipment of shipping boxes and airbill labels occurred at the start of ADNI. Such supplies are not provided upon startup of ADNI GO. If you have run out of shipping supplies or airbill labels please order manually through the US Resupply order form located in the document repository.

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_2004)

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

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

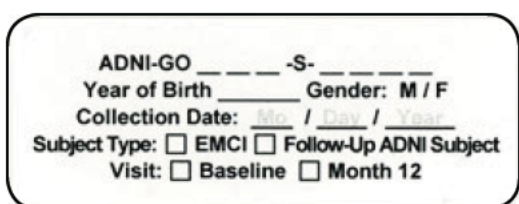
A single 10 mL EDTA (lavender top) tube of whole blood will be collected at baseline for newly enrolled EMCI subjects and at the first ADNI GO Visit for subjects continuing from ADNI 1.

- ➔ The single 10 mL EDTA (lavender top) tube of whole blood will be used for the genome-wide association study across all subjects.
- ➔ ApoE genotyping will only be done for the newly enrolled EMCI subjects, 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 and securely place the label onto the EDTA (lavender top) tube **BEFORE** the blood draw.



ADNI-GO ____-S-____
Year of Birth ____ Gender: M / F
Collection Date: ____ / ____ / ____
Subject Type: ☐ EMCI ☐ Follow-Up ADNI Subject
Visit: ☐ Baseline ☐ Month 12

Please note that the visit field “**baseline**” refers to the baseline visit for EMCI subjects **AND** the initial ADNI GO visit for subjects continuing from ADNI 1. Please ensure the correct visit is checked on the label for all GWAS/ApoE genotyping samples.

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: APOE/GWAS/RNA 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 and shipped at ambient temperature.

Biofluids: Collection, Processing And Shipment

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 an ice pack 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: ApoE/GWAS/RNA 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 ApoE/GWAS/RNA electronic case report form located in the ADNI GO EDC system 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.

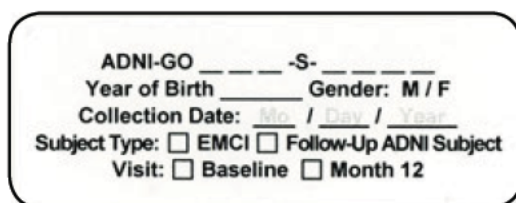
Biofluids: Collection, Processing And Shipment

CELLS FOR IMMORTALIZATION

Blood samples will be collected for Cell Immortalization at Baseline for all newly enrolled EMCI subjects 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 subject 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 and securely place the label onto each ACD-A (yellow top) tube before the blood draw.



ADNI-GO ____ -S- ____
Year of Birth ____ Gender: M / F
Collection Date: ____ / ____ / ____
Subject Type: ☐ EMCI ☐ Follow-Up ADNI Subject
Visit: ☐ Baseline ☐ Month 12

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 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.

Biofluids: Collection, Processing And Shipment

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 ADNI GO EDC system 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 Month 12 across all ADNI GO subjects. 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 and securely place the label onto each tube before the blood draw.

ADNI-GO ____ -S- ____
Year of Birth ____ Gender: M / F
Collection Date: Mo. / Day / Year
Subject Type: ☐ EMCI ☐ Follow-Up ADNI Subject
Visit: ☐ Baseline ☐ Month 12

Please note that the visit field “**Month 12**” refers to the Month 12 visit for EMCI subjects **AND** the subsequent annual visit for the continuing subjects from ADNI 1 after their initial ADNI GO visit. If the label you are using includes protocol (ADNI-GO or ADNI2) indicate the protocol this visit was conducted under.

BLOOD COLLECTION:

3 x 2.5 mL PAXgene Blood RNA tubes will be collected at Baseline and “Month 12” visits using the RNA sample collection kit provided by the ADCS.

- 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.

Training video on how to perform a PAXgene blood draw:
http://www.preanalytix.com/videos/PAXgene_Collect_lg.wmv



How to Collect Blood Using the PAXgene Blood RNA Tube

For Molecular Diagnostic Testing

1

A: Discard Tube
B: PAXgene Blood RNA Tube
C: BD Vacutainer Safety-Lok[™] Blood Collection Set
D: Single-use holder (Ref# 364815)

2

A: BD Vacutainer Safety-Lok Blood Collection Set
B: PAXgene Blood RNA Tube

3

4

x 10

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.*

Before Blood Collection

RNA Stabilization Reagent

Ref# 762165

After Blood Collection

RNA Stabilized Whole Blood

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.
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Biofluids: Collection, Processing And Shipment

RNA SAMPLES (Cont'd)

COMPLETION OF SAMPLE COLLECTION: APOE/GWAS/RNA 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 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
Tel: (800) 526-2839
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 pack(s).

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 the following Monday for Friday study visits. One shipper would include an ice pack 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: ApoE/GWAS/RNA 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 ApoE/GWAS/RNA electronic case report form located in the ADNI GO EDC system 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
(EMCI Baseline Only)



RNA
Tubes



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

*ApoE genotyping will only be done for the newly enrolled EMCI subjects

1b. Fill out NCRAD label and attach to each tube prior to collecting sample.

ADNI-GO ____ -S- ____

Year of Birth ____ Gender: M / F

Collection Date: ____ / ____ / ____

Subject Type: ☐ EMCI ☐ Follow-Up ADNI Subject

Visit: ☐ Baseline ☐ Month 12

2. Genetics samples shipping supplies



INCLUDES:

- 1 medium 95kPa canister,
- Aquipak 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 canister in bubble wrap

List of Contents

This item list must be placed between the secondary receptacle(s) and outer packaging in accordance with IATA Packing Instruction 650.

<input checked="" type="checkbox"/> Diagnostic Specimens	<input type="checkbox"/> Absorbent Pad(s)
<input checked="" type="checkbox"/> (Human, No Animal Matter)	<input type="checkbox"/> Requisition
<input checked="" type="checkbox"/> Glass and/or Plastic Tubes	<input type="checkbox"/> Instruction Sheet
<input checked="" type="checkbox"/> Glass Slides/Slide Mailer	<input type="checkbox"/> Transport Media or Preservative
<input checked="" type="checkbox"/> Tube Separator Bag(s)	<input type="checkbox"/> Dry Ice
<input checked="" type="checkbox"/> Secondary Container/Canister	<input type="checkbox"/> Gel Pack/Refrigerant
<input type="checkbox"/> Other	

Therapak Corporation

54765

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 month 12 visits for EMCI subjects. For ADNI 1 follow up subjects plasma and serum for biomarkers will be collected at their initial ADNI GO visit and their annual follow up visit (referred to in the protocol as baseline and month 12).

All biomarker samples must 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.

An initial supply of Biomarker Lab Kits will be sent to each site upon approval to screen participants. Detailed processing information will be required for these samples.

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!**

Subject ID #	_____ S _____
Time	____:____
Date	____/____/____
Circle : M or F	
Biomarkers	
ADNI	
Lavender Cap	716832
Vst 7/Month 36	
BLD EDT	

Biofluids: Collection, Processing And Shipment

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 clean transfer 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 clean transfer 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

CEREBROSPINAL FLUID COLLECTION:

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

Next, complete the information on the UPENN label for CSF collection. Ensure all fields on the CSF label are complete and place each of these on two 13 mL polypropylene transfer tubes (clear screw cap) **PRIOR** to transfer of CSF samples.

ADNI Subject ID #: ____ S ____ Gender: M or F Date ____ / ____ / ____ Time ____ : ____ Visit #: ____ Month ____ Sample Type: CSF License Plate Number: _____	Subject ID #: ____ S ____ Time ____ : ____ Date ____ / ____ / ____ Circle: M or F Biomarkers ADNI VST 2/Baseline Clear Cap CSF NON 221296 
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PLEASE NOTE: There are 2 different CSF labels. The one on the left above is to be used for ADNI 1 subjects switching into ADNI GO. On this label please indicate the visit number and number of months from ADNI 1 baseline (e.g., Visit 8 Month 48). 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 eMCI subjects, as it is pre-printed for 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).
- For those instances in which a Friday study visit is necessary, **be sure to clearly check Saturday Delivery on the FedEx form and apply orange "Saturday Delivery" labels prominently to the package.**
- 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 ADNI GO EDC system (**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



Biofluids: Collection, Processing And Shipment

SUPPLIES FOR BIOMARKER SAMPLES FROM ADCS:

USING THE EXTENSION TUBE (suction collection only):



After inserting Sprout 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.

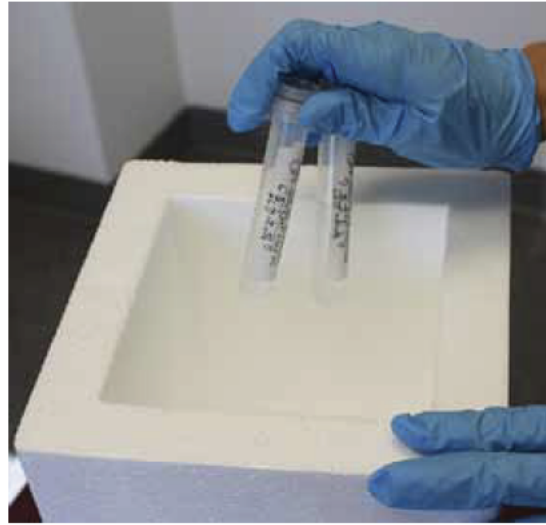


Biofluids: Collection, Processing And Shipment

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.

Biofluids: Collection, Processing And Shipment

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 cardboard 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 EMCI subjects at the Baseline Visit. CSF will be collected from all ADNI 1 follow-up subjects who are willing at their initial ADNI GO visit. 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.

Biofluids: Collection, Processing And Shipment

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.

Initial supply of Lumbar Puncture Materials (provided by the ADCS) for sites using DRIP:

- (4) - Smith's Lumbar Puncture Trays*
- (4) - 22g Sprotte Atraumatic Spinal Needles and Introducers
- (4) - 25g 1 1/2" needles for deep local anesthesia
- (16) - 7 cc sterile polypropylene collection tubes
- (8) - 13 mL transfer tubes with clear caps
- (8) - 2 mL cryogenic vial (for local laboratory testing)
- (16) - Pipette (for transferring CSF from collection to shipping tubes)

Initial supply of Lumbar Puncture Materials (provided by the ADCS) for sites using SUCTION:

- (4) - Smith's Lumbar Puncture Trays*
- (4) - 25g 1 1/2" needles for deep local anesthesia
- (20) - 5 cc sterile syringes
- (8) - 13 mL transfer tubes with clear caps
- (8) - 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.**

- 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**)
- Infiltration needle (25g x 1/2") for skin infiltration for local anesthesia
- 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

Please note all Smith's lumbar puncture trays contain the following items: introducer needle, 24g Sprotte needles, and extension tube.

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

* The Smith's LP trays are not approved for use in Canada. Canadian sites will receive LP trays similar to those used in ADNI 1. The same recommendation applies (22g Sprotte needle using the gravity method).

Biofluids: Collection, Processing And Shipment

LUMBAR PUNCTURE SUPPLIES (Cont'd)

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

Biofluids: Collection, Processing And Shipment

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.

Biofluids: Collection, Processing And Shipment

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.

Biofluids: Collection, Processing And Shipment

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.

Biofluids: Collection, Processing And Shipment

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

ALIUOTTING 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. Keep ambient, enter results on the CSF Local Labs results eCRF.
 - ➡ 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 **ambient** 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 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 ADNI-GO EDC as soon as they are received.

Biofluids: Collection, Processing And Shipment

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: Collection, Processing And Shipment

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

EMCI Screening Procedures

SUMMARY

The purpose of the ADNI GO screening will be to confirm eligibility for the study. The diagnostic category of EMCI (Early Mild Cognitive Impairment) is new and not every person identified as MCI will qualify for the study. Ask potential participants to bring with them copies of medical records and any medications that they are currently taking.

The following items will be covered in this section:

PARTICIPANT IDENTIFIERS

DATAFLOW

SCREEN FAILURES AND RESCREENS

INCLUSION CRITERIA

EXCLUSION CRITERIA

EXCLUDED MEDICATIONS

PERMITTED MEDICATIONS

SCREENING ASSESSMENTS

SCREENING BLOOD DRAWS

NOTIFICATION OF PRIVATE MD

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.

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. Subjects from ADNI 1 began at 0001. EMCI Participants enrolled into ADNI GO will begin at 2001.

Example: A participant from site 900 who is the third subject assigned for ADNI GO is: 900-S-2003.

Use the Subject 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.

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.


EMCI Screening Procedures




To assign an ADNI PTID for new EMCI Participants:

- ➡ Log on to the ADNI Clinical Data Portal (adcs.org/ADCS Investigators/Study Resources/ADNI GO EDC).
- ➡ 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.

ADNIGO > TEST > Participant Menu

 Add a New Participant

Please select a participant from the following list:

Participant	Status	Last Visit
TST_S_9002		

Register Participant

New participant registered: TST_S_9509

Please click [here](#) to start entering data.

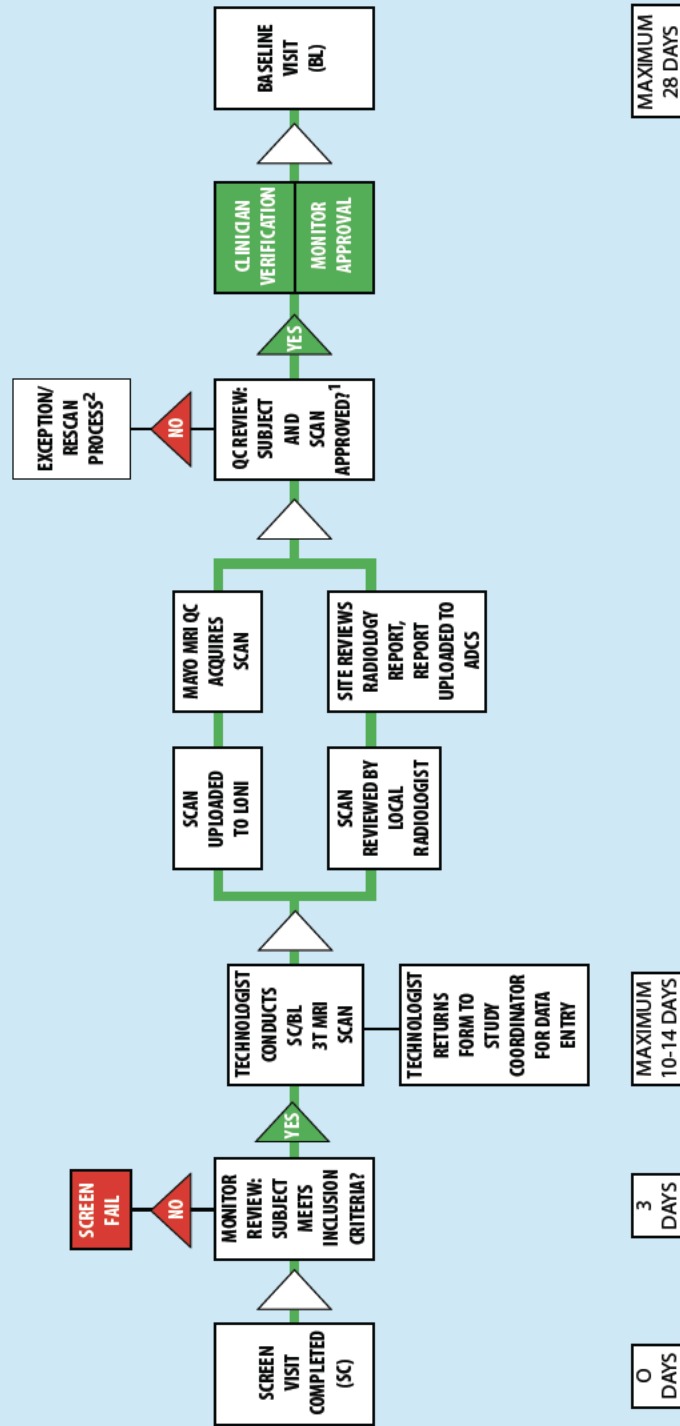
Please note, that the ADNI-GO web portal is separate from the ADNI web portal. Within 48 hours of site approval, all team members will be sent their username and temporary password for the ADNI GO EDC.

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 ADNI-GO visit (even if the participant screen fails).
3. The examination date is the date the first part of the ADNI GO screening visit was completed.

You will see a question that states "Would you like to change this visit's track or the participant's visit schedule" and it defaults to "no". Do not modify this item as it is NOT applicable for new EMCI screening visits.

Screening Process



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.

EMCI Screening Procedures

DATA FLOW

Please see the dataflow 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 ADNI GO Clinical Data Portal within 3 business days of screen ([adcs.org/ADCS Investigators/Study Resources/ADNI GO EDC](https://adcs.org/ADCS_Investigators/Study_Resources/ADNI_GO_EDC)).
- Upload worksheets in the Administration Portal ([adcs.org /ADCS investigators / study resources / ADCS Admin Portal / Study File Upload](https://adcs.org/ADCS_investigators/study_resources/ADCS_Admin_Portal/Study_File_Upload)).

Enter Clinician Eligibility after completing review of all required Screening Assessments.

THE FOLLOWING WORKSHEETS MUST BE UPLOADED FOR MONITOR REVIEW OF SCREEN:

- MMSE
- Logical Memory (I and II)
- CDR Worksheets
- Concurrent medications
- Under Miscellaneous upload all remaining Screening Visit worksheets: Participant Demographics, Medical History, GDS, Modified Hachinski, Physical and Neurological Exam

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.

EMCI Screening Procedures



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/ADCS Investigators/ Study Resources/ADNI GO EDC](https://adcs.org/ADCS_Investigators/Study_Resources/ADNI_GO_EDC)).
- 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/ADCS investigators/study resources/ADCS Admin Portal/Study File Upload](https://adcs.org/ADCS_investigators/study_resources/ADCS_Admin_Portal/Study_File_Upload)). Ensure any identifiers are blacked out on the copy uploaded to the ADCS including Medical Record #s, telephone numbers, and date of birth.

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!

EMCI Screening Procedures

SCREEN FAILURES AND RESCREENS

All participants who sign consent must be assigned an ADNI GO 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 ADNI GO Participant ID (PTID). Ensure Clinician Verification for initial PTID is entered as 'ineligible'. Indicate under Visit Comments in the new ID that the participant has been screened before and provide the previous ADCS PTID. The new PTID should be used on all screen documents, image file headers and biofluid samples.

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.

INCLUSION CRITERIA

1. Participant must have a memory complaint by subject or study partner that is verified by a study partner.
2. Abnormal memory function documented by scoring below the education adjusted cutoff on the Logical Memory II subscale (Delayed Paragraph Recall) 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.
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.
4. Clinical Dementia Rating = 0.5. Memory Box score must be at least 0.5.
5. 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.

EMCI Screening Procedures



6. Stability of Permitted Medications for 4 weeks. In particular, participants 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.
7. Geriatric Depression Scale less than 6.
8. Age between 55-90 (inclusive).
9. 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.
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. Six grade 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 banking.
19. Agrees to collection of blood for biomarker testing.
20. Agrees to at least one lumbar puncture for the collection of CSF.

EXCLUSION CRITERIA

1. 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

EMCI Screening Procedures

hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic deficits or known structural brain abnormalities.

2. Screening/baseline MRI scans 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.
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).
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 18F –AV-45: Current or recent participation in any procedures involving radioactive agents such that the total radiation dose exposure to the subject 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).

EXCLUDED MEDICATIONS

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.

EMCI Screening Procedures

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, selegiline) 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.

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.

EMCI Screening Procedures

EXCLUDED MEDICATIONS

Please note: This is not a complete list of all excluded medications. For drugs not on this list, please bring to the attention of your monitor prior to screening.

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
Benztrapine	Cogentin
Cyproheptadine	Periactin
Dicyclomine	Bentyl
Diphenhydramine	Benadryl, Somnex 2
Diphenoxylate with atropine	Lomotil
Hydroxyzine	Vistaril, Atarax
Hyoscyamine	Levsin
Meclizine	Antivert, Bonine
Prochlorperazine	Compazine
Trihexyphenidyl	Artane
Trimethobenzamide	Tigan

EMCI Screening Procedures



ANTIPARKINSONIAN MEDICATIONS: NOT ALLOWED WITHIN 4 WEEKS PRIOR TO SCREENING:

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

INVESTIGATIONAL DRUGS: NOT ALLOWED WITHIN 4 WEEKS PRIOR TO SCREENING

SEDATIVES / BENZODIAZEPINES: NOT ALLOWED WITHIN 4 WEEKS PRIOR TO 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 prior to screening:

Clonidine	Catapres
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EMCI Screening Procedures

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
- Baseline Symptoms Log and Adverse Events
- Publicity Tracking
- MRI (3T) Only after Monitor approval of Screening Visit.

SCREENING BLOOD DRAWS

EMCI participants must have screening blood draws to aid in assessing eligibility. Please refer to the Clinical Laboratory Samples at Screening section in the Biofluid Section for more detailed information regarding clinical labs at the screening visit. Laboratory reports must be reviewed, signed and filed in the source documents for monitor review.

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.

EMCI Baseline and Follow-Up Visit Procedures

BASELINE VISIT:

KEY REMINDERS

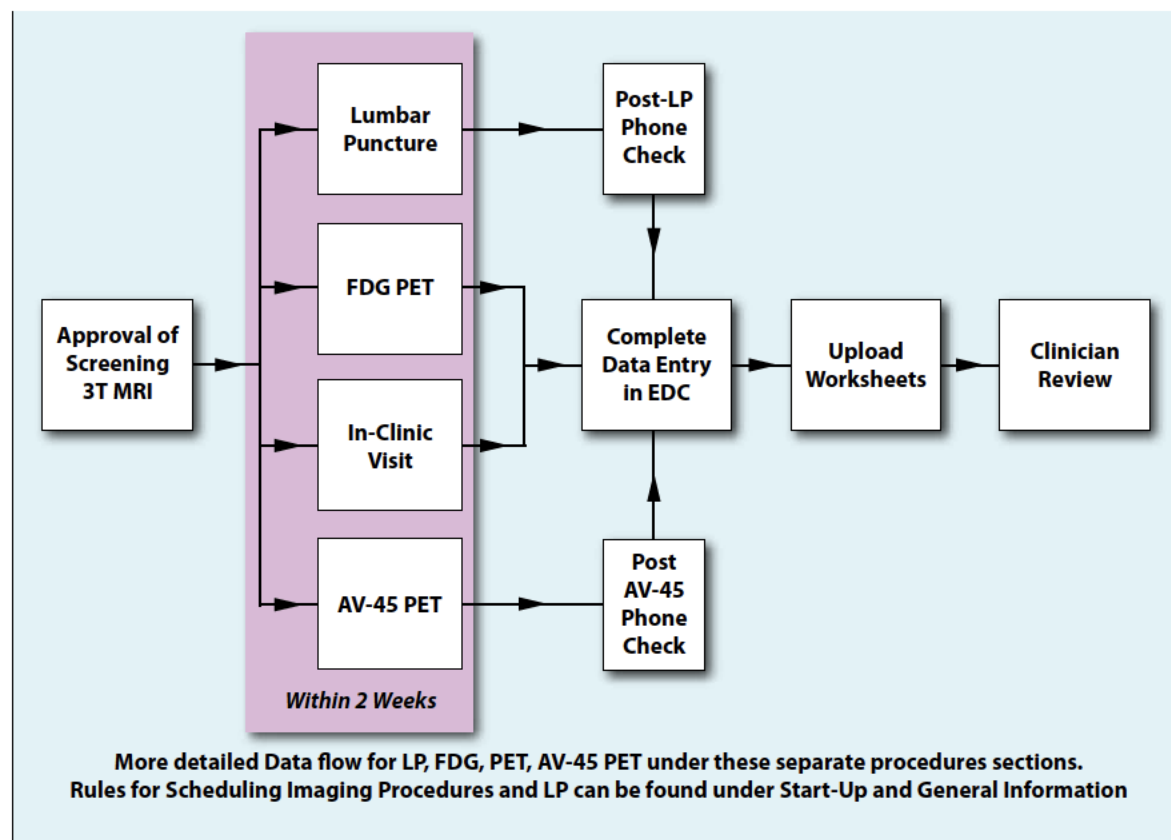
- The window from Screening to Baseline is 28 days.
- Participants must meet all inclusion/exclusion criteria.
- Complete Data Entry within 5 business days of the visit

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.



EMCI Baseline and Follow-Up Visit Procedures

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. 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 /ADCS investigators/study resources/ ADCS Admin Portal/Study File Upload](https://adcs.org/ADCS_investigators/study_resources/ADCS_Admin_Portal/Study_File_Upload)).

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 Q
- 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

* Fasting

THE FOLLOWING WORKSHEETS MUST BE UPLOADED FOR BASELINE:

- Neuropsychological Battery (include stimuli)
- Adverse Events/Hospitalizations Log
- Concurrent Medications
- ADAS (include stimuli, drawings)
- MRI

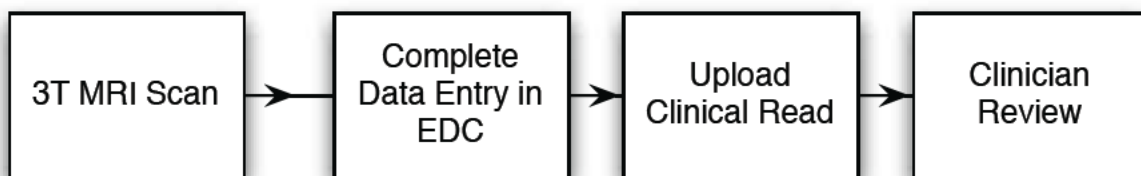
EMCI Baseline and Follow-Up Visit Procedures

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 /ADCS investigators/study resources/ ADCS Admin Portal/ Study File Upload](https://adcs.org/ADCS_investigators/study_resources/ADCS_Admin_Portal/Study_File_Upload)). 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

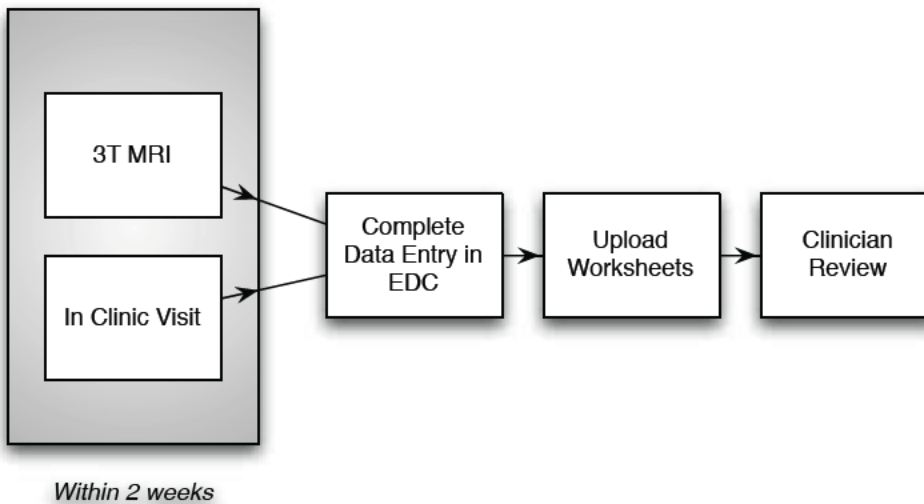
EMCI Baseline and Follow-Up Visit Procedures

MONTH 6 VISIT:

KEY REMINDERS

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

DATA FLOW



Plasma and Serum collected for Biomarker analysis are after at least a 6 hour fast. 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 /ADCS investigators/study resources/ ADCS Admin Portal/ Study File Upload](https://adcs.org/ADCS_investigators/study_resources/ADCS_Admin_Portal/Study_File_Upload)).

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

EMCI Baseline and Follow-Up Visit Procedures

MONTH 6 ASSESSMENTS (CONT)

- ➔ Vital Signs
- ➔ Concurrent Medications Review
- ➔ Diagnostic Summary
- ➔ Adverse Event Review
- ➔ Clinician Review

* Fasting

THE FOLLOWING WORKSHEETS MUST BE UPLOADED FOR MONTH 6:

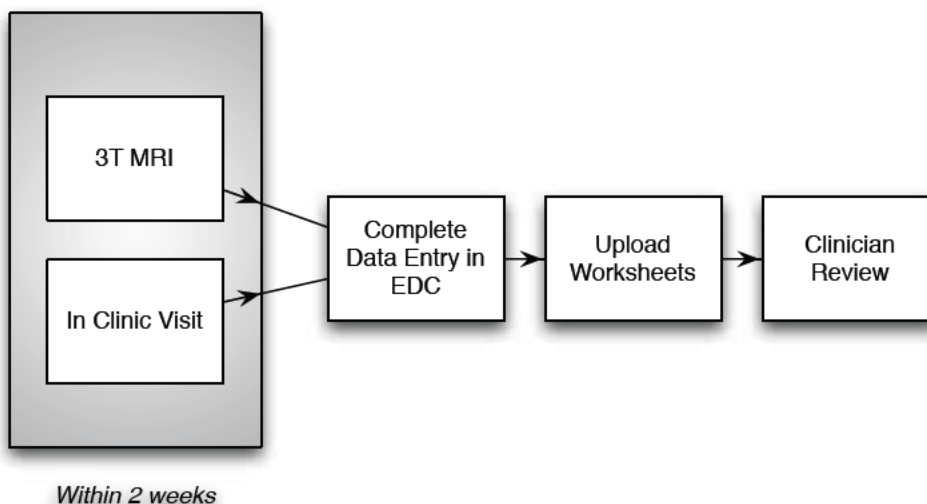
- ➔ CDR
- ➔ MMSE (include stimuli)
- ➔ Neuropsychological Battery (include stimuli)
- ➔ Adverse Events/Hospitalizations Log
- ➔ Concurrent Medications
- ➔ ADAS (include stimuli, drawings)
- ➔ MRI
- ➔ MRI Report: Site Clinical Read - 3.0T

MONTH 12 VISIT:

KEY REMINDERS

- ➔ The Month 12 visit is scheduled 12 months from the date of the Baseline in clinic visit

DATA FLOW



EMCI Baseline and Follow-Up Visit Procedures

Plasma and Serum collected for Biomarker analysis are after at least a 6 hour fast. 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 /ADCS investigators/study resources/ ADCS Admin Portal/ Study File Upload](https://adcs.org/ADCS_investigators/study_resources/ADCS_Admin_Portal/Study_File_Upload)).

MONTH 12 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 Q
- ➔ Functional Assessment Questionnaire
- ➔ 3T MRI Scan
- ➔ Vital Signs
- ➔ Concurrent Medications Review
- ➔ Diagnostic Summary
- ➔ Adverse Event Review
- ➔ Clinician Review

* Fasting

THE FOLLOWING WORKSHEETS MUST BE UPLOADED FOR MONTH 12:

- ➔ CDR
- ➔ Logical Memory
- ➔ MMSE (include stimuli)
- ➔ Neuropsychological Battery (include stimuli)
- ➔ Adverse Events/Hospitalizations Log
- ➔ Concurrent Medications
- ➔ ADAS (include stimuli, drawings)
- ➔ MRI
- ➔ MRI Report: Site Clinical Read - 3.0T

EMCI Baseline and Follow-Up Visit Procedures

MONTH 18 VISIT:

KEY REMINDERS

- The Month 18 visit is conducted over the telephone, scheduled 18 months from the date of the Baseline in clinic visit.
- The purpose of this visit is to retain contact with the participant and study partner to increase retention in the study.

DATA FLOW



Complete Data entry within 5 business days of the visit. Scan and Upload worksheets to the Administration Portal ([adcs.org /ADCS investigators/study resources/ ADCS Admin Portal/Study File Upload](https://adcs.org/ADCS_investigators/study_resources/ADCS_Admin_Portal/Study_File_Upload)).

MONTH 18 ASSESSMENTS

- Concurrent Medications Review
- Adverse Event Review
- Clinician Review

THE FOLLOWING WORKSHEETS MUST BE UPLOADED FOR MONTH 18:

- Adverse Events/Hospitalizations Log
- Concurrent Medications

ADNI 1 Follow-Up Visit Procedures

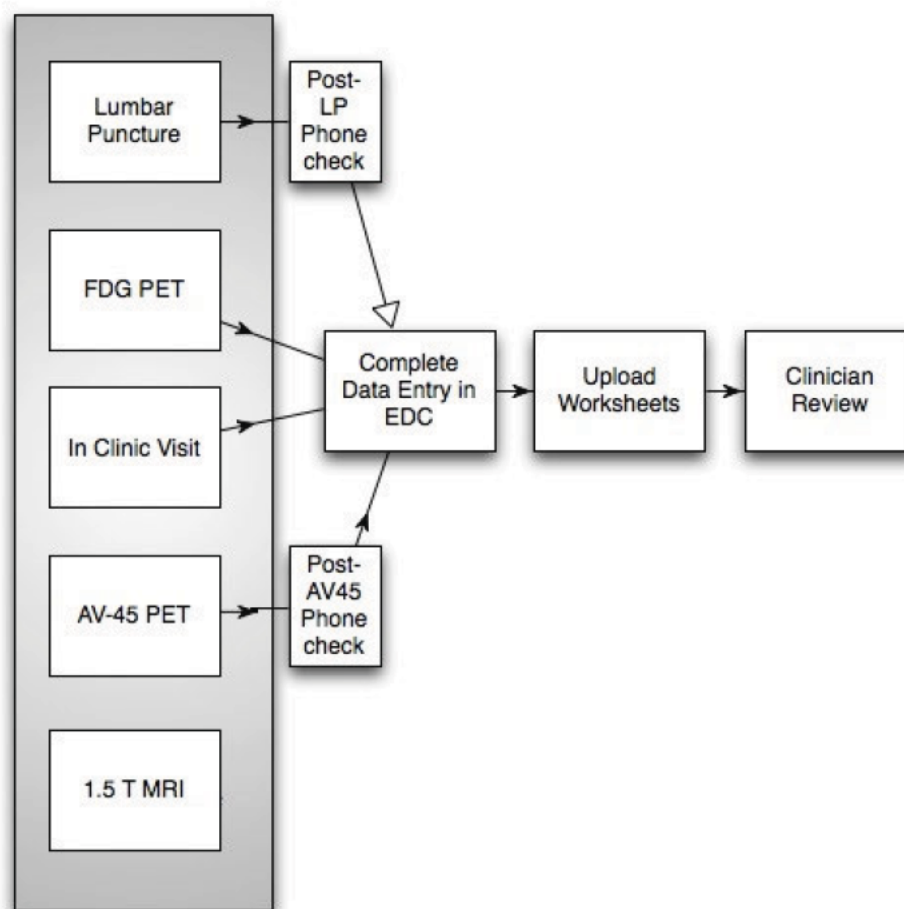
FOLLOW-UP VISIT 1:

KEY REMINDERS

- Participants originally enrolled as EMCI or Normal Control (NL), even if converted to AD during the course of ADNI1, are eligible to be followed under the ADNIGO protocol.
- ADNI1 participants should be approached at their annual in-clinic visit to enroll in ADNIGO.
- Participants must be asked if they will agree to all procedures, but if a participant does not agree to all procedures, he/she should still be followed.

Enter The 'Screening Visit' in the EDC to confirm Participant Demographics. This is not a separate visit.

DATA FLOW



More detailed Data flow for LP, FDG PET, AV45 PET under these separate procedures sections
Rules for Scheduling Imaging Procedures and LP can be found under Start up and General Information

Participant should enroll in the ADNIGO 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.

ADNI 1 Follow-Up Visit Procedures

Keep in mind that the CSF, Plasma and Serum collected for Biomarker analysis are after at least a 6 hour fast. 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 /ADCS investigators/study resources/ ADCS Admin Portal/ Study File Upload](https://adcs.org/ADCS_investigators/study_resources/ADCS_Admin_Portal/Study_File_Upload)).

FOLLOW UP VISIT 1 ASSESSMENTS

- ➔ Plasma and Serum Biomarker Collection *
- ➔ CSF Collection *
- ➔ Genetic Sample Collection (DNA, 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 Q
- ➔ Functional Assessment Questionnaire
- ➔ Medical History
- ➔ Physical and Neurological Exam
- ➔ Vital Signs
- ➔ Concurrent Medications Review
- ➔ Diagnostic Summary
- ➔ Adverse Event
- ➔ 1.5 T MRI Scan (3T Scans are done only at MRI Core request)
- ➔ FDG PET Scan *
- ➔ AV-45 PET Scan
- ➔ AV-45 24-48 Hour Follow-Up
- ➔ Post LP phone call
- ➔ Clinician Review

* Fasting

THE FOLLOWING WORKSHEETS MUST BE UPLOADED FOR FOLLOW UP VISIT 1:

- | | |
|--|---|
| ➔ CDR | ➔ Concurrent Medications |
| ➔ Logical Memory | ➔ ADAS (include stimuli, drawings) |
| ➔ MMSE (include stimuli) | ➔ MRI |
| ➔ Neuropsychological Battery (include stimuli) | ➔ MRI Report: Site Clinical Read - 1.5T |
| ➔ MoCA | |
| ➔ ADAS-Cog 13 | |
| ➔ Adverse Events/Hospitalizations Log | |

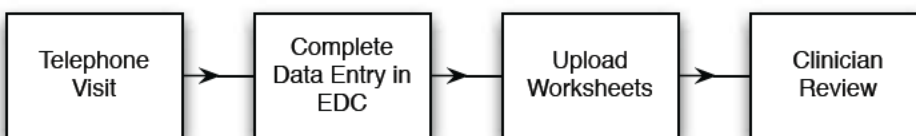
ADNI 1 Follow-Up Visit Procedures

FOLLOW-UP VISIT 1:

KEY REMINDERS

- The Follow up Interim Telephone Check is conducted over the telephone, scheduled 6 months from the target date of the annual visit.
- The purpose of this visit is to retain contact with the participant and study partner to increase retention in the study.
- The next annual visit for these participants should be conducted under the ADNI 2 protocol. If your site does not have approval for this, please email adcs-clinops@ucsd.edu.

DATA FLOW



Complete Data entry within 5 business days of the visit. Scan and Upload worksheets to the Administration Portal ([adcs.org /ADCS investigators/study resources/ ADCS Admin Portal/ Study File Upload](https://adcs.org/ADCS_investigators/study_resources/ADCS_Admin_Portal/Study_File_Upload)).

INTERIM PHONE CHECK ASSESSMENTS

- Concurrent Medications Review
- Adverse Event Review
- Clinician Review

THE FOLLOWING WORKSHEETS MUST BE UPLOADED FOR INTERIM PHONE CHECKS:

- Adverse Events/Hospitalizations Log
- Concurrent Medications

Cognitive Assessments

General Guidelines

The goal of ADNI GO 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 ADNI GO 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, 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.

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.

ADNI 1 FOLLOW-UP SUBJECTS

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)

EMCI AND ADNI 1 SUBJECTS

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)

EMCI SUBJECTS

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). Avoid any verbal memory tests during this period, including the MMSE and CDR. Other activities (including depression questionnaire (GDS), patient demographics etc.) are permissible.]*
- Logical Memory II (30-40 minute delay)

EMCI Subjects 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)

EMCI Subjects 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)

Cognitive Assessments

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 formal testing begins, engage the Participant in a short conversation about neutral topics (*i.e.*, weather, the Participant's trip to the clinic, or what the Participant had for breakfast). 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.

The rating of the Participant's language ability (*i.e.*, spoken language, word finding 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.

**Adapted from the Administration and Scoring Manual for the
Alzheimer's Disease Assessment Scale,
1994 Revised Edition, Richard C. Mohs, Ph.D. Copyright © 1994 by
The Mount Sinai School of Medicine**

**Present manual modified by:
Donald Connor, Ph.D., Ph.D.
Kimberly Schafer, M.S.
(3/98)**

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.

EMCI	VISIT	LIST
	BL	LIST 1
	M6	LIST 2
	M12	LIST 1
ADNI 1 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.).
- ➔ 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: 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

Cognitive Assessments

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."

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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 send the envelope, or a copy of the envelope, to the ADCS Coordinating Center. Clinical Monitors 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
- Day of the Week
- Month
- Date
- Year
- Season
- Time of Day
- 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 below.

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 one week prior to onset or within two weeks after termination.
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").

For 2011:	
Winter =	12/22/10 – 3/19/11
Spring =	3/20 – 6/20
Summer =	6/21 – 9/22
Fall =	9/23 – 12/21
For 2012:	
Winter =	12/22/11 – 3/19/12
Spring =	3/20 – 6/19
Summer =	6/20 – 9/21
Fall =	9/22 – 12/21
For 2013:	
Winter =	12/21/12 – 3/19/13
Spring =	3/20 – 6/20
Summer =	6/21 – 9/22
Fall =	9/23 – 12/20
For 2014:	
Winter =	12/21/13 – 3/19/14
Spring =	3/20 – 6/20
Summer =	6/21 – 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.



Cognitive Assessments

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 E DC 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 matches 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

Cognitive Assessments

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 the higher scores (4-5) on 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 face up in front of the participant and say:	<p>"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..."</p> <p>(point to the beginning of the first line),</p> <p>"...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."</p>
--	---

Discontinue the example after 30 seconds.

TASK INSTRUCTIONS

Place the form face up in front of the participant and say:	<p>"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..."</p> <p>(point to the beginning of the first line),</p> <p>"...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."</p>
If the first cancellation done by the participant is incorrect, say:	<p>"These are the correct numbers to cross out," and point to the numbers at the top of the page in the heading.</p>

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:

- Follow-Up participants will complete Version A annually.
- EMCI participants will complete version A at Baseline, B at Month 6, and A at Month 12.

Cognitive Assessments

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 must complete the Standardization/Certification Questionnaire.

To request an ADAS Certification Package:

Email the ADCS Helpdesk:
adcs-clinops@ucsd.edu

Cognitive Assessments

American National Adult Reading Test (ANART) - Instructions

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 - Instructions

BOSTON NAMING TEST (BNT) - 30 ODD ITEMS

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).

Cognitive Assessments

Boston Naming Test - Instructions (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 ECRF.

- 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. 'escalator'), 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.

Cognitive Assessments

Category Fluency Test - Instructions

CATEGORY FLUENCY TEST

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

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:

[SAY]: **"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:

[SAY] **"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.

Cognitive Assessments

Category Fluency Test - Instructions

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 - Instructions

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 subject. To begin, present the participant with a felt-tipped pen (or a pencil without an eraser) and an 8 1/2" x 11" blank sheet of white paper and say, "Draw the face of a clock showing the numbers and two hands set to ten after eleven." Allow the participant to work without feedback; interrupt only if the patient starts to scratch out or destroy any of their drawing. If the participant tries to erase or scratch out an error, immediately intervene and gently instruct them to try again by saying, "Don't take the time to make corrections." While pointing to a clean area of the paper, say, "You may start over here and draw the clock again. Remember you are to draw the face of a clock showing the numbers and two hands set to ten after eleven." Allow only two attempts on the clock drawing task. If a participant needs an additional reminder about the specific time that is to be indicated on the clock, the examiner may repeat the time again, e.g., "set the clock to ten after eleven." Although this task is not timed, keep the participant actively engaged in the task; the examiner may use their clinical judgment as to when the task should be abandoned in order to spare the participant undue anxiety or frustration when they are unable to perform the clock drawing task.

Clock Copying Administration

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

Allow the participant to work without feedback; interrupt only if the patient starts to scratch out or destroy any of their drawing. If the participant tries to erase or scratch out an error, immediately intervene and gently instruct them to try again. Allow only two attempts on the clock copying task. Although this task is not timed, keep the participant actively engaged in the task; the examiner may use their clinical judgment as to when the task should be abandoned in order to spare the participant undue anxiety or frustration when they are unable to perform the clock copying task.

Scoring

Cognitive Assessments

Clock Drawing Test - Instructions (Cont'd)

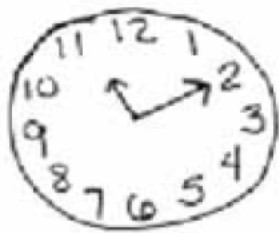
Clock drawings from both the command and copy conditions are scored in the same manner. Determine if each of the criteria listed below has been met:

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 could 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.

Cognitive Assessments

Clock Drawing Test - Instructions (Cont'd)

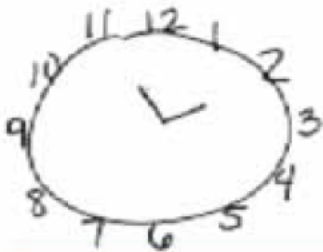


5 points



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 - Instructions

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

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

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 ADNI GO, 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 the testing worksheets and are to be read verbatim.

Say, “I am going to read to you a little story of just a few lines. Listen carefully and try to remember it just the way I say it, as close to the same words as you can remember. When I am through I want you to tell me everything I read to you. You should tell me all you can remember even if you are not sure. Are you ready?”

When the examiner has finished reading the story, say to the participant, “Now what did I read to you? Tell me everything and begin at the beginning.”

Always permit the participant to include additional information by prompting with “Anything else?” Record any additional “bits of information” and score appropriately.

After the participant appears to be able to recall no more of the story, say, “Later on I will ask you to tell me this story again, so try not to forget it.”

RECORDING

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

SCORING

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

Cognitive Assessments

Logical Memory - Instructions (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 testing 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.

Cognitive Assessments

Mini Mental State Exam - Instructions

MINI-MENTAL STATE EXAM (MMSE)



ORIENTATION

[Redacted text for Orientation section]

IMMEDIATE RECALL

[Redacted text for Immediate Recall section]

ATTENTION

[Redacted text for Attention section]

DELAYED RECALL

[Redacted text for Delayed Recall section]

LANGUAGE NAMING

[Redacted text for Language Naming section]

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Cognitive Assessments

Mini Mental State Exam - Instructions (Cont'd)



COMMAND

[Redacted text block for COMMAND section]

REPETITION

[Redacted text block for REPETITION section]

READING

[Redacted text block for READING section]

WRITING

[Redacted text block for WRITING section]

CONSTRUCTION

[Redacted text block for CONSTRUCTION section]

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.

Cognitive Assessments

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.

Cognitive Assessments

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).

Cognitive Assessments

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.

Cognitive Assessments

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

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 - Instructions

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

REY AUDITORY VERBAL LEARNING TEST (AVLT)

This is a test of episodic memory that assesses the ability to acquire 15 words across five immediate learning trials, to recall the words immediately after an intervening interference list, and to recall and recognize the words after a 30-minute delay interval.

For 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 - Instructions

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 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.

SOURCE

This test, originally called Partington's Pathways, was a component of the Army Individual Test Battery. It was popularized by Reitan and colleagues and subsequently became part of the Halstead-Reitan Neuropsychological Battery. The instructions for administration are adapted from Spreen and Strauss.

ADMINISTRATION

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

[SAY]: "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.

Cognitive Assessments

Trail Making Test - Instructions (Cont'd)



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

[SAY]: “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 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 subject 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 subject 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 subject 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

CLINICAL DEMENTIA RATING (CDR)

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

The scores acquired from the CDR are key for inclusion criteria in the EMCI group and are critical for detecting conversion to another diagnosis. The CDR is conducted at Screening, Month 6 and then annually. For ADNI 1 follow-up participants, the CDR is conducted at all annual visits.

CDR RATER

CDR certification is required prior to administering the CDR for ADNI GO. 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/>. 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 858-452-0573.

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. The Protocol PI will be available to site personnel and PIs to assist in any part of this process.

- 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.

Global, Functional, and Behavioral Assessments

DETERMINING GLOBAL CDR SCORE

The eCRF will automatically calculate the global CDR as data is entered.

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.

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.

To verify the global CDR, you may also access the Washington University CDR web page: <http://alzheimer.wustl.edu/cdr/application/step1.htm>.

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. The ECog (participant and study partner) are conducted at Baseline, Month 6 and then annually for EMCI participants. For ADNI 1 follow-up participants, the ECog is conducted at all annual visits.

- ➡ Participants and their study partners will independently complete a separate questionnaire, within the clinic, at the time of their ADNI GO 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 JJ, 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 meant to The GDS is conducted at Screening, Month 6 and then annually for EMCI participants. For ADNI 1 follow-up participants, the GDS is conducted at all annual visits. should be administered by site staff as a direct interview with the participant. The form should not be administered to the study partner.

INSTRUCTIONS

"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."

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 then annually for EMCI participants. For ADNI 1 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.

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 EMCI 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'.

Global, Functional, and Behavioral Assessments

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 Neuropsychometric Inventory. The NPI-Q is conducted at Baseline, Month 6 and then annually for EMCI participants. For ADNI 1 follow-up participants, the NPI-Q is conducted at all annual visits.

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.