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STUDY SUPPLIES

Case Report Forms, Stimuli & Worksheets for Psychometric Testing:
https://adni.ucsd.edu
ADCS Supplied Materials can be requested by sending a supply request form to:
support@adni.ucsd.edu

Clinical Laboratory and Biomarker Kits:
Covance Laboratory
(800) 327-7270

HELP DESKS

ADNI Central Help Desk:
https://adni.ucsd.edu under 'Help'

LONI Help Desk:
adni@loni.ucla.edu

MRI Help Desk:
ADNIMRI@mayo.edu

PET Help Desk:
adnipet@adni.ucsd.edu

Biomarkers Help Desk:
adni@uphs.upenn.edu

Coordinating Center Support:
support@adni.ucsd.edu

NCRAD Help Desk:
alzstudy@iupui.edu

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If you have an urgent question please contact your clinical monitor or phone the central ADCS number: 858-622-5895 x 1895 (8:00 am - 4:00 pm Pacific Standard Time). If there is an emergency, and you are unable to make any contacts, please phone or page Dr. Weiner.

ADNI Protocol

Title	**Alzheimer's Disease Neuroimaging Initiative (ADNI)**
Primary Objectives	The major goals of the ADNI are to:

1. Develop improved methods which will lead to uniform standards for acquiring longitudinal, multi-site MRI and PET data on patients with Alzheimer's disease (AD), mild cognitive impairment (MCI), and elderly controls.

2. Acquire a generally accessible data repository which describes longitudinal changes in brain structure and metabolism. In parallel, acquire clinical cognitive and biomarker data for validation of imaging surrogates.

3. Develop methods which will provide maximum power to determine treatment effects in trials involving these patients.

4. Test a series of hypotheses based on the clinical and biomarker data as outlined in the statistical analysis section.

Study Design	This is a non-randomized natural history non-treatment study in which a total of 800 subjects including 200 normal controls, 400 individuals with MCI, and 200 subjects with mild AD will be recruited at approximately 50 sites in the United States and Canada for longitudinal follow up.
Sample Size	Eight hundred subjects from 50 sites from the United States and Canada.
Key Eligibility Criteria	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. Between twenty and fifty percent must be willing to undergo two lumbar punctures, spaced one year apart. Specific psychoactive medications will be excluded. General inclusion/exclusion criteria are as follows:

1. Normal subjects: MMSE scores between 24-30 (inclusive), a CDR of 0, non-depressed, non MCI, and nondemented. The age range of normal subjects will be roughly matched to that of MCI and AD subjects. Therefore, there should be minimal enrollment of normals under the age of 70.

2. MCI subjects: MMSE scores between 24-30 (inclusive), a memory complaint, have objective memory loss measured by education adjusted scores on Wechsler Memory Scale Logical Memory II, 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.

3. Mild AD: MMSE scores between 20-26 (inclusive), CDR of 0.5 or 1.0, and meets NINCDS/ADRDA criteria for probable AD.

Procedures

All subjects will have clinical/cognitive assessments and 1.5 T structural MRI at specified intervals (6 or 12 month) for 2-3 years. Approximately 50% of subjects will also have FDG PET scans at the same time intervals and 25% of subjects (who have not been scanned using PET) will have MRI at 3 Tesla.

AD subjects (n=200) will be studied at 0, 6, 12, and 24 months. MCI subjects at high risk for conversion to AD (n= 400) will be studied at 0, 6, 12, 18, 24 and 36 months. Age matched controls (n=200) will be studied at 0, 6, 12, 24 and 36 months. 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 the ADCS. U Penn will collect biomarker samples. All raw and processed image data will be archived at LONI.

Outcome Measures

1. Rate of conversion from MCI to AD.

2. Rate of volume change of whole brain, hippocampus, and entorhinal cortex.
3. Rates of change for each specified biomarker.
4. Rates of change of glucose metabolism for specified regions of interest on PET scanning.
5. Group differences for each imaging and biomarker measurement.
6. Tensor based and voxel based morphometric maps.

Safety Parameters

Adverse events, symptom checklist, vital signs, physical,neurological examination and laboratory tests.

Statistical Considerations

As specified in the protocol. Additionally, many other statistical analyses not specified in the protocol will be carried out on this data set.

Sponsors

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University of California, San Diego

SCHEDULE OF ASSESSMENTS: NORMAL SUBJECTS

	Screen	Baseline	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36
Explain Study	●							
Obtain Consent	●							
Demographics, Family History, Inclusion and Exclusion Criteria	●							
Medical History, Physical Exam, Neurological Exam, Hachinski	●							
Vital Signs	●	●	●	●		●		●
Screening Labs	●							
APOE	●							
American National Adult Reading Test		●						
Mini Mental State Examination	●		●	●		●		●
Logical Memory I and II	●			●		●		●
Digit Span		●	●	●		●		●
Category Fluency		●	●	●		●		●
Trails A & B		●	●	●		●		●
Digit Symbol		●	●	●		●		●
Boston Naming Test		●	●	●		●		●
Auditory Verbal Learning Test		●	●	●		●		●
Geriatric Depression Scale	●			●		●		●
Clock Drawing		●	●	●		●		●
Neuropsychiatric Inventory Q		●	●	●		●		●
ADAS-Cog		●	●	●		●		●
Clinical Dementia Rating Scale	●		●	●		●		●
Activities of Daily Living (FAQ)		●	●	●		●		●
Collect and Process Biomarkers		●*	●	●		●		●
Concomitant Medications	●	●	●	●		●		●
Subject Payments	●	●	●	●		●		●
Phone Contact					●		●	
Adverse Events	●	●	●	●	●	●	●	●
Diagnostic Summary		●	●	●		●		●
MRI (1.5 T) (100%)	●**		●	●		●		●
MRI (3 T) (25%)		●	●	●		●		●
PET (50%)		●	●	●		●		●
L.P. (minimum of 20%)		●		●				

* Includes blood draw for Immortalized cell lines.
** Screening 1.5T MRI becomes Baseline 1.5T MRI after approval.

SCHEDULE OF ASSESSMENTS: MCI SUBJECTS

	Screen	Baseline	Month 6	Month 12	Month 18	Month 24	Month 30	Month 36
Explain Study	●							
Obtain Consent	●							
Demographics, Family History, Inclusion and Exclusion Criteria	●							
Medical History, Physical Exam, Neurological Exam, Hachinski	●							
Vital Signs	●	●	●	●	●	●		●
Screening Labs	●							
APOE	●							
American National Adult Reading Test		●						
Mini Mental State Examination	●		●	●	●	●		●
Logical Memory I and II	●			●		●		●
Digit Span		●	●	●	●	●		●
Category Fluency		●	●	●	●	●		●
Trails A & B		●	●	●	●	●		●
Digit Symbol		●	●	●	●	●		●
Boston Naming Test		●	●	●	●	●		●
Auditory Verbal Learning Test		●	●	●	●	●		●
Geriatric Depression Scale	●			●		●		●
Clock Drawing		●	●	●	●	●		●
Neuropsychiatric Inventory Q		●	●	●	●	●		●
ADAS-Cog		●	●	●	●	●		●
Clinical Dementia Rating Scale	●		●	●	●	●		●
Activities of Daily Living (FAQ)		●	●	●	●	●		●
Collect and Process Biomarkers		●*	●	●	●	●		●
Concomitant Medications	●	●	●	●	●	●		●
Subject Payments	●	●	●	●	●	●		●
Phone Contact							●	
Adverse Events	●	●	●	●	●	●	●	●
Diagnostic Summary		●	●	●	●	●		●
MRI (1.5 T) (100%)	●**		●	●	●	●		●
MRI (3 T) (25%)		●	●	●	●	●		●
PET (50%)		●	●	●	●	●		●
L.P. (minimum of 20%)		●		●				

* Includes blood draw for Immortalized cell lines.
** Screening 1.5T MRI becomes Baseline 1.5T MRI after approval.

SCHEDULE OF ASSESSMENTS: AD SUBJECTS

	Screen	Baseline	Month 6	Month 12	Month 18	Month 24
Explain Study	●					
Obtain Consent	●					
Demographics, Family History, Inclusion and Exclusion Criteria	●					
Medical History, Physical Exam, Neurological Exam, Hachinski	●					
Vital Signs	●	●	●	●		●
Screening Labs	●					
APOE	●					
American National Adult Reading Test		●				
Mini Mental State Examination	●		●	●		●
Logical Memory I and II	●			●		●
Digit Span		●	●	●		●
Category Fluency		●	●	●		●
Trails A & B		●	●	●		●
Digit Symbol		●	●	●		●
Boston Naming Test		●	●	●		●
Auditory Verbal Learning Test		●	●	●		●
Geriatric Depression Scale	●			●		●
Clock Drawing		●	●	●		●
Neuropsychiatric Inventory Q		●	●	●		●
ADAS-Cog		●	●	●		●
Clinical Dementia Rating Scale	●		●	●		●
Activities of Daily Living (FAQ)		●	●	●		●
Collect and Process Biomarkers		●*	●	●		●
Concomitant Medications	●	●	●	●		●
Subject Payments	●	●	●	●		●
Phone Contact					●	
Adverse Events	●	●	●	●	●	●
Diagnostic Summary		●	●	●		●
MRI (1.5 T) (100%)	●**		●	●		●
MRI (3 T) (25%)		●	●	●		●
PET (50%)		●	●	●		●
L.P. (minimum of 20%)		●		●		

* Includes blood draw for Immortalized cell lines.

** Screening 1.5T MRI becomes Baseline 1.5T MRI after approval.

PERSONNEL REQUIREMENTS

Site Principal Investigator (PI)

This person is responsible for overseeing all ADNI related activities at their site and ensuring that the local IRB approves the protocol. The Site PI will supervise the study coordinator and psychometrist. The site PI is responsible for identifying the physicians or scientists who are responsible for overseeing or performing the MRI (both 1.5 and 3 Tesla) and PET scans. The Site PI may also serve as the Study Physician.

Study Physician

This person is responsible for the following:

⇨ Conducting or supervising the clinical evaluation of all subjects, including physical and neurological examinations, reviewing adverse events, interpreting laboratory results.

⇨ Ensuring enrollment quotas and protocol adherence.

⇨ The Study Physician will supervise project personnel and ensure that raters maintain a high level of skill and accuracy in conducting assessments.

⇨ The Study Physician is responsible for ensuring that lumbar punctures are performed correctly and that adequate CSF is collected.

The neurological exam, physical exam, MRI Radiology Report, Adverse Events and Serious Adverse Events must be signed off in the online Signature Log by a clinician trained in the administration/review of these assessments (MD, PA, DO, NP). Only clinicians with these credentials are allowed to sign off on these assessments. If this is not possible due to staffing issues, contact the Project Director. Please see the Data Entry Manual for an explanation of electronic signatures.

Study Coordinator

This person is responsible for the following:

⇨ Managing the day-to-day conduct of the trial

⇨ Ensuring accurate administration of all instruments

⇨ Ensuring accurate data entry, updating and correcting of data through the distributed data entry system

⇨ Processing laboratory samples

⇨ Serving as a liaison with the Clinical Monitor and Project Director

⇨ Coordinating clinic visits and imaging appointments

Note: It is preferable that this person be a nurse or nurse practitioner.

Psychometrist

This person is responsible for administering the ADAS-Cog and the neuropsychological battery of tests.

Clinical Dementia Rating Scale (CDR) Rater

The same person cannot administer both the CDR and ADAS during a single clinic visit. If possible, the same person should administer the CDR at each visit for a given subject.

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.

IMPORTANT NOTE: All site personnel conducting ADAS and CDR for ADNI must complete ADAS and CDR certifications.

Imaging Center Contact

Every site must also identify the primary contact for 1.5T MRI, 3.0T MRI (often the same as 1.5T) and PET Imaging who is responsible for the completion of Start-Up Certification requirements, technical compliance of MRI/PET, and uploading scan data to LONI. The site PI is responsible for ensuring these individuals are identified and updated with protocol changes.

Depending on the site the Imaging Center Contact(s) could be a Radiologist, Nuclear Medicine Specialist, Imaging Scientist or Technologist.

Changes in Site Personnel

When personnel at your site change, please remember to do the following:
1. Complete the ADNI Contact Update Form indicating 'inactive' for personnel leaving, and adding any new personnel. This form can be found in the document repository (http://adni.ucsd.edu/dav).
2. Go to http://adni.ucsd.edu and click 'Help' to submit a request to deactivate online accounts.
3. The Site P.I. will need to request an account for any new personnel by going to: http://adni.ucsd.edu, under 'Account Management'.
4. Update your regulatory file by submitting the Signature Log, FDA 1572 form, CV(s) and Human Subject Training Certification(s).

All new personnel must also complete required certifications before participating in the ADNI.

If site personnel leave, his/her account for access to the ADCS distributed data entry system must be cancelled within 24 hours.

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. Thal.**

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. Thal 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 ADCS distributed data entry system from all locations. The ADNI Coordinating Center (support@adni.ucsd.edu) 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 Certification

ADNI Start-up Certification

Before being approved to begin screening for ADNI, all sites must meet all requirements for ADCS start-up and have completed the MRI certification for 1.5T MRI and 3T MRI if this is part of the site's ADNI participation. Sites participating in the PET portion of the study will also need to complete this certification prior to beginning enrollment for ADNI.

For both MRI and PET, each site's radiology centers will be contacted directly by the ADNI MRI Core (Mayo Clinic) and ADNI PET Core and asked to complete certification. Each research site will need to be in contact with their imaging centers and verify that the center understands their responsibility to complete ADNI certification. The site PI and study coordinator will be contacted if problems arise in imaging certification. Please email support@adni.ucsd.edu if you have questions about the certification process.

ADCS START-UP REQUIREMENTS

The following certifications are needed by the ADCS prior to a site enrolling for ADNI. If you have questions about any of these requirements or need to request forms, please contact the ADCS helpdesk at: support@adni.ucsd.edu.

Contact Details

The first requirement that should be met is updating the ADCS contacts. One form must be completed for each individual involved in recruitment, data collection and entry for ADNI. These forms were made available at the training meeting and may also be requested by emailing: support@adni.ucsd.edu.

> **Remember to consistently update** the Coordinating Center at the ADCS with any changes in contacts or personnel at the site, as many of the procedures for ADNI are **automated** and rely on this information being accurate and up to date.

Based on the Contact Information you provide, online accounts for the ADCS distributed data entry system will be established for the study coordinator and site PI. Accounts for other personnel at the site will need to be requested individually by the site PI, who is responsible for the integrity of data collected at the site. For instructions on requesting online accounts, please refer to the Data Entry Manual in the document repository (http://adni.ucsd.edu/dav).

EDC Certification

Electronic Data Capture Certification is required for each site prior to scheduling the first screening visit. Once online accounts have been established, the study coordinator will receive an email request and instructions for completing EDC Certification.

In order to complete EDC Certification the following are needed:

- ❏ Computer with broadband internet connection
- ❏ Current version of web browser (Internet Explorer, Safari, Firefox, or Mozilla)
- ❏ Current version of Acrobat Reader (7.0)
- ❏ Full Page Scanner: We would like to recommend a scanner with an automatic feeder. An example of this scanner type would be the HP Scanjet 5550c. You may also be able to add an automatic document feeder on to your existing scanner. Please check with your institution's IT support if you have questions about scanners.

NPI-Q Recommended Training

Training for the NPI-Q is recommended and can be found at: https://www.alz.washington.edu/npiq.

ADAS

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 ADNI.

Certification is required for those who are ADAS-naïve and for those who 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 support@adni.ucsd.edu. The questionnaire must be completed and returned to the same address. After being scored the rater will receive ADAS certification by email. Certification is valid for 5 years; after this time the rater must recertify.

If you are unsure whether it has been more than 5 years, please refer to the list of ADAS raters approved for ADNI (provided at the training meeting) or email support@adni.ucsd.edu.

CDR

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 training 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/CDRTraining/ADNI/ Password: ADNI123

> **Questions specific to the online CDR training should be directed to: adrcedu@abraxas.wustl.edu. Please include "CDR" in the subject line.**

MRI CERTIFICATION

Prior to any ADNI subjects being scanned at a particular site, that site must first meet the "Site Qualification Guidelines" as specified below for 1.5 T MRI. If a site is participating in MRI 3.0 Tesla scanning, this scanner will need to go through the same procedure for 3 T MRI prior to enrollment of subjects.

Certification requirements are as follows:

1. **Phantom Scan:** Each site must first scan a phantom using the selected ADNI protocol. (*Note: This can be done prior to IRB approval*) Each site will be sent an MRI phantom to be used for certification. The phantom number will accompany the phantom. After the protocol has been scanned on a phantom, the site will send the phantom data to LONI. ADNI QC will examine the phantom scan and determine whether the correct parameters have been met and ensure there are no other underlying problems seen during the scanning session.

2. **Volunteer Scan:** *After* receiving institutional IRB approval for the ADNI protocol and passing the phantom scan evaluation each site must then scan one human volunteer using the selected ADNI scanning protocol. This volunteer will need to sign an ADNI consent form and have been assigned an ADNI subject number on the ADCS database. A Phantom Scan should be performed immediately after the volunteer scan and all MRIs (volunteer and phantom) must be uploaded to LONI. ADNI QC will again determine if the correct parameters have been met and ensure there are no other underlying problems seen during scanning this session.

After these two requirements have been successfully completed the site is considered certified for the MRI portion of the ADNI and ready to scan patients.

Once recruitment begins and ADNI subjects are scanned, imaging of a phantom is required to accompany each ADNI subject scan. If the imaging site is not compliant with the phantom scanning, certification could be revoked and the site will not be allowed to scan subjects.

> **With questions or concerns about MRI certification email: ADNIMRI@mayo.edu**

Note: Hardware/Software Upgrades. It is likely that most MR scanners in the ADNI will be require software and/or hardware upgrades throughout the duration of the study. *Prior* to any software of hardware upgrading the site must inform the ADNI MRI Team at Mayo by emailing ADNIMRI@mayo.edu. Please provide as much advance notice as is possible. At least 2 months notice of hardware or software changes should be provided. Depending on the impact of the upgrade the site may be asked to scan a phantom and/or volunteer prior to scanning ADNI subjects.

PET CERTIFICATION

Prior to any patients being scanned at a particular site, that site must first meet the "PET Qualification Guidelines". Each scanner at a site must be ADNI certified. At the beginning of the study, sites have indicated the scanner that will be used for the study. This scanner will be the one on which phantom imaging is performed. It may not change during the study. If changes must occur, the PET QC group must be notified by emailing adnipet@adni.ucsd.edu.

Phantom Scan: Each site will perform scanning on a Hoffman Brain phantom. Some sites will have these phantoms, but if not, one will be provided by ADNI. The phantom must be imaged using the specified ADNI protocol. **(Note: This can be done prior to IRB approval).** Scanning must be performed twice, on 2 different days. After the phantom has been scanned the site will send the phantom data to LONI. ADNI QC will acquire and examine the phantom study, determine whether the correct parameters have been met, and ensure there are no other underlying problems seen during the scanning session.

After the phantom scan is approved the site is considered certified for the PET portion of the ADNI and ready to scan patients. No further scanning will be necessary unless there has been a change in hardware or software.

> **For questions or concerns about PET certification email: adnipet@adni.ucsd.edu**

Screening Process

SUMMARY AND DATA FLOW

An illustration of the Screening Flow follows this description.

Prescreening

1. A review of diagnoses, medications, and last MMSE score (e.g., using the site database) is used to identify possible subjects.
2. The MRI pre-screening form is completed with the subject and study partner and all issues are resolved before scheduling the screening visit.
3. If the site is participating in PET, the PET pre-screening questions are asked and the subject is asked to consent to PET (subject will only know whether he/she will have PET after approval of screen and 1.5 T MRI).
4. Subjects/study partners who seem eligible and are interested are scheduled for a Screening Visit and Screening/Baseline 1.5 T MRI (10-14 days after Screening Visit).

Screening Visit

1. The subject and study partner are seen in the clinic. Consent is obtained. The Screening Visit is completed, all data from the screening visit is entered on the ADCS distributed data entry system, and all errors are resolved.
2. The site determines whether or not the subject meets all inclusion/exclusion criteria. If the subject meets all criteria, and is eligible for enrollment, the Study Physician or Site Principal Investigator signs off in the online Signature Log, confirming the subject's eligibility. If at any point in the Screening Visit it becomes apparent that the subject is not eligible, the visit should be discontinued. There is no need to collect screening clinical labs on screen fails. All collected data from screen fails should be entered online.
3. If the subject does not meet criteria, and if the site feels that an exception may be warranted, the site should complete and submit an online Inclusion/Exclusion Exceptions request. Dr. Petersen will review the request, either approve or deny, and the site will receive email notification of the decision. If the exception is approved, the site will need to log on and "Final Submit" the Screening Visit online. If the request is denied, the subject will become a screen failure, and is dropped from the study.

Monitor Review

1. The Clinical Monitor reviews the Screening Visit for eligibility into ADNI. This includes verifying subject is suitable for MRI.
2. The Clinical Monitor ensures that, for each site, at least one (1) of every three (3) subjects in each group (NL, MCI and AD) have consented to lumbar puncture. If the site has not met this minimum requirement, the monitor will either screen fail the participant or delay randomization until the site has screened another participant in that diagnostic category who consents to LP.
3. The monitor enters questions and corrections online via the Quality Assurance application.
4. The site makes all monitor-requested changes on the ADCS distributed data entry system.

> As age-matching across the diagnostic categories is important, age of Normal Controls will temporarily be limited to 70 years old.

5. The Clinical Monitor approves the subject, the site is notified via email and the Screening/Baseline 1.5 T MRI can take place. If the Clinical Monitor fails the screen, the Screening/Baseline MRI must be cancelled.
6. At this point the Baseline Visit should be scheduled. DO NOT schedule the Baseline Scan (3 T MRI or PET) until the Screening/Baseline MRI scan has been approved and the Scan Assignment Report has been received.

Screening/Baseline MRI (1.5 Tesla)

1. Screening/Baseline MRI is conducted within 10-14 days of the Screening Visit. **If the subject is unable to complete the scan and unable to schedule a repeat study,** contact the Protocol PI, as he/she will need to be withdrawn from the study.

   Note that subject withdrawal due to screening MRI failure is applicable only if the failure was due to the subject's inability to complete the exam. It is not applicable if the failure was due to a technical problem with the scanner or the MRI protocol. In those cases the Screening/Baseline 1.5 T MRI will need to be repeated before the subject can be included in the study.
2. The scan is immediately uploaded to LONI by the radiology center. (The study coordinator should contact LONI adni@loni.ucla.edu if their radiologists are unable to upload scans to LONI).
3. A local Radiologist must review the MRI and **as soon as the report/clinical read is available** the site must immediately upload it to the ADCS distributed data entry system.
4. The MRI QC Team at Mayo will download the scan from LONI. They will review the scan and the radiology report (uploaded to the ADCS) concurrently when possible. This results in the final QC review of this scan and determines MRI eligibility of the subject.
5. The Site receives the results of the QC review done at Mayo Clinic. If the subject fails the review due to clinically relevant findings, the baseline visit is cancelled and the subject is screen failed. If the subject fails QC review due to motion or technical problems, the site will be notified and the subject may be rescheduled for another screening 1.5 T scan. If the subject passes QC review, this 1.5 T scan now becomes the baseline 1.5 T MRI.
6. Scan Category Assignment occurs **automatically** after MRI QC Review, Monitor Approval, and APOE results are all collected in the ADCS system. This process is detailed in the next section of this procedures manual.
7. Site will then schedule the Baseline Scan (3 Tesla MRI or PET) **only if subject is assigned to this scan category**. The Screening 1.5 Tesla MRI, once approved, becomes the Baseline 1.5 T MRI for this subject.

> There will be continued monitoring of the percentage of subjects who have LP's at each site. The percentage of subjects in each diagnostic group must remain equal to or greater than 20%.

Screening Process

```
SCREEN                    MONITOR              TECHNOLOGIST                                                                                                                        BASELINE
VISIT          ──YES──►   REVIEW:     ──YES──► CONDUCTS                                                                                                    QC REVIEW:  ──YES──►    VISIT      ──►   BASELINE
COMPLETED                 SUBJECT              SC/BL                                                                                                       SUBJECT                 (BL)            SCAN
(SC)                      MEETS                1.5T MRI                                                                                                    AND                                     (ONLY
                          INCLUSION            SCAN                                                                                                        SCAN                                    3T OR PET)
                          CRITERIA?                                                                                                                        APPROVED?²
```

SCREEN FAIL¹ ◄──NO── MONITOR REVIEW: SUBJECT MEETS INCLUSION CRITERIA?

SCAN UPLOADED TO LONI

MAYO MRI QC ACQUIRES SCAN

SCAN REVIEWED BY RADIOLOGIST

SITE REVIEWS RADIOLOGY REPORT, REPORT UPLOADED TO ADCS

TECHNOLOGIST RETURNS FORM TO STUDY COORDINATOR FOR DATA ENTRY

EXCEPTION/RESCAN PROCESS³ ◄──NO── QC REVIEW: SUBJECT AND SCAN APPROVED?²

APPROVAL AND SUBJECT SCAN CATEGORY ASSIGNMENT⁴

TIMELINE

| O DAYS | 3 DAYS | MAXIMUM 10-14 DAYS | MAXIMUM 28 DAYS | MAXIMUM 14 DAYS FROM BASELINE |

1. Email sent notifying Study Coordinator of fail and reminding to cancel Screen MRI.
2. The Mayo QC team reviews the scan and the report from the site radiologist side by side. If a significant abnormality is seen (e.g., hemispheric infarction), 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.
3. See MRI Dataflow chart for further details.
4. Subject Scan Category Assignment incorporates APOE results. If subject consents to both PET and 3T, subject allocation report will notify site which scan to schedule for Baseline.

SCAN CATEGORY ASSIGNMENT

The purpose of assigning subjects to a scan category is to:

1. Ensure Recruitment targets are met
2. Ensure the three subject groups are equally distributed in the scan sub-studies

Scan assignment begins with the screening process for subjects. The first decision that must be made is whether the subject is eligible for enrollment. This is determined by the site (during the screening visit), by the clinical monitor when reviewing the screen, and by the QC review of the Screening/Baseline 1.5 T MRI.

Using the ADCS distributed data entry system, the site will enter information at the screening visit that will be used in the scan category assignment, including what the subject has consented to and diagnosis. Sites will only be prompted to answer questions online that are relevant to their site. If a site is not doing 3 Tesla MRI or PET, the question will not appear on the screen.

Entered at Screen:
- ❏ Suitable for and consents to Lumbar Puncture?
- ❏ Suitable for and consents to PET?
- ❏ Suitable for and consents to 3 Tesla MRI?
- ❏ Diagnosis & Age
- ❏ Does Subject satisfy inclusion/exclusion criteria?

In addition to the data entered by the site, ApoE results and MRI QC results will be collected into the ADCS distributed data entry system. Subjects within each diagnostic category will be distributed amongst the scan categories based on age, apoe genotyping and participant consent.

Scan Assignment is automatic once each of these are completed in the system:
- ❏ Screening data entered (including uploaded forms)
- ❏ All errors resolved (including electronic signatures, exceptions approved)
- ❏ Monitor Approval
- ❏ Site Clinician Review of screen 1.5 T MRI radiology report
- ❏ Screen 1.5 T MRI approved by MRI QC group at Mayo
- ❏ APOE results from UPenn

Sites should use the Quality Assurance tool at http://adni.ucsd.edu to identify any errors that could be holding a subject back from scan assignment. The Participant Enrollment tool tracks subjects pending scan assignment, subjects that have been assigned to a particular scan category, and screen fails. Please see the Data Entry Manual for more detail on this.

Scan assignment will be sent to the Site PI and Study Coordinator automatically stating whether the subject will have one of the following:

1. Only 1.5 Tesla MRI
2. 1.5 Tesla MRI plus PET
3. 1.5 Tesla MRI plus 3 Tesla MRI

Scan Assignment will take into account whether a site is participating in this scan category. For example, if a site is only participating in 1.5 Tesla MRI and 3 Tesla MRI, only options 1 and 3 will be available to subjects that consent to both. During the consenting process it should be explained to subjects that there is a chance they will be assigned to one of the three options above. Subjects should not be promised 3T or PET scanning, even if a site only offers one of the 2 options.

> **Note: The Subject may only be assigned to the scan category that he/she has consented to.**

The baseline scan should be scheduled within 14 days of the baseline visit.

Real-Time reporting of scan assignments for all ADNI subjects are available on the ADCS distributed data entry system Reports Menu (https://adni.ucsd.edu). These reports should be checked frequently by the Site PI and used to help target recruitment at each site. In addition to this, the Project Director and Core Leaders will be closely monitoring overall recruitment and will provide direction to sites on where to focus recruitment.

PROCEDURES FOR NOTIFYING PRIVATE MD OF STUDY PARTICIPATION

As soon as the site receives final approval and scan category assignment for a screened subject, a letter should be sent by the site to his/her private MD, notifying the MD of the subject's involvement and outlining the ADNI procedures. Consent from the subject 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 to send to the private MD when a subject consents to ADNI is available in the document repository (http://adni.ucsd.edu). Please use the letter that reflects the subject's scan assignment (1.5 T MRI only, 1.5 + 3.0 T MRI, 1.5 T MRI + PET) and include whether the subject will be having Lumbar Punctures.

INCLUSION/EXCLUSION CRITERIA
Inclusion Criteria for all Subjects

- ⇨ Hachinski less than or equal to 4
- ⇨ Age between 55-90
- ⇨ Stability of Permitted Medications for 4 weeks (see following pages for examples of excluded medications)
- ⇨ Geriatric Depression Scale less than 6
- ⇨ Study partner with 10+ hr/wk contact (can be in person and telephone), accompanies to visits
- ⇨ Visual and auditory acuity adequate for neuropsychological testing
- ⇨ Good general health with no diseases precluding enrollment.
- ⇨ Women must be sterile or two years past childbearing potential
- ⇨ Willing and able to complete a 3 year imaging study (2 years for AD subjects)
- ⇨ 6 grades education or work history
- ⇨ Must speak English/Spanish fluently
- ⇨ Commitment to Neuroimaging and no medical contraindications to MRI
- ⇨ Agrees to DNA for ApoE testing and banking
- ⇨ Agrees to Blood and Urine for Biomarkers
- ⇨ Not enrolled in other trials or studies

Group Specific Inclusion Criteria
Normal Controls (NL)

- ⇨ No Memory Complaints aside from those common to other normal subjects of that age range.
- ⇨ Normal memory function documented by scoring at specific cutoffs on the Logical Memory II subscale (delayed Paragraph Recall) from the Wechsler Memory Scaled - Revised (the maximum score is 25):
   - a) greater than or equal to 9 for 16 or more years of education
   - b) greater than or equal to 5 for 8-15 years of education
   - c) greater than or equal to 3 for 0-7 years of education.
- ⇨ 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).
- ⇨ Clinical Dementia Rating = 0. Memory Box score must be 0.
- ⇨ Cognitively normal, based on an absence of significant impairment in cognitive functions or activities of daily living.

Mild Cognitive Impairment (MCI)

⇨ Memory complaint by subject or study partner that is verified by a study partner.

⇨ 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) less than or equal to 8 for 16 or more years of education

    b) less than or equal to 4 for 8-15 years of education

    c) less than or equal to 2 for 0-7 years of education.

⇨ 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).

⇨ Clinical Dementia Rating = 0.5. Memory Box score must be at least 0.5.

⇨ 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.

Alzheimer's Disease (AD)

⇨ Memory complaint by subject or study partner that is verified by a study partner.

⇨ 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) less than or equal to 8 for 16 or more years of education

    b) less than or equal to 4 for 8-15 years of education

    c) less than or equal to 2 for 0-7 years of education.

⇨ MMSE between 20 and 26 (inclusive) (Exceptions may be made for subjects with less than 8 years of education at the discretion of the protocol PI).

⇨ Clinical Dementia Rating = 0.5, 1.0

⇨ NINCDS/ADRDA criteria for probable AD.

EXCLUDED MEDICATIONS

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

Any change in medication (including dose or frequency) should be recorded on the 'Concurrent Medications Log' for the visit it is reported. If a subject begins an excluded medication, the site must document this by requesting an exception from the Protocol PI (Dr. Petersen).

If a subject begins a cholinesterase inhibitor or memantine after being approved for enrollment into the study, this should be documented by completing an additional comment form describing the reason for the protocol deviation.

List of Excluded Medications

Please note: This is not a complete list of excluded medications. For drugs not on this list, query the Protocol PI (Dr. Petersen).

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

ANTICHOLINERGIC AGENTS: Not allowed within 4 weeks prior to screening:

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

ANTIPARKINSONIAN MEDICATIONS: Not allowed within 4 weeks prior to screening:

GENERIC NAME	BRAND NAME
Bromocriptine	Parlodel
Deprenyl/Selegiline	Eldepryl
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

ANTIDEPRESSANTS: Not allowed within 4 weeks prior to screening:

GENERIC NAME	BRAND NAME
Amitriptyline	Elavil
Amoxapine	Asendin
Clomipramine	Anafranil
Desipramine	Norpramin
Doxepin	Sinequan
Imipramine	Tofranil
Isocarboxazide	Marplan
Lithium	Lithobid, Lithane, Lithotab
Maprotiline	Ludiomil
Nortriptyline	Aventyl, Pamelor
Phenelzine	Nardil
Protriptyline	Vivactil
Tranylcypromine	Parnate
Trimipramine	Surmontil

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

Bupropion	Wellbutrin, Zyban
Citalopram	Celexa
Escitalopram	Lexapro
Fluoxetine	Prozac
Mirtazapine	Remeron
Nefazodone	Serzone
Paroxetine	Paxil
Sertraline	Zoloft
Trazodone	Desyrel
Venlafaxine	Effexor

PRN RECOMMENDATIONS

If a subject requires medication for various conditions during the protocol, the following are recommended:

CONDITION	RECOMMENDATION
Analgesia	Tylenol (acetaminophen) 325mg-650mg orally every 4hrs as needed
Back Pain	Tylenol; 325mg-650mg orally every 4hrs as needed
Constipation	Dulcolax suppository 10 mg once daily
Diarrhea	No treatment unless severe
Fever	Use clinical judgement for fever work-up
Hypertension	Observe - unless it increases to medically dangerous levels
Sleep / Insomnia	Tylenol (for pain); warm milk; counting backwards; (it is preferred not to prescribe hypnotic agents.)

Study Visit Procedures

SCREENING VISIT PROCEDURES
Site

1. **Prescreen** to determine diagnostic category for the subject.
2. **Register the new subject.** On the distributed data entry system click 'forms' and then 'participant enrollment'; then click 'assign a new ID number'.
3. **Print** out worksheets for cognitive testing and CDR from the Document Repository. If the visit will not be directly entered while the subject is present, print out the Screening case report forms (see data entry manual).
4. **Complete** Screening Visit online within three days of the visit. **Upload**:
   - ➩ Cognitive Testing Worksheets (MMSE & Logical Memory)
   - ➩ CDR Worksheets
   - ➩ Radiology Report/Clinical Read of Screening/ Baseline I.5 T MRI (as soon as it is available).
5. **Review** eligibility criteria; addressing any issues that are flagged by the online checks. If subject is eligible, either the PI or Study Physician *must* sign off in the online Signature Log confirming that subject meets criteria for entry into the study. Complete Final Submit. Clinical Monitor will be automatically notified that the visit is ready for review.
6. **Contact** Clinical Monitor if there are any questions about eligibility.
7. **Respond to** all monitor requests for feedback or corrections online via Quality Assurance. Ensure changes are reflected in source documentation.
8. **Store** all source documentation (if used) and testing worksheets in the subject binder behind the "Screening Visit" tab.

Coordinating Center

1. Monitors review screening visit and request feedback or corrections from the site via 'Quality Assurance'.
2. Upon resolution of pending queries, the clinical monitor approves the subject for enrollment into the study, and the site is notified by email that Screening/Baseline MRI can be conducted.
3. Scan QC Results are entered by MRI group for the Screening/Baseline I.5 T MRI.
4. The ADNI Coordinating Center provides Scan Category Assignment after all necessary data is captured and all errors are resolved. Errors holding up randomization can be viewed using 'Quality Assurance'. Final approval and Scan Category Assignment for that subject are reported in an automated email to the Study Coordinator and Site PI, and in the database under 'Participant Enrollment'.

For detailed directions on how to upload a form into the ADCS distributed data entry system please see the data entry manual: http:// adni.ucsd.edu under 'Document Repository'.

> Please note: AS SOON AS IT IS AVAILABLE, the radiology report should be uploaded for the Screening/Baseline I.5T MRI. This report is required before a subject receives final approval and the Baseline Visit can take place.

SCREEN FAIL VISIT PROCEDURES

Site

1. **Indicate 'Fail'** under Participant Enrollment.
2. **Enter** all data collected. At the very least, the following online forms should be entered:
   ⇨ Registry
   ⇨ Eligibility Confirmation (indicate 'subject not eligible and provide reason)
   ⇨ Participant Demographic Information
   ⇨ Enrollment Tracking
3. **Store** Supplemental materials, Cognitive testing worksheets and any other source documents onsite.

NOTE: Once a screen is changed to 'fail' you will be able to enter partially complete forms. Please be very careful when entering screen fail data.

Coordinating Center

1. Monitors will confirm that consent documentation exists for all screen fails during onsite monitoring visits.

BASELINE THROUGH FINAL VISIT PROCEDURES

Site

1. **Print** out Cognitive Testing and CDR Worksheets from the Document Repository. If the visit will not be directly entered while the subject is present, print out the case report forms.
2. **Complete** the visit including online entries within three days of the visit. Upload:
   ⇨ CDR Worksheets (not completed at Baseline)
   ⇨ Radiology Report (1.5T MRI and, if applicable, 3T)
4. **Respond to** all monitor requests for feedback or corrections online via Quality Assurance. Ensure changes are reflected in source documentation.
5. **Store** Supplemental materials, Cognitive testing worksheets and any other source documents in the subject binder behind the appropriate visit tab.

Coordinating Center

1. Monitors reviews visit and requests feedback or corrections using 'Quality Assurance'.
2. Scan QC Results are entered by MRI and PET reviewers. These results are available to sites under Reports on http://adni.ucsd.edu.

Note: After the Baseline visit is entered, a projection of Target Visit dates for all subsequent visits will be available at http://adni.ucsd.edu under 'Reports'. Both the study visit and applicable scans should be conducted within this window.

RESCREEN PROCEDURES

Site

1. Assign a new subject number on the Participant Enrollment tool. Ensure diagnostic category is accurate.

2. Under Registry Form question 'Is this a Rescreen?' select 'yes' and record initial ADNI subject id. For multiple rescreens, please use the very first ADNI subject id used for this subject.

3. If Clinical Laboratory Tests and APOE were not completed at the previous screen, follow usual screening procedures.

4. If previously acquired Clinical Laboratory Tests *will* be used, phone Covance (1800-327-7270) to ask that subject number be updated. You will need to provide the initial subject id and the new subject id. An updated laboratory report with the new subject id will be faxed to you.

5. If an APOE sample was previously drawn for this subject please email the Biomarker Help Desk at: adni@uphs.upenn.edu to alert them to the rescreen, and request that APOE results can be entered under the new subject id.

Coordinating Center

Follow usual Screening Procedures (see previous pages).

PROCEDURES TO CHANGE DIAGNOSTIC CATEGORY OF A SCREEN

Site

1. Follow Screen Fail Visit Procedures (previous page).

2. Attempt to establish whether subject will meet inclusion and exclusion criteria for the new diagnostic category. If your Site PI and study physician(s) feel the subject will qualify, obtain approval from Dr. Petersen (via email) to rescreen the subject under a new category.

3. Follow Rescreen Procedures (above).

Coordinating Center

Follow usual Screening Procedures (see previous pages).

Please note that any change to diagnostic category *after screen* should be documented by completing the Diagnostic Summary and Diagnostic Summary Baseline Changes Form.

RULES FOR SCHEDULING SUBJECT VISITS

The Screening Visit should only be conducted on subjects who appear to be eligible based on review of their medical history and record and who are likely to remain in the area for the full 2 or 3 years of the study. The target date for all visits after baseline will be calculated in reference to the date of the baseline visit. For each subject, the Coordinating Center will provide an online projection of all visits subsequent to Baseline, available at http://adni.ucsd.edu under Reports.

EVERY EFFORT SHOULD BE MADE TO COMPLETE THE CLINIC VISITS AND SCANS AS CLOSE TO THE TARGET DATE AS POSSIBLE.

Required Timing of ADNI Visits and Scans		
Visit	**Scheduling Rule**	**For Exception**
Screening Scan (MRI 1.5 T only)	Not to be conducted until after a monitor has approved the screening visit. We recommend scheduling the scan 10-14 days after screening.	Contact Project Director
Baseline Visit	Only conducted after final approval of 1.5 T MRI and scan category assignment. Within 28 days of the *Screening* visit.	Complete online exception request
Baseline Scan (MRI 3T and PET)	Completed after final approval of 1.5T MRI and scan category assignment. Within 14 days of the *Baseline* visit.	Provide reason for protocol deviation on an additional comment form
Month 6 - Final Visit	Completed within 14 days of target date	Provide reason for protocol deviation on an additional comment form
All Scans after Baseline	Completed within 14 days of target date	Provide reason for protocol deviation on an additional comment form
Baseline and Month 12	Lumbar Punctures should always been done <u>after</u> MRI or PET scan. If this is not possible, schedule scan more than 3 days after LP.	Provide reason for protocol deviation on an additional comment form

If a visit or scan is missed, it should be rescheduled. If a subject misses a visit or a scan and it can not be rescheduled, contact your clinical monitor immediately. The reason for missed visits and scans should be recorded on the ADCS distributed data entry system.

If it is not possible to obtain ALL required data at a visit, please contact your clinical monitor immediately. It is critical to obtain all requested data at each visit. If data is missed, please make every effort to bring the subject back immediately to capture all data.

Transfers Not Allowed

Because of the importance of using the same MRI or PET machines for ADNI analysis subjects will not be allowed to transfer sites and continue in the ADNI. If a subject lives in another city half of the year, the site should ensure the subject will return for subsequent visits prior to enrolling the subject.

IMPORTANT NOTE: Prior to scheduling any visit, ensure that SUFFICIENT STUDY SUPPLIES are on-site to allow successful completion of the visit.

EARLY DISCONTINUATION FROM STUDY

If a subject wishes to withdraw from one or more study procedures, he/she should be asked to consider continuing in the ADNI study, as long as he/she is willing to continue with biomarker sampling and psychometric assessments.

Partial Withdrawal (from LP, 3T MRI, or PET) should be documented by completing the Early Discontinuation and Withdrawal Form online. If a subject withdraws consent to lumbar puncture prior to the Baseline Visit, the site should:
1. Complete Early Discontinuation and Withdrawal Form
2. Update 'Inclusion Criteria' form under Screening Visit by unchecking LP.

Please note that another subject who consents to LP could be required if this drops the site below a 20% LP rate within that diagnostic category.

If the subject withdraws from 1.5 T MRI, but agrees to be followed, the site must request permission to follow the subject by emailing the Project Director (Dr. Weiner), and Protocol PI (Dr. Petersen) and copying your clinical monitor. This will be decided on a case-by-case basis.

Unscheduled Visits

A Unscheduled Visit should be considered for any subject who completes a Month 6 visit, discontinues prematurely, and does not wish to return for subsequent study visits.

An Unscheduled Visit must be requested by the site by completing an Exceptions Log for that subject. The site will need to indicate on the request whether a full (all procedures assigned to that subject) or partial unscheduled visit is required. The protocol PI will assess whether conducting an unscheduled visit is useful to the protocol as a whole and will either approve or deny the request.

Once approved to conduct an Unscheduled Visit, the reason for discontinuation should be recorded. When an in-person visit is not possible, site personnel should complete as much of the Unscheduled Visit as possible by telephone.

Final Visits

A final visit (Month 24 for AD subjects and Month 36 for MCI and NL) should also be conducted for subjects who discontinue the study prematurely (after 6 months) and are willing to return for the final visit.

Discontinuation Prior to Baseline

If a subject completes the screening visit, the Screening MRI, and is then assigned to a scan category but then withdraws consent or discontinues **prior to the baseline visit**, the subject will need to be un-assigned from that scan category and dropped from the study. Complete the Early Discontinuation and Withdrawal Form online and request that a subject be unassigned by contacting the online helpdesk (http://adni.ucsd.edu and then 'Help').

The Protocol Includes The Following Reasons For Discontinuation From The Study:

1. **Adverse event:** The subject has experienced an adverse event that, in the opinion of the investigator, requires early termination. This may include abnormal laboratory values, clinically significant MRI findings, or other serious adverse event.
2. **Death**
3. **Safety risk:** Any subject who has become a safety risk at any time during the trial; for example, having a pacemaker implanted or an aneurysm clip in the head.
4. **Protocol violation:** The subject fails to meet protocol entry criteria or did not adhere to protocol requirements.
5. **Non-compliance:** The subject is non-compliant with completion of study procedures. Inability to perform MRI because of 1) metal or device in the body, 2) severe claustrophobia preventing MRI, 3) inability to cooperate in the MRI, 4) Two successive failures to complete 1.5 Tesla MRI.
6. **Investigator judgment:** Subject may be withdrawn if, in the investigator's judgment, it is in the subject's best interest.
7. **Consent is withdrawn:** The subject wishes to withdraw from the study, in the absence of a medical need as determined by the investigator.
8. **Study is terminated:** The study may be terminated by the Project Director alone or at the recommendation of the Data and Safety Monitoring Board.
9. **Loss of Study Partner:** The subject no longer has a responsible study partner to provide important information concerning subject's cognition (CDR) and activities of daily living.
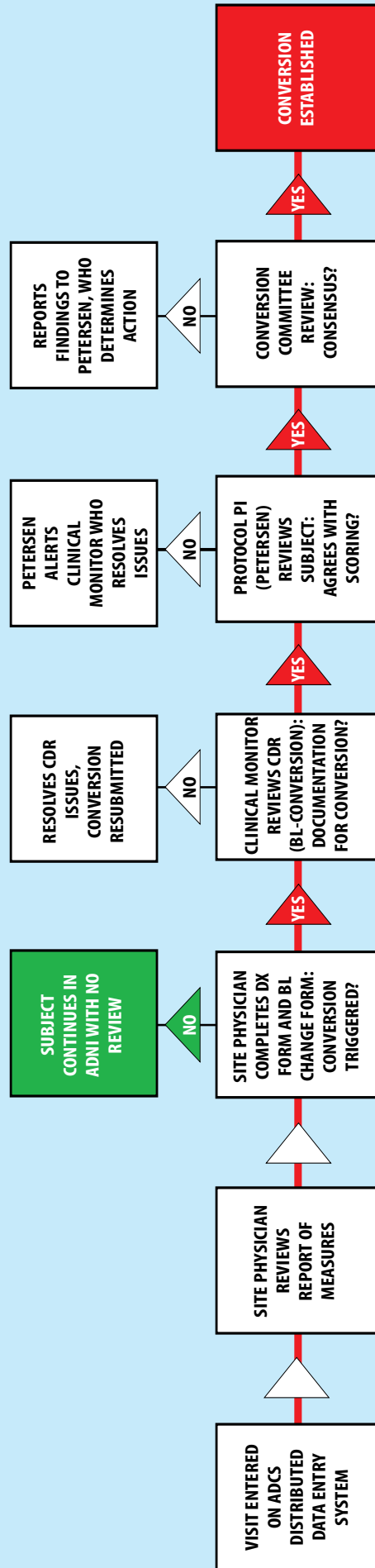10. **Loss to Follow-up:** The subject can no longer be contacted.

A narrative description of the reason(s) for early withdrawal/discontinuation will also be entered on the Early Discontinuation and Withdrawal Form.

CONVERSION TO MCI OR AD

Tracking the rate of conversion from normal to MCI and MCI to AD is a primary outcome measure of the ADNI protocol. Conversion will not affect the subject's schedule of visits; the subject will have all visits assigned as part of their original diagnostic category (NL or MCI).

1. Study Coordinator Enters all visit data on ADCS distributed data entry system.
2. Site Physician reviews visit measures and completes Diagnostic Summary and Diagnostic Summary Baseline Changes forms.
3. When Conversion is initially triggered, the site's clinical monitor will review the CDR for that visit. The monitor will resolve any issues with Site PI and instruct the site to reverse the conversion if incorrectly reported.
4. Dr. Petersen then reviews scores or asks for the clinical monitor to resolve scoring issues.
5. After Petersen's review, an alert email is sent to Conversion Committee to review subject. This email contains a link to the online page where diagnosis summary, progress report, and consensus diagnosis form can be viewed.
6. The Conversion Committee reviews reports and completes the Consensus Diagnosis and Conversion form online.
7. Differences in diagnosis are resolved.

ADNI Conversion Flow

```
VISIT ENTERED
ON ADCS
DISTRIBUTED
DATA ENTRY
SYSTEM
```
△
```
SITE PHYSICIAN
REVIEWS
REPORT OF
MEASURES
```
△
```
SITE PHYSICIAN
COMPLETES DX
FORM AND BL
CHANGE FORM:
CONVERSION
TRIGGERED?
```
── NO ──▷
```
SUBJECT
CONTINUES IN
ADNI WITH NO
REVIEW
```

YES
```
CLINICAL MONITOR
REVIEWS CDR
(BL-CONVERSION):
DOCUMENTATION
FOR CONVERSION?
```
── NO ──▷
```
RESOLVES CDR
ISSUES,
CONVERSION
RESUBMITTED
```

YES
```
PROTOCOL PI
(PETERSEN)
REVIEWS
SUBJECT:
AGREES WITH
SCORING?
```
── NO ──▷
```
PETERSEN
ALERTS
CLINICAL
MONITOR WHO
RESOLVES
ISSUES
```

YES
```
CONVERSION
COMMITTEE
REVIEW:
CONSENSUS?
```
── NO ──▷
```
REPORTS
FINDINGS TO
PETERSEN, WHO
DETERMINES
ACTION
```

YES
```
CONVERSION
ESTABLISHED
```

CLINICAL MONITORING AND SOURCE DOCUMENTS

A clinical monitor is assigned to each site in the ADNI protocol. The site is notified of the clinical monitor upon approval to begin enrolling. The clinical monitor will review every screening visit in full to confirm eligibility for the ADNI study. Clinical monitors will also be reviewing the concurrent medications, Adverse Events, and Serious Adverse Events for every subject throughout the study. Clinical Monitors will also be reviewing the CDRs of select visits, including all visits where a Conversion is triggered.

On-Site Visits

The site's clinical monitor will visit each site for on-site monitoring visits.
  - ⇨ Monitor will review source documents
  - ⇨ The monitor will request corrections as needed during the visit.
  - ⇨ Following the visit, the monitor will complete an On-site Visit Report. Copies will be sent to the Site Principal Investigator and Study Coordinator.

Monitor Review of Source Documents

During the on-site visit, clinical monitors will review source documents to confirm the following:
  - ❏ Consent form signed for every subject screened, including partial screens and screen failures.
  - ❏ Inclusion/Exclusion criteria.
  - ❏ Verification of concurrent medications and adverse events.

> Important: All source documents must be accessible to clinical monitors during on-site visits.

Description of Source Documents

The completed online CRF may be a source document, if it is the first time clinical data is recorded. All worksheets used in psychometric testing are source documents.
Source documents may include:
  - ❏ Clinic chart
  - ❏ Laboratory reports
  - ❏ MRI/CT reports

Data Corrections for any Paper Source Documents

  - ⇨ Identify errors with a single line through the error and record the correct data next to the error.
  - ⇨ Initial and date each correction.
  - ⇨ Do not use eraser or correction fluid.
  - ⇨ Corrected items must be clearly readable.

> When copies of radiology reports are uploaded to ADCS distributed data entry system, the subject's name and any identifying ID numbers from local hospitals should be blacked out and the ADNI subject ID should be written in.

NOTE: Any corrections to data that occur due to quality control checks online must be changed on paper documents as well.

The following are examples of correct and incorrect methods of correcting errors:

CORRECT

6. Yes ☑ No ☑ *ABG 9/29/99* Has the patient's study partner changed?

INCORRECT

6. Yes ☑ No ☒ Has the patient's study partner changed?

6. Yes ☑ No ☒ *KAS* Has the patient's study partner changed?

6. Yes ☑ No ☑ *9/29/99* Has the patient's study partner changed?

6. Yes ☑ No ☒ *ERROR* Has the patient's study partner changed?

STUDY SUPPLIES

Initial Supplies

Once your site has been approved to begin screening subjects, you will receive a formal approval letter. An initial shipment of supplies will be sent from the ADCS by Federal Express for receipt within 7-10 working days. All case report forms and worksheets are available online at http://adni.ucsd.edu. For instructions on printing case report forms please see the Data Entry Manual. A detailed inventory list will accompany each initial shipment.

The initial shipment will include the following materials:
- ❏ Procedures Manual
- ❏ Subject binders with visit tabs
- ❏ ADAS word lists
- ❏ Fed-ex airbills (to NCRAD and U Penn)
- ❏ Sample Identification labels (for V1 and V2: ApoE, Cell Immortalization and Biomarker samples)

Sites will also be sent lumbar puncture kits from the ADCS. Please see the Cerebral Spinal Fluid Collection pages for detailed lists of these kit contents.

The following items must be requested by completing an ADNI supply request form:
- ❏ Boston Naming Test booklet
- ❏ ADAS Kit
- ❏ WAIS-R Digit Symbol Key

> ADAS Word Lists are available in Spanish and should be requested only if you have a Spanish-speaking subject scheduled for a Screening Visit.

To request resupply or to report damaged or missing items, please email support@adni.ucsd.edu.

Once the site has been approved to enroll for ADNI, Covance will be notified to send a supply of clinical laboratory kits. To ensure that subject visits go smoothly, please inventory all supplies as soon as you receive them.

- ❏ Screening Laboratory Sample Kits
- ❏ ApoE kits
- ❏ Cell Immortalization kits
- ❏ Biomarker kits (identical for each visit)
- ❏ Urine Collection Containers
- ❏ Shipping Boxes - Ambient
- ❏ Shipping Boxes - Frozen

Only Clinical Laboratory Screening Kits will be automatically resupplied.
Kits for APOE, Cell Immortalization and Biomarkers must be requested from Covance.
To order supplies, or to report damaged or expired kits contact Covance at: (800) 327-7270.

Re-Ordering Study Supplies

Complete a re-supply request form (**http://adni.ucsd.edu Document Repository)** and email to support@adni.ucsd.edu.

When emailing a supply request, please state the protocol (ADNI), site number, and how you would like it sent:

- ❏ Priority Overnight (PO): will arrive by 10:30 the next morning.
- ❏ Standard Overnight (SO): will arrive by close of business the following day.
- ❏ 2 - Day Delivery
- ❏ Express Delivery (3 days)
- ❏ US Mail

> **IMPORTANT: Saturday Delivery is not available for supply shipments.**

Re-supplies that can be ordered from the ADCS for ADNI include:

- ❏ FedEx airbills for U Penn (ApoE and Biomarkers)
- ❏ FedEx airbills for NCRAD (cell immortalization)
- ❏ Subject binders (5 per pack)
- ❏ Procedures manuals
- ❏ Spanish ADAS Word Lists
- ❏ Sample Identification labels (for ApoE, Cell Immortalization and Biomarkers) (specify number of subjects)
- ❏ Lumbar Puncture Trays (5 per pack)
- ❏ Sprotte Needles and introducers (10 per pack)
- ❏ 1 ½" needles (for administering lidocaine during LP) (25 per pack)
- ❏ 5 mL syringes (25 per pack)
- ❏ CSF transfer tubes with clear caps (13 mL / 20 per pack)
- ❏ Bubble bags (30)
- ❏ Outer ziplock bags (30)

MRI Procedures

SUMMARY

Magnetic Resonance Imaging (MRI) is a principle component of the Alzheimer's Disease Neuroimaging Initiative (ADNI). All study subjects will have 1.5 Telsa MRI scans completed at regular intervals throughout the study. The collection of these images is central to meeting the ADNI objective of developing biomarkers to track both the progression of Alzheimer's Disease and change in underlying pathology. The initial scan will occur between screening and baseline and subsequent scans will occur at every in-clinic visit.

All research sites will conduct 1.5 Tesla MRI scans, and some will also conduct 3.0 Tesla MRI Scans. Subjects will only receive both if (1) the site offers 3.0 T, (2) the subject agrees to 3.0 T on the consent, and (3) when the subject is allocated to this arm of the study.

All sites will need to meet MRI certification requirements in order to begin enrolling for ADNI. 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.

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 will follow this flow of data. Study Coordinators are responsible for collecting some basic information on each MRI scan from the radiologist conducting the scan. This basic information will be captured on the MRI Scan Information Form. The form will need to be printed from the online forms and given to the radiologist conducting the scan; please see the data entry manual for specific instructions for printing online forms. Please ensure the radiologist has a copy of this form for every scan scheduled and that a process for transferring this form back to the study coordinator is established. The study coordinator will then need to ensure the data from the MRI Scan Information Form is entered on the ADCS distributed data entry system within 24 hours of the scan.
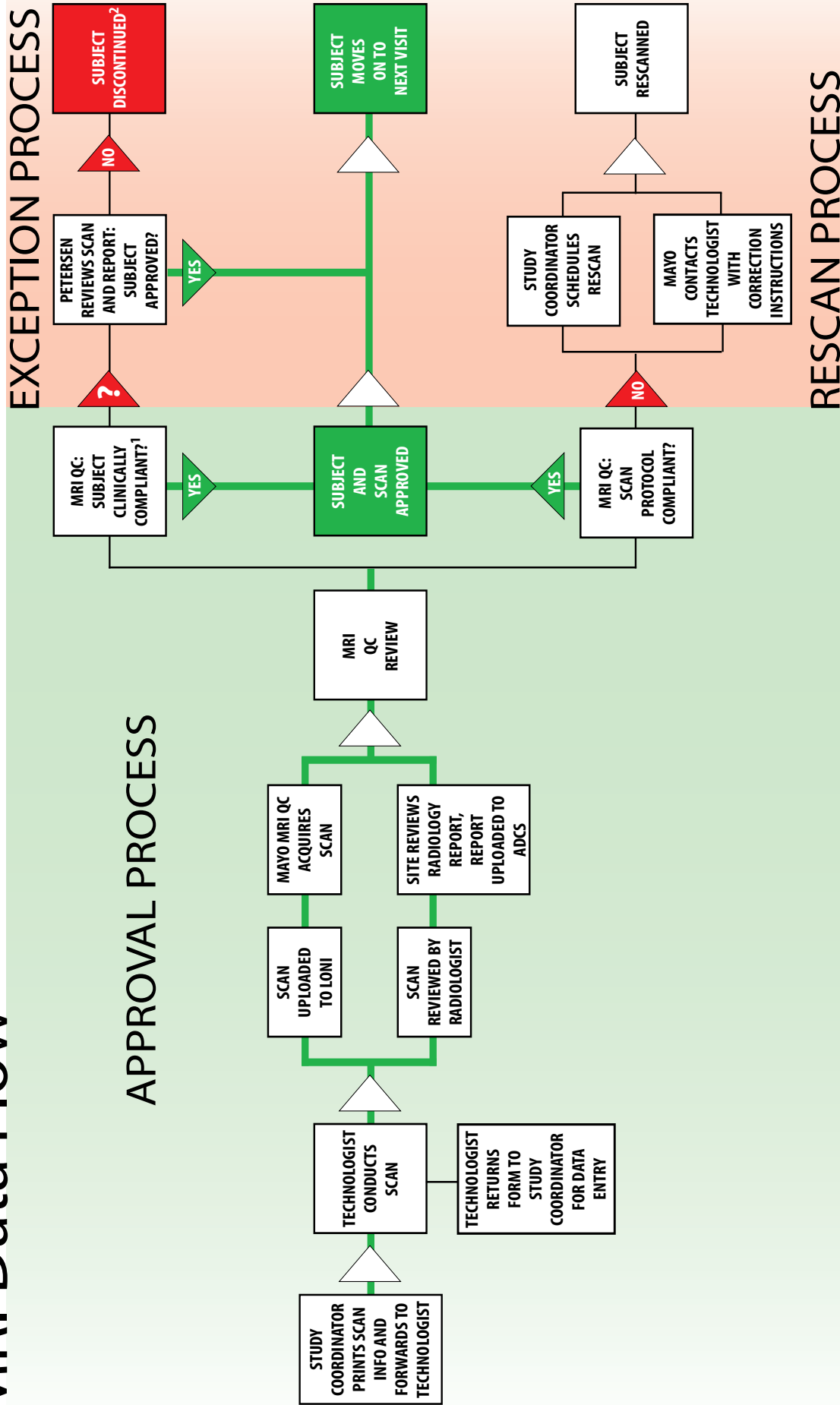
The radiology center will upload each MRI scan to the Laboratory of Neuroimaging (LONI). In some institutions the study coordinator may be asked to do this uploading. If this is the case, please request training by emailing: adni@loni.ucla.edu.

After each scan is completed, each site will be responsible to acquire a clinical read of the scan and upload that clinical read onto the ADCS distributed data entry system. For detailed instructions on uploading, please refer to the data entry manual. A site clinician will need to indicate whether the radiology report shows results 'normal for age' or 'abnormal for age'. If 'abnormal for age' the site clinician will be prompted to provide more information. The result of the site clinician's review will be forwarded to the ADNI MRI QC team at the Mayo Clinic.

A local radiological interpretation of all 1.5 T MRI studies is required. Clinical interpretation of 3 T studies is optional. Some sites may wish to omit radiological interpretation of 3 T scans, while local practice parameters at others may require a clinical interpretation of all research studies. This is left to the discretion of each site. Please inform ADCS whether your site plans on providing radiological interpretation of 3 T studies or not.

MRI Data Flow

APPROVAL PROCESS

```
STUDY
COORDINATOR
PRINTS SCAN
INFO AND
FORWARDS TO
TECHNOLOGIST
   │
   ▽
TECHNOLOGIST
CONDUCTS
SCAN ───────── TECHNOLOGIST
   │            RETURNS
   ▽            FORM TO
              STUDY
SCAN            COORDINATOR
UPLOADED        FOR DATA
TO LONI         ENTRY
   │
MAYO MRI QC
ACQUIRES
SCAN
   │
SCAN
REVIEWED BY
RADIOLOGIST
   │
SITE REVIEWS
RADIOLOGY
REPORT,
REPORT
UPLOADED TO
ADCS
   │
   ▽
MRI
QC
REVIEW
```

EXCEPTION PROCESS

```
MRI QC:                    SUBJECT
SUBJECT          SUBJECT   DISCONTINUED[2]
CLINICALLY  ──?── PETERSEN ──NO──
COMPLIANT?[1]      REVIEWS SCAN
   │ YES          AND REPORT:
                  SUBJECT
                  APPROVED?
                     │ YES
SUBJECT AND          ▽
SCAN        ──────► SUBJECT
APPROVED            MOVES
                    ON TO
                    NEXT VISIT
```

RESCAN PROCESS

```
MRI QC:          STUDY
SCAN      ──NO── COORDINATOR ──── SUBJECT
PROTOCOL         SCHEDULES         RESCANNED
COMPLIANT?       RESCAN
   │ YES
                 MAYO
                 CONTACTS
                 TECHNOLOGIST
                 WITH
                 CORRECTION
                 INSTRUCTIONS
```

1. The Mayo QC team reviews the scan and the report from the site radiologist side by side. If a significant abnormality is seen (*e.g.*, hemispheric infarction), 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. When a scan is failed or approved, the ADCS will email notification to the Site PI, Study Coordinator, QC Group and Protocol PI so as to prevent duplication.

QUALITY REVIEW OF SCANS

The ADNI MRI QC team at Mayo will review the scan (acquired from LONI) and the radiologist report (uploaded by the site) concurrently. The QC team will check whether the scan meets protocol specifications and for clinically significant findings. This process will occur for every MRI scan conducted for the ADNI.

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 or withdrawn from MRI, please refer to the Study 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 two weeks of the original scanning date. If the scan is outside of this window an additional comments form should be completed for this visit documenting the reasons for deviation.

> 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.

Required Phantom Scanning at the Site

The radiology center for each site will be required to scan a phantom when scanning ADNI subjects in order to ensure that the scanners are in compliance with ADNI 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. Detailed instructions are provided in the ADNI MRI technical manual (available in the document repository).

GUIDELINES FOR SCHEDULING MRI SCANS

Screen/Baseline 1.5T MRI

Most sites will need more than 2 weeks in order to obtain an imaging slot at their local MRI center. We would like to recommend that sites schedule the Screening/Baseline 1.5 T MRI between 10-14 days after the screen visit date. When a clinical monitor has completed a review of the screening visit the site will receive either a preliminary approval or screen fail notification. If the subject is a screen fail the Screening/Baseline MRI must be cancelled. **A subject should not receive the screening MRI unless monitor approval has been received.** To request that the Screening/Baseline MRI be conducted prior to monitor approval, please contact Dr. Petersen (peter8@mayo.edu).

> Please note: The screening 1.5 T MRI will be used to confirm subject's eligibility for ADNI. If confirmed as eligible the screening 1.5 T MRI will serve as the baseline 1.5 T MRI. A scan within 2 weeks of the baseline visit will only be necessary if the subject is part of the 3 T MRI or PET studies.

After the Screening/Baseline MRI is reviewed and approved by the MRI QC team the site will receive final approval for the subject. Included in this final approval will be the subject's scan assignment, which will determine whether the subject has PET or 3 T MRI, when both are available at the site and a subject consents to both. The baseline scan should not be scheduled until final approval has been received. The baseline scan must take place within 2 weeks of the baseline visit.

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 baseline 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 2 weeks of the original scan date. If a scan or rescan is conducted outside of the allotted window an additional comment form documenting the reason for protocol deviation will be required.

> If a subject consents to lumbar puncture, this procedure should be done **after** any 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.

No sedation medications are allowed for ADNI. If a subject is not comfortable with MRI he/she should not be enrolled in ADNI.

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 that the ADNI MRI protocol should be used in scanning this subject.

Hardware/Software Upgrades: It is likely that most MR scanners in the ADNI will require software and/or hardware upgrades throughout the duration of the study. *Prior* to any software of hardware upgrading the site must inform the ADNI MRI Team at Mayo 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 subjects.

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 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"** please do not include the subject in the ADNI. 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. Please keep in mind that subjects requiring sedation for MRI should not be included in ADNI.

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.
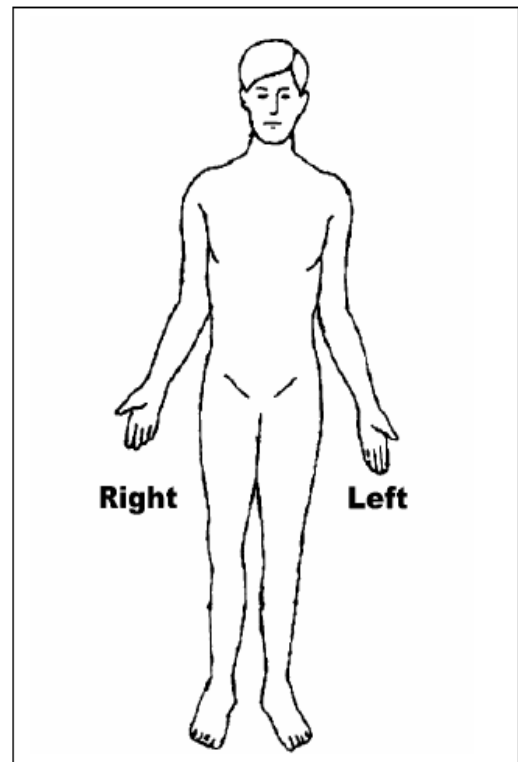
Date _____/_____/___

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

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

Right   **Left**

Remove all metallic objects prior to your MRI examination

Explanation _____

_____   _____
Signature of subject or subject's representative   *Name of Representative*

_____   Date _____/_____/_____
Signature of person administering screening form

Date _____/_____/_____

MRI PAMPHLET

The MRI pamphlet should be distributed to subjects in the Alzheimer's Disease Neuroimaging Initiative.

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 caretaker.

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 protocol.

Alzheimer's Disease Neuroimaging Study

Magnetic Resonance Imaging

Information for Volunteers

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

PET Procedures

SUMMARY

PET Imaging with fluorodeoxyglucose (FDG) is a major component of the Alzheimer's Disease Neuroimaging Initiative (ADNI). 50% of all subjects will have PET scans completed at regular intervals throughout the study in addition to 1.5T MR scans. The initial PET scan will occur at baseline and follow-up scans will occur at every subsequent in-clinic visit. The timing of visits and scans depends upon subject group (Normal, MCI, AD), please refer to the Schedule of Assessments under the ADNI Protocol section of this manual.

Subjects will only receive PET scans if (1) a site offers PET as part of ADNI, (2) the subject has no specific exclusions to PET, (3) the subject agrees to PET on the consent, and (4) the subject has been assigned to the PET scan category by the Coordinating Center at the ADCS. For more detail on scan category assignment, please see the Screening Process section of this manual.

All PET sites will need to meet PET certification requirements in order to begin enrolling for ADNI. This certification process includes scanning of a phantom and can be completed prior to regulatory approval. Please refer to the Startup Certification section for specific instructions on how to become certified for PET. PET scanning of a phantom is only required during certification and may be required if a site is consistently performing poorly.

All subjects who choose 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, or a history of receiving radiation for research purposes within the past year. Subjects will have had a screening MRI as part of ADNI 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.
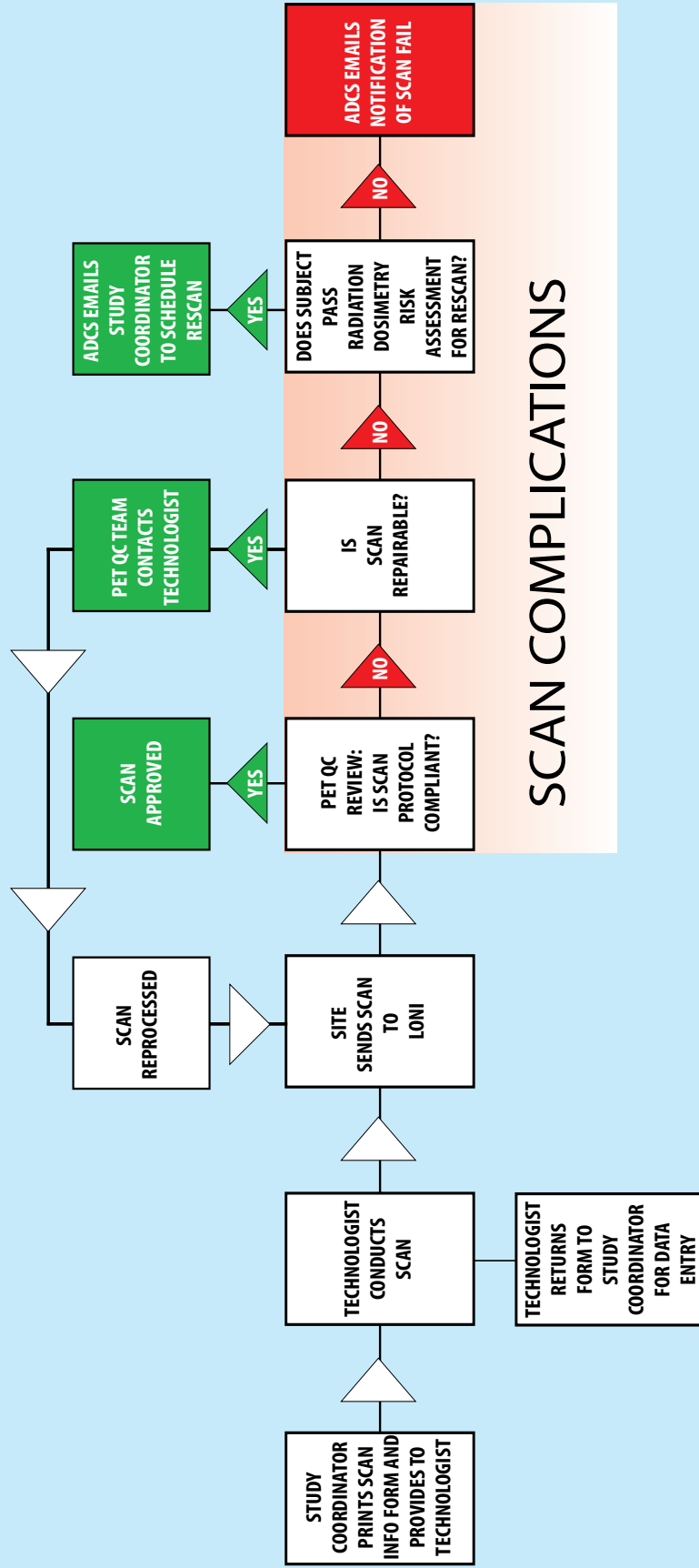
❏ Yes ❏ No Is there a history of radiation therapy?
❏ Yes ❏ No Is there a history of having radiation for research in the past year?
❏ Yes ❏ No Would there be problems with the subject's ability to cooperate with scan?

DATA FLOW

Please refer to the PET Data Flow on the next page 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 Certified Nuclear Medicine Technologist (CNMT) who will usually be the individual conducting the study. They must ensure the CNMT has a copy of the PET Scan Information Form for every scan session scheduled and a process has been worked out between the study coordinator and 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 ADCS distributed data entry 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 Imaging Technical Manual. If your radiology center is unable to upload scans to LONI, please request training for uploading by emailing: adni@loni.ucla.edu.

PET Data Flow

STUDY COORDINATOR PRINTS SCAN INFO FORM AND PROVIDES TO TECHNOLOGIST

TECHNOLOGIST CONDUCTS SCAN

TECHNOLOGIST RETURNS FORM TO STUDY COORDINATOR FOR DATA ENTRY

SITE SENDS SCAN TO LONI

SCAN REPROCESSED

PET QC REVIEW: IS SCAN PROTOCOL COMPLIANT?

SCAN APPROVED — YES

IS SCAN REPAIRABLE?

PET QC TEAM CONTACTS TECHNOLOGIST — YES

NO

DOES SUBJECT PASS RADIATION DOSIMETRY RISK ASSESSMENT FOR RESCAN?

ADCS EMAILS STUDY COORDINATOR TO SCHEDULE RESCAN — YES

NO

ADCS EMAILS NOTIFICATION OF SCAN FAIL

SCAN COMPLICATIONS

NOTE: When a scan is failed or approved, the ADCS will email notification to the Site PI, Study Coordinator, QC Group and Protocol PI so as to prevent duplication

QUALITY REVIEW OF SCANS

Every 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. If a problem is found with the way the scan was done and it can be fixed, the PET QC team will contact the technologist directly.

If the problem with the scan is not fixable, the PET QC team will provide the 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 an additional comment form documenting the reason for the protocol deviation will be required.

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 PET Scan Information Form. As for all rescans for PET, the subject's overall radiation exposure will be assessed before a rescan is requested. 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. If the rescan also fails due to subject motion or non-compliance the subject should be dropped from the PET study. In cases where the site believes the failure to be correctable, an exception should be requested to allow the subject to remain in the PET study. The exception request should sufficiently document the reason for the failed scan and why the site believes the problem to be correctable.

> Questions on PET Technical issues: **adnipet@adni.ucsd.edu**

Poor Performance on PET Scanning

If a PET site produces three technically inadequate PET scans the site will be reviewed and suspended from the PET study pending further instruction. Additional scanning of brain phantoms may be required for sites consistently performing poorly.

GUIDELINES FOR SCHEDULING 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 should be scheduled after the Screening/Baseline MRI scan is reviewed and final approval has been sent to the site PI and study coordinator. At this point sites will also receive the subject's scan category, which will determine whether the subject will participate in the PET component of the study. Even if a site has only PET and not a 3 T MRI scanner, it is possible that a subject will **not** be asked to have a PET scan.

> **It is very important that the baseline PET scan not be scheduled until the site receives final approval and the subject is assigned to the PET scan category.**

If a baseline scan is scheduled prior to final approval the site may have to cancel scans, inconveniencing the subject and the radiology center.

PET scans should be scheduled as far in advance as possible, taking the subject's availability into account. After the Baseline data has been entered, a report of the subject's target visit/scan date and visit windows will be available at http://adni.ucsd.edu under 'Reports'. Scans for all visits should take place within 2 weeks of the target date. If scans take place outside of the allowed time window sites should provide the reason for the protocol deviation on an additional comment form.

> If a subject consents to lumbar puncture, this procedure should be done **after** any 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 imaging session.

No sedation medications are allowed for ADNI. If a subject is not comfortable with PET he/she should not be enrolled in this arm of the study.

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 technologists.

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 PET scan information form with ADNI subject ID.
- ❏ Scan uploaded to LONI (by technologist if possible).
- ❏ PET Scan Information form received and data entered 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 that the ADNI PET protocol should be used in scanning this subject.

PET PAMPHLET

The PET pamphlet should be distributed to subjects in the Alzheimer's Disease Neuroimaging Initiative who are assigned to the PET scan category.

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

Subjects should have plenty of time to review this information before their PET appointment so the pamphlet should be distributed to subjects when they are scheduled for their 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 appointment (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 appointment and display it when they check in to assure that they are scanned with the appropriate Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol.

Alzheimer's Disease Neuroimaging Initiative
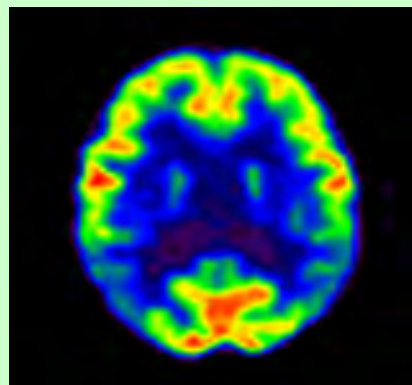
PET IMAGING

Information for Volunteers

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

Promising biomarkers that will be measured in ADNI fluids:

    ⇨ Tau in CSF

    ⇨ Amyloid beta in CSF

    ⇨ Isoprostanes in CSF, plasma, urine

    ⇨ Homocysteine in plasma, CSF

    ⇨ APOE genotyping-blood

    ⇨ DNA from blood cells

This section includes procedures for the collection, processing and shipment of clinical laboratory and APOE samples at screen, cell immortalization samples at baseline, blood and urine samples for biomarkers, and lastly cerebral spinal fluid samples. A glossary of terms is at the end of this section.

Number of Tubes Collected per Subject by Visit

SAMPLES SENT TO:	TEST TYPE	SC	BL	M6	M12	M18 MCI only	M24	M36 NL & MCI
Covance	Clinical Labs	2 BLD SER 1 BLD EDT PL 1 URN						
UPenn	ApoE	1 BLD EDT						
NCRAD	Cell Immortalization		2 BLD ACD					
UPenn	Biomarker Labs		2 BLD EDT PL 2 BLD SER 2 CSF 1 URN	2 BLD EDT PL 2 BLD SER 1 URN	2 BLD EDT PL 2 BLD SER 2 CSF 1 URN	2 BLD EDT PL 2 BLD SER 1 URN	2 BLD EDT PL 2 BLD SER 1 URN	2 BLD EDT PL 2 BLD SER 1 URN
Total # tubes per visit per subject		5	9	5	7	5	5	5

SAMPLE IDENTIFICATION AND TRACKING

All samples for ADNI will be identified using barcoding. Clinical Laboratory Samples at Screen will use Covance's barcode system. All other samples (APOE, Cell Immortalization, Blood, Urine and CSF) must be identified using the ADNI Sample Identification label (see image).

Sample Identification labels for Visits I and 2 (Screening and Baseline) will be sent to sites by the Coordinating Center when the site has completed all certification requirements. Labels for subsequent visits (Month 6 and on) will need to be requested by completing the Supply Order Form and emailing to: support@adni.ucsd.edu. Labels will be grouped and should ONLY be used for the visit printed on the barcode.

ADNI Sample Identification Label

Please confirm you have barcodes for each visit before scheduling the visit.

License Plate

Covance bar code - DO NOT USE for ApoE, Biomarkers or Cell Immortalization!

Visit Numbering

Visit	Number	Abbreviation
Screen	I	VST I
Baseline	2	VST 2
6 months	3	VST 3
12 months	4	VST 4
18 months	5	VST 5
24 months	6	VST 6
36 months	7	VST 7

SAMPLE TRACKING

All samples (except for clinical laboratory samples sent to Covance) will be tracked online using the barcode label License Plate and Fedex Tracking number. The APOE Collection Form and Biomarker Collection Form must be completed **on the day of each visit**. This form includes information used to track the sample, confirm receipt of the sample, and information essential to processing and analysis.

Once completed online, a printed copy of the Biomarker Collection Form should be included in the sample box. Please follow specific collection, processing and shipment procedures as detailed in the following pages.

SAMPLE QUALITY CHECKS

In addition to being tracked online, the condition and amount of samples received will be tracked by the Biomarker Core. 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 Biomarker Collection Form and a reason should be provided.

Sample Amounts Obtained at each visit (mL)

Sample Type	Amount	Visit
Urine	10 mL	All Visits
Plasma from blood	20 mL	All Visits
Serum from blood	20 mL	All Visits
CSF	15 - 20 mL	BL and M12
Blood for NCRAD	2 x 8.5 mL	BL
Blood for APOE	10 mL	SC

Important: Each barcode has the visit and sample type in print. It is very important that this match the sample and visit collected.

CLINICAL LABORATORY SAMPLES AT SCREENING

Clinical Laboratory Kits

Covance will send an initial supply of clinical laboratory kits to each site. Instructions on how to correctly complete the Laboratory Requisition form and prepare and ship samples are provided with the kits.

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

Each Clinical Lab Kit Contains:

➪ Tubes (expiration date noted on outside of box)
➪ 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
➪ Diff-safe (Be sure to REMOVE this from the tube before shipping)
➪ Pipettes
➪ Test tube sleeve
➪ Absorbent material
➪ Bag with sleeve for requisition
➪ Gel-pack (Do not put specimens into the gel; wrap the whole gel pack around the specimens)

You Will Need To Provide:

➪ Tourniquet
➪ Alcohol
➪ Gauze
➪ Bandage
➪ Dry ice

Covance Will Also Send:

➪ Investigator Manual (with CAP, CLIA, and Medical Director CV)
➪ Shipping boxes: ambient, frozen, and combination
➪ Airborne labels

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 miltary, or 24-hour clock

⇒ Dates use the international convention: DD_MMM_YYYY. Example: 0 1 J A N 2 0 0 4

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 Airborne 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, or ship supplies, please call Covance at: (800) 327-7270

It is the responsibility of each site to monitor the expiration date of each kit.

To call Airborne for a Covance specimen pickup, call (888) 708-8825
To contact Covance, call (800) 327-7270 and listen to the messages.

> **Please refer to the Covance Procedures Manual for specific instructions on sample collection, processing and shipment.**

APOE SAMPLES AT SCREENING

APOE sampling is required for final approval in ADNI. For more details on this, please refer to the section on scan category assignment. One blood sample will be collected at the screening visit for APOE genotyping.

Begin by completing the information on the BLD EDT tube label, as described below, and secure the label onto the lavender top tube.

Sample Bar Code Labels will contain the following information:
- ➪ Bar Code & License Plate
- ➪ ADNI
- ➪ Lavender Top
- ➪ Visit (VST 1)
- ➪ Sample type (BLD EDT)

In addition, write in the subject ID number, the date/time of collection and circle M or F to indicate subject gender, on the bar code label specific for BLD EDT VST 1. Secure this label on the BLD EDT tube prior to the blood draw.

Collection Tube: 1 10cc Lavender Top tube; gently mix by inversion, 10 -12 times, to assure that the EDTA anticoagulant is well-mixed with the whole blood sample.

Temperature Requirements: The whole blood sample must be received by the UPenn Biomarker repository within 24 hours of collection. The whole blood sample is maintained at room temperature and shipped at ambient temperature.

Sample Tracking: Complete online form with sampling date, time, bar code License Plate and FedEx tracking number. Print out the completed form and include it with the shipment.

Shipping: APOE sample shipping kits, including blood tubes & blood collection set, will be provided by Covance. Sites must request resupply of these kits. Samples will be shipped by Federal Express – Priority Overnight to UPenn. 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.
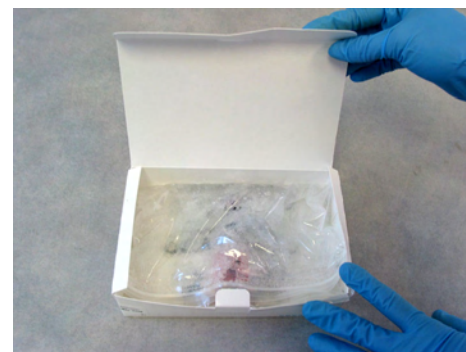
UPenn Address: ADNI Biomarker Core Laboratory
7 Maloney South
University of Pennsylvania Medical Center
3400 Spruce Street
Philadelphia, PA 19104

Biomarker Helpdesk: adni@uphs.upenn.edu
Fax: 215-349-5092

Packaging Procedures for ApoE Samples at Screening

1. Place filled lavender top tube with completed sample identification label into the Specimen Collection Bag containing an absorbent packet. Place bag on flat surface to minimize wrinkles, especially at adhesive sealing area. Remove tape backing to expose adhesive. Carefully fold top of bag at the slit opening *(When folded properly, the star will be visible inside of the small box outline).* Starting at the center of the folded edge and working outward to the edges, firmly rub the entire folded area to complete the closure.

2. Prepare gel pak to insulate sample. Fill to the indicator line with cool tap water. Lightly press the absorbent pack to expel its contents. Massage the bag until water has been absorbed and a gel material has formed. Evenly distribute gel in bag, express air and reseal. Place specimen collection bag on top of the gel pak. Wrap the gel pak around the specimen collection bag, sandwiching the specimens in the middle. Place the specimens and gel pak into the white kit box. Place the ADNI shipping label on the top of the white kit box. **The license plate on this label should match the sample inside the box.** Remember to package samples from separate individuals in separate white kit boxes!

3. Place the kit into the large plain zip bag. Place the ambient kit box into shipping carton. Fill the excess space with filler paper (e.g. newspaper). Insert the tabs to close the box Complete and affix the Fed Ex airbill (University of Pennsylvania) to the designated spot on the box. Send Priority Overnight.

CELLS FOR IMMORTALIZATION

Blood will be collected at the Baseline visit that will be sent to the National Cell Repository for AD.

Begin by completing the information on the two BLD ACD tube bar code labels, and secure one label onto each of two yellow top tubes.

Sample Bar Code Labels will contain the following information:
- ⇨ Bar Code & License Plate
- ⇨ ADNI
- ⇨ Yellow Top
- ⇨ Visit (VST 2)
- ⇨ Sample type (BLD ACD)

In addition, write in the subject ID number, date/time of collection and circle M or F to indicate subject gender, on each of two bar code labels specific for BLD ACD and place each on the yellow top blood collection tubes.

Collection Tube: Two 8.5 cc Yellow Top tubes; fill each bar code labeled tube with blood and gently mix by inversion 6-10 times to assure complete mixing of the blood sample with the anticoagulant Acid Citrate Dextrose.

Temperature Requirements: The whole blood sample must be received by the National Cell Repository within 24 hrs of collection. The whole blood sample is maintained at room temperature and shipped at ambient temperature.

Sample Tracking: Complete online form with sampling date, time, bar code License Plate and FedEx tracking number. Print out the completed form and include it with the shipment.

Shipping: Sample shipping kits for shipment to the National Cell Repository for AD will be provided by Covance. Sites must request resupply of these kits. Shipping of all samples will be done by Federal Express, priority overnight to NCRAD. All shipping materials will be provided by Covance. For those instances in which a Friday study visit is necessary, store the tubes at room temperature and ship on Monday by Federal Express, priority overnight.
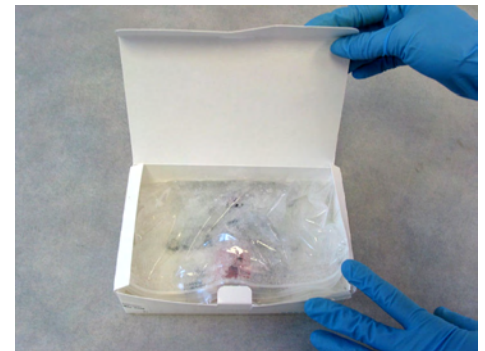
NCRAD Address:	Michelle Goodman
	National Cell Repository for AD
	Department of Medical and Molecular Genetics
	975 W. Walnut Street, IB-130
	Indianapolis, IN 46202
NCRAD Helpdesk:	alzstudy@iupui.edu
	1 (800) 526-2839

Packaging Procedures for Cell Immortalization (NCRAD) Samples at Baseline

1. Place two filled yellow top tube with completed sample identification label into the Specimen Collection Bag containing an absorbent packet. Place bag on flat surface to minimize wrinkles, especially at adhesive sealing area. Remove tape backing to expose adhesive. Carefully fold top of bag at the slit opening *(When folded properly, the star will be visible inside of the small box outline).* Starting at the center of the folded edge and working outward to the edges, firmly rub the entire folded area to complete the closure.

2. Prepare gel pak to insulate sample. Fill to the indicator line with cool tap water. Lightly press the absorbent pack to expel its contents. Massage the bag until water has been absorbed and a gel material has formed. Evenly distribute gel in bag, express air and reseal. Place specimen collection bag on top of the gel pak. Wrap the gel pak around the specimen collection bag, sandwiching the specimens in the middle. Place the specimens and gel pak into the white kit box. Place the ADNI shipping label on the top of the white kit box. **The license plate on this label should match the sample inside the box.** Remember to package samples from separate individuals in separate white kit boxes!

3. Place the kit into the large plain zip bag. Place the ambient kit box into shipping carton. Fill the excess space with filler paper (e.g. newspaper). Insert the tabs to close the box Complete and affix the Fed Ex airbill (National Cell Repository) to the designated spot on the box. Send Priority Overnight.

BIOMARKERS: BLOOD AND URINE SAMPLES
Blood and Urine Samples will be collected at every study visit from Baseline. All biomarker 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.

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 printing out a PDF of the Biomarkers Samples Form from the ADCS distributed data entry system and completing the Sample Identification labels. The Sample Identification label must be placed on the transfer tube prior to freezing!

Order of Fluids to be Collected:
1. Biomarker plain red-top tubes (2 blood collection tubes)
2. Biomarker lavender-top (2 blood collection tubes)
3. Urine collection container
4. CSF Collection (if applicable)

FOLLOW SAFE BLOOD-HANDLING PROCEDURES THROUGHOUT!

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.
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 plasma 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.
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.

Urine collection:

1. Write the Subject Identification Number on the side of one urine collection cup prior to urine collection.
2. Ask study subject to collect urine specimen in the collection cup.
3. Pour enough of the urine specimen to at least half-fill one 50 mL centrifuge tube and cap with the screw-cap.
4. Centrifuge the tube at room temperature within one (1) hour of collection. Spin for 15 minutes to remove sediment and cells using the Sorvall T 6000D Centrifuge (rotor H-1000B swinging bucket rotor) at 2500 rpm (1050 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 URN and place this on one 13 mL plastic transfer tube (yellow screw cap), place in a tube rack in the vertical position.
6. Using a clean transfer pipette carefully transfer urine from the 50 mL centrifuge tube into the bar code-labeled 13 mL plastic transfer tube, then firmly cap with the yellow screw cap.
7. After the urine aliquot has been transferred to the plastic labeled tube and capped, place the yellow screw-capped URN-labeled tube upright in dry ice and allow to completely freeze the urine sample.

Cerebrospinal fluid collection:

1. Write in the Subject Identification Number, the time and date of collection and circle M or F to indicate subject gender, on two bar code labels specific for CSF and place each of these on two 13 mL plastic transfer tubes (clear screw cap) prior to transfer of the CSF samples.
2. Follow the detailed procedure as described in the Instructions for Assisting with the LP Procedure section of the Procedures Manual for the CSF collection **(end of this section).**
3. Aliquoting the first 2 mL of CSF for cell counts, glucose and total protein, transfer the remainder of the CSF collection into two 13 mL plastic transfer tubes, firmly cap with clear screw caps.
4. Place the clear screw-capped CSF-labeled tubes upright in dry ice and allow to completely freeze the CSF sample.

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

Sample Tracking:

Enter the sample collection data on the ADCS distributed data entry system (http://adni.ucsd.edu). 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.

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. Use the Federal Express Airbill that has the ADNI Biomarker Core Laboratory shipping address information printed on it:

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

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

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

### Supplies for Biomarker Samples from Covance:

1. 10-ml, plain red top plastic Vacutainer blood tubes
2. 10-ml, lavender top plastic Vacutainer blood tubes
3. Urine collection containers
4. 50-mL screw-cap centrifuge tube
5. 13-mL polypropylene transfer tubes with colored screw caps
6. Disposable sterile transfer pipettes
7. Blood collection set with 21-gauge butterfly needle
8. Vacutainer tube holder
9. Styrofoam inner shipping container
10. Cardboard shipping box

⇨ **To order additional Biomarker kits, please contact Covance at (800) 327-7270.**

Supplies for Biomarker Samples from ADCS:

1. Sample bar code labels
2. Shipping labels
3. Lumbar Puncture supplies
4. Bubble-wrap bags
5. Outer ziplock bags

Biomarker Sample Transfer Tubes

Red-top transfer tube (serum)

Lavender-top transfer tube (plasma)

Yellow-top transfer tube (urine)

Clear-top transfer tube (CSF)

Biomarker Kit Contents

Vacutainer tube holder

50 mL screw-cap centrifuge tube

Blood collection set

Disposable sterile transfer pipettes

Urine collection Container

Lavender-top tubes

Plain Red-top tubes
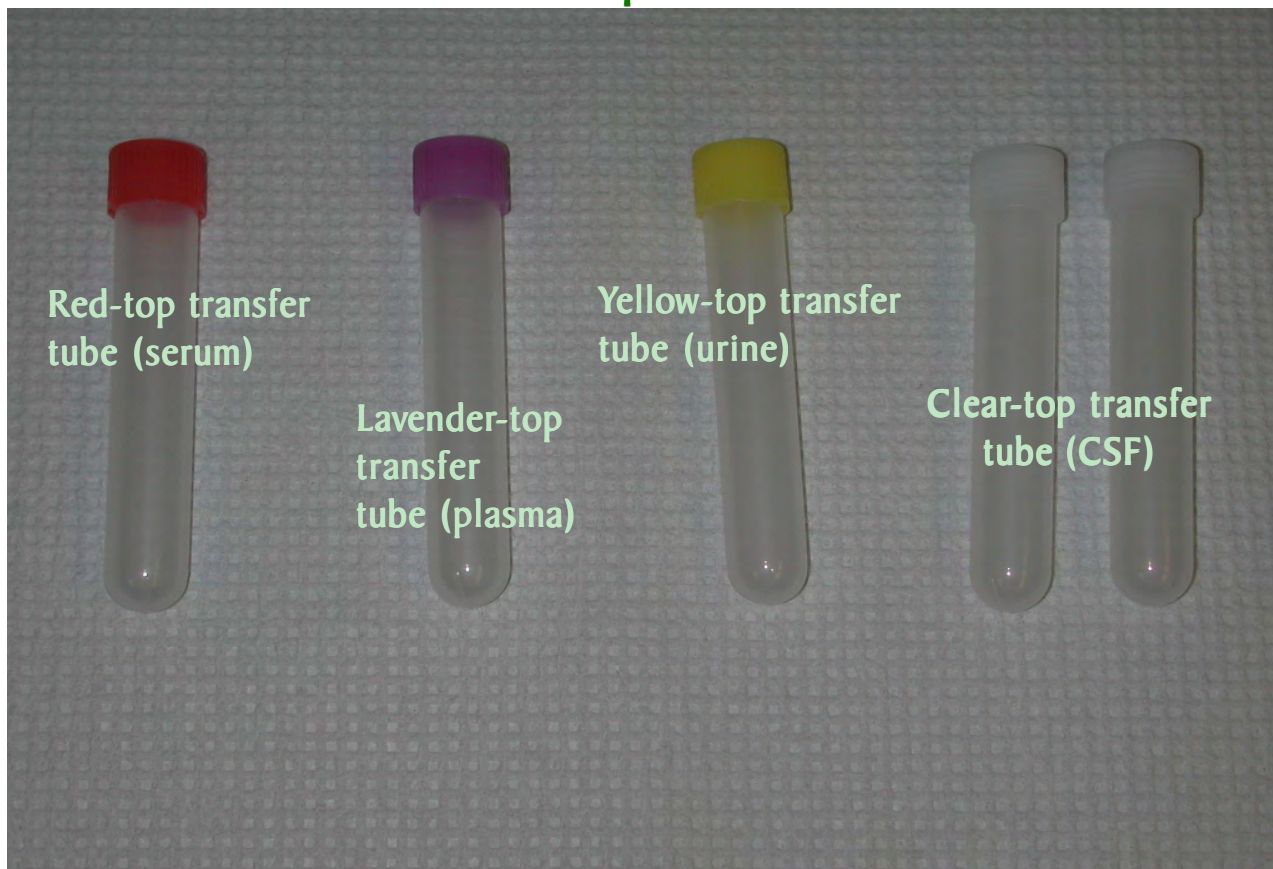
Polypropylene transfer tubes with screw-caps

Packaging Procedures for Biomarker Samples

1. After samples have been completely frozen upright in dry ice, package them for shipment. Place small pieces of dry ice in a bubble-wrap bag. Quickly transfer the labeled sample transfer tubes from dry ice to the bubble-wrap bag and seal the bag with the self-adhesive flap.

2. Quickly place the bubble bag with contents into the large ziplock bag and seal. Place the poly bag and contents directly on dry ice in styrofoam shipping box. Fill the box with dry ice and cover. Place container into cardboard box; affix Federal Express (University of Pennsylvania) shipping label and call for pick up. Ensure box is labeled with 'biohazard' and 'dry ice' labels prior to shipment.

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

BIOMARKERS: CEREBRAL SPINAL FLUID

CSF samples will be collected from all subjects who are willing at the Baseline and M12 Visit. A video describing the LP procedure will be provided to all sites. All biomarker samples should be collected in the morning before breakfast and after an overnight fast. Only water is permitted until blood draws and the lumbar puncture are completed.

> If a subject consents to lumbar puncture, this procedure should be done **after** any 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.

Prevention of Post-Lumbar Puncture headache:

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

Mild to Moderate headache after a lumbar puncture:

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

Treatment of Mild to Moderate headache:

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

Severe headache after a lumbar puncture:

Severe headache which may be accompanied by nausea, vomiting, tinnitus, and/or visual disturbances and which is relieved by supine posture requires epidural blood patch to provide rapid relief. This type of headache most commonly occurs on the morning following LP, when the person arises from bed. Posturally-sensitive severe post-LP headache can last as long as a week even with bedrest and analgesics if not treated with epidural blood patch. **IT IS HIGHLY RECOMMENDED** that each site identify an anesthesiologist who is agreeable to performing an EPIDURAL BLOOD PATCH for any subject who experiences severe post lumbar puncture headache. Sites should find out ahead of time who to call to schedule and perform a blood patch at their center, should the need arise, as well as how their study account will be billed.

Lumbar Puncture Supplies

Supplies for collecting and for shipping the CSF are sent separately to the site.

I. Initial supply of Lumber Puncture Materials (provided by the ADCS):
- ❏ Lumbar Puncture Trays (5)
- ❏ 24g Sprotte Atraumatic Spinal Needles and Introducers (10)
- ❏ 25g 1 1/2" needles for deep local anesthesia (25)
- ❏ 5 cc sterile syringes (25)
- ❏ 13 mL transfer tubes with clear caps (20)

Additional Lumbar Puncture kits and needles can be ordered by contacting: support@adni.ucsd.edu

The lumbar puncture tray contains the following items which will be used to perform lumbar puncture. Check the dates of expiration: these reflect the expiration date of the lidocaine.

- ❏ Three Sponge Sticks
- ❏ Three 2 X 2 Gauze pads
- ❏ Paper drape
- ❏ Fenestrated Paper Drape
- ❏ Lidocaine Hydrochloride USP, 1%, 2 ml ampule
- ❏ 20g needle for drawing up lidocaine into syringe (will not be used to inject lidocaine)
- ❏ Infiltration needle (25g x 1/2") for skin infiltration for local anesthesia
- ❏ Prep Well
- ❏ Four pre-labeled Specimen vials with Caps, 10 ml (for cell count and glucose)
- ❏ Adhesive Bandage (Band-Aid)

The lumbar puncture tray contains the following items which will NOT be used when following the ADNI guidelines for Sprotte Needle use:

- ⇨ 20g spinal needle, plastic manometer and extension tube.

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 (in case more lidocaine is needed)
- ❏ Sterile 4 by 4 gauze pads (extras)
- ❏ Extra adhesive bandages (Band-Aids)
- ❏ clean washcloths and towels
- ❏ Sharps container
- ❏ Lumbar Puncture Fact Sheet and Post-LP instructions for subjects

Instructions for Assisting with the LP Procedure

SETTING UP FOR THE LP

- ⇨ On the bedside table nearest where the person performing the Lumbar Puncture will sit, place a pair of sterile gloves (in their packaging) and a blue pad. They will need these at the beginning of the Lumbar Puncture. Have all other supplies on hand.
- ⇨ The Lumbar Puncture may be done with the subject either lying down on their side, or sitting.
- ⇨ It is critical to try to optimize this positioning, and usually requires an assistant.
- ⇨ On an over-bed table, remove the contents of the Lumbar Puncture kit from the outer plastic packaging, leaving the contents wrapped in their sterile drape. Leave everything wrapped until the person performing the Lumbar Puncture is seated, and begins examining the subject.
- ⇨ Feel the outside of the Lumbar Puncture kit (still wrapped up) to determine which end contains the spongy swabs. Turn this end toward the person performing the Lumbar Puncture and begin unwrapping the kit. Touch only the outside of the paper wrapper. When you grab an edge to unfold it, touch only the folded under portions of the outside of the wrapper. Also, don't let the outside of the wrapper touch any part of the inside. If you touch any part of the inside of the paper wrapper, or if any non-sterile object or 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 I/4 inch deep. Spend as little time as possible lingering over the kit.

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.

⇨ Also, 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 I I/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.

➪ The 25 g I I/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.

ALIQUOTTING THE CSF

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

⇨ As the person performing the Lumbar Puncture fills the 5 cc syringes, 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.

Hand the first full syringe to the aliquoter, have them aliquot 1ml for red and white cell count and 1ml for total protein and glucose into the tubes taken from the kit for local laboratory testing. Transfer each 5 cc syringe-ful of CSF into the barcode-labeled transfer tubes. Each transfer tube can hold the volume from two 5 cc syringes so the first two 5 cc syringe-fuls are transferred into one transfer tube, labeled with a CSF bar code, and the subsequent 5 cc syringe-fuls are transferred into the second CSF bar code-labeled tube.

⇨ 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 Biofluid Processing Procedure 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 distributed data entry system (http://adni.ucsd.edu) as soon as they are received.**

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 OR the spinal introducer all the way. Use only about 2/3 of their length (to prevent entering the subarachnoid space with anything other than the Sprotte 24g 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 a Sprotte needle (ADNI recommended procedure) is used for the lumbar puncture, the CSF is drawn in four or more 5 ml sterile syringes.

If a conventional needle was used, then CSF is dripped into the large collection tubes in the Lumbar Puncture kit, and the transfer pipet is used to transfer CSF to the transfer tubes with the clear top.

1. Place 1 ml of CSF in the tube for cell count, send at room temperature to local lab.

2. Place 1ml of CSF for protein and glucose into the tube from the LP tray and ship to your local lab.

3. Aliquoting the first 2 mL of CSF for cell counts, glucose and total protein, transfer the remainder of the CSF collection into two bar code labeled 13 mL plastic transfer tubes, firmly cap.

4. Place the clear screw-capped CSF-labeled tubes upright in dry ice and allow to completely freeze the CSF sample.

5. Package and ship along with Biomarker Blood and Urine samples as directed previously in this section.

NOTE: If the initial CSF was blood-tinged, discard the first 1-2 ml until later CSF begins to clear.

> A Lumbar Puncture Information Sheet is available which includes instructions for the subject to take home. To request a copy, please email: brainlink@ucsd.edu.

Biofluids Glossary

ADNI	Alzheimer's Disease Neuroimaging Initiative
AD	Alzheimer's disease subject
NC	Normal Control subject
MCI	Mildly Cognitively Impaired subject
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
NCRAD	National Cell Repository for Alzheimer's Disease
LP	Lumbar Puncture

Adverse Events and Serious Adverse Events

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 should 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. Please see the Data Entry Manual for an explanation of electronic signatures.

At each study visit, the AE/H online forms should be reviewed with the study partner and appropriate changes made.

Event

The AE/H form is designed for reporting one adverse event (AE) per online form. If the AE is a known diagnosis, enter the diagnosis in the box labeled "Event." If an AE is reported to the interviewer as a group of symptoms for which there is no apparent unifying diagnosis, each symptom should be listed as a separate AE. If you believe a group of symptoms may be related to one diagnosis but no diagnosis has yet been 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.

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

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

Comments

The Comments section should be used 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'.

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.

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.

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

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.

Reporting Procedure
1. Report Serious Adverse Events (SAE) by completing the on-line Adverse Events and Hospitalizations form within 24 hours. This form is on each visit menu at: **https://adni.ucsd.edu.**

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.

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.**

Cognitive Assessment

GENERAL GUIDELINES

The goal of ADNI neuropsychological testing is to use standardized procedures to objectively and reliably assess a subject'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 subject'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 subject 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 protocol. Following these guidelines at your site will help generate valid and accurate measurements with a minimum of stress and discomfort for test subjects.

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. In addition, every effort should be made to conduct testing at approximately the same time of day each time the battery is administered in order to reduce variability due to circadian (i.e., time of day) effects. 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 subject and the study partner about the subject's ability to hear and see and make sure the subject 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 subject may take breaks. After answering any questions, instruct the study partner to wait outside the test room in the designated waiting area. (Most subjects test better if they are not observed by people they know.) If the subject 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 subject will not easily turn to him/her for feedback.

Managing Testing Time

The tests should be given in the order indicated, with adherence to time limits and standardized instructions. This may be challenging with subjects who interrupt testing or digress into excessive conversation. In these cases, the examiner must regain control and "reorient" the subject back to the task at hand.

Keeping Subjects Focused

If the subject is exhibiting signs of frustration or requests to terminate the test, the examiner should acknowledge the subject'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 subject who refuses to continue a task from the subject who cannot continue a task due to physical or severe cognitive impairment. (This is made more difficult by the fact that a subject may refuse testing due to frustration over their inability to perform a task.) Whether a subject is fatigued, frustrated or merely distracted, there is no one approach that will work with all subjects, but the examiner should have a flexible style that acknowledges the subject's concerns, while gently diverting their attention back to the task.

Assessing Subject Comprehension

It is the examiner's responsibility to see that the subject 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 subject, 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 subject will give more than one answer. If that should occur, encourage the subject 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 subject to choose a single answer.

Scoring and Recording

Since it is better to score an incorrect response than no response, subjects 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 subject understood the question. **Record the subject's responses in full and verbatim. More notes are better than too few notes.**

Many examiners prefer to tape record their subject's response, and then transcribe any words they may have missed after the session. This is acceptable if appropriate consent has been obtained.

ALZHEIMER'S DISEASE ASSESSMENT SCALE - COGNITIVE (ADAS-COG)

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)

Description

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

Feedback to the subject 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 subject is trying. If the subject specifically asks whether or not they were correct, feedback can be given.

Administration

At the start of the ADAS test session before formal testing begins, engage the subject in a short conversation about neutral topics (i.e., the weather, the subject's trip to the clinic, or what the subject had for breakfast). This conversation will help to put the subject at ease before testing begins and will give the examiner an opportunity to observe how well the subject can use and understand language.

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

Word Recall Task

On this task, the subject 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 and are presented one at a time. At the start of the first trial, the examiner 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 subject cannot read the word or is slow, the examiner can say the word out loud and have the subject repeat it. In some cases (e.g., anopsia), the examiner may have to say all of the words and have the subject repeat them. Regardless, make sure the subject looks at each word while repeating it.
Note: The presentation of each word is not timed.

After presentation of the 10 words, the examiner asks the subject 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 subject appears to have recalled as many words as possible, prompt with: **"Any others?"**

For trials 2 and 3, say to the subject: **"Now I'm going to show you that same list of words again. Read each word out loud and try to remember it."** After presentation of the list is completed say: **"Good, now tell me all the words you remember that were on the list."**
Note: Encouragement can be given if the subject is nervous or giving up.

Word Recall Scoring: On the online CRF, check each word recalled correctly and record total number of words recalled on each trial.

Commands

This task is designed to assess receptive speech. The subject is asked to carry out five separate commands with 1 to 5 steps per command. All commands should be given to every subject. Speak in a clear voice with adequate volume. To begin testing, say: **"Now I am going to ask you to do a few things. First…".** 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 subject demonstrates hearing or attentional difficulties, orient them prior to each command by saying: **"Ready?"** or **"Now, I want you to…".**
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 items (pens, paper, etc.) near these test materials during the commands, and the test materials should be removed before giving the last command ("tap each shoulder…").

Commands Scoring: Each command is scored as a whole (no partial credit). All components must be correct for the response to be scored as correct. On the online CRF, check each command performed correctly.

Constructional Praxis

This test assesses the subject's ability to copy 4 geometric figures ranging from a very simple one (circle) to a fairly difficult one (cube). The examiner should give the subject a pencil with an eraser and presents each figure one at a time. The figures should be presented in the following order: Circle, Overlapping Rectangles, Diamond, Cube. For each figure, the instructions to the subject should be similar to the following: **"On this piece of paper is a shape. Try to draw another one that looks just like this, somewhere on the page."** (Examiner may point to figure). The subject then attempts the drawing. They are allowed to spontaneously erase and correct (without prompting from the examiner) if they so desire. After the subject completes their drawing, a second attempt is allowed if the subject asks or indicates a problem with his/her drawing. The subject is allowed up to two attempts for each figure (make sure that attempts are clearly numbered). If the subject draws on top of the printed figure, count this as one attempt and indicate that they should try again on an empty part of the page. If the subject indicates the reproduction is poor after the first attempt, query if they would like another try. When two attempts are made, ask the subject to indicate which one is best, and then score that attempt. If the subject cannot reproduce the figure in two attempts, the examiner should go on to the next item. **NOTE : The examiner can write brief explanations or comments on the stimulus page regarding the subject's efforts on the drawings.**

Constructional Praxis Scoring: A drawing should be scored correct if the subject has reproduced all of the essential geometric features of the original. Changes in size do not count as errors. Small gaps between lines do not indicate an error, as long as the figure has been correctly reproduced as follows:
CIRCLE: A closed curved figure.
OVERLAPPING RECTANGLES: The two figures must be four-sided and overlap in a similar manner to the presented stimulus.
DIAMOND: The figure must be four-sided, oriented so that the points are at the top and bottom, and the sides are of approximately equal length (e.g., longest side is not >1.5 times the length of the shortest side).
CUBE: The figure is 3-dimensional, with the front face in the correct orientation, and internal lines drawn correctly between corners. Opposite faces of the cube should be approximately parallel.
On the online CRF, check each figure drawn correctly.

Delayed Word Recall

Delayed free recall of the word list should be attempted approximately 5 minutes after trial 3 of the Word Recall Task. The interval should be filled by the ADAS Commands and Constructional Praxis items. If these tasks are completed in less than 5 minutes, the delay interval should be filled with the continuation of the interview to assess language, concentration, etc. before beginning delayed word recall. To begin the Delayed Word Recall task say: **"A few minutes ago I had you read some words printed on these cards (point to word list). Tell me all of the words you can remember that were on the cards."** Prompt with: **"Any others?"** as necessary. Discontinue when there is no further response or if the subject indicates that he/she cannot recall any more words after prompting.

Delayed Word Recall Scoring: On the online CRF, check "Yes" for every word recalled correctly and record total number of words recalled.

Naming Task

In this task, the subject is asked to first name 12 randomly presented real objects that have high (Flower, Bed, Whistle, Pencil), medium (Rattle, Mask, Scissors, Comb), or low (Wallet, Harmonica, Stethoscope, Tongs) frequency values, and then to name the fingers on his/her dominant hand. The real objects should be presented in random order. Show the object to the subject but do not allow the object to be touched or handled. Give the subject instructions similar to the following: **"Now I am going to show you some objects. I want you to tell me what their names are."** Present the first object and say **"What is this called?"** or **"What is the name of this thing?"** Continue in this manner until all 12 objects have been presented (in a random order). If the subject responds with the object's function say: **"Yes, that's what it does, but what is its name?"** If the subject does not respond at all or says they don't know, the examiner should give the cue for that item as provided below. If the subject still does not respond or makes an error, go on to the next object.

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

Following object naming, the subject is 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). Ask the subject to lay their dominant hand flat on the table (palm down) and give instructions similar to the following: **"Now I am going to point to a finger on your hand and I want you to tell me what it's called. What is this finger called?"** If an unusual name is provided (e.g., baby finger), the following query can be given: **"What is another name for this finger?"** Note: **little finger and pinky are both acceptable responses.**

Naming Task Scoring: On the online CRF, check each object and finger named correctly. The hardest part of scoring the naming task is determination of the range of correct responses based on the subject'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 subject. 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, and semantic or phonemic paraphasic errors should not be scored as correct. **EXAMPLES OF INCORRECT RESPONSES: "listening thing"** for **Stethoscope, "cutter"** for **Scissors,** or **"prongs"** for **Tongs.**

Ideational Praxis

This task is designed to determine whether the subject 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 subject. (Do not permit the subject to handle any of the materials yet.) Give the subject 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."** If the subject forgets part of the task, or is having difficulty, the examiner should repeat the instruction for the component of the task where the subject is having difficulty. For example, if the subject stops after folding the paper and putting it into the envelope, the examiner should give one reminder on the next component: **"Now seal the envelope."** If the subject cannot do this part, move on and give one reminder for the next component: **"Now address the letter to yourself."** Only one additional reminder should be given for each component of the task.

⇨ Have subject place an "X" on the envelope to indicate where the stamp goes. If the subject merely points to where the stamp goes, the examiner should write the "X" on the envelope.

⇨ Any address which would enable a postal worker to deliver the envelope is considered correct, even though it might not contain the subject's current address. Zip Code is not required, but City and State are both needed.

> **NOTE:** **To maintain subject 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.**

Ideational Praxis Scoring: On the online CRF, check each component of the task correctly completed.

Orientation

This task is designed to determine how well-oriented the subject is with regard to time and place. The components of orientation are: ⇨ Person ⇨ Year ⇨ Day of the Week ⇨ Season ⇨ Month ⇨ Time of Day ⇨ Date ⇨ Place. Ask the subject for each of these pieces of information **one at a time**. One restatement of each question is allowed (e.g., if subject confuses day and date). Make sure no watches, clocks, calendars, etc. are visible to the subject. 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** provide a clue about the location with questions such as: "What's the name of this hospital?"

Orientation Scoring: On the online CRF, check each item answered correctly. Guidelines regarding the range of appropriate correct responses and information about the seasons are provided below.

2005	
Winter	12/22/04 – 3/20/05
Spring	3/21/05 – 6/20/05
Summer	6/21/05 – 9/22/05
Fall	9/23/05 – 12/21/05
2006	
Winter	12/22/05 - 3/20/06
Spring	3/21/06 - 6/21/06
Summer	6/22/06 - 9/23/06
Fall	9/24/06 - 12/22/06
2007	
Winter	12/23/06 - 3/21/07
Spring	3/22/07 – 6/21/07
Summer	6/22/07 - 9/23/07
Fall	9/24/07 - 12/22/07

Full Name:	Must be exact (first and last)
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").

Word Recognition Task

On this task, the subject 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. To start the task, the examiner 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 subject cannot read the word or is slow, the examiner can say the word out loud and have the subject repeat it. In some cases (e.g., anopsia), the examiner may have to say all of the words and have the subject repeat them. Regardless, make sure the subject looks at each word while repeating it.
Note: The presentation of each word is not timed.

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 or not it is one of the words I just showed you."** The examiner 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 examiner should say: **"How about this one?"** If the subject indicates they are not sure, they may be encouraged with: **"Just take your best guess".** If the subject does not remember the task (e.g., reads the word rather than responding yes or no), the examiner should repeat or rephrase the entire question and check "Reminder" indicating that the subject had to be reminded of the task instructions. The subject's ability to stay on task will be reflected in Question 9 of the ADAS (Remembering Test Instructions). Please note that the subject is prompted for the first two words as part of standard instructions. The rating reflected in Question 9 (Remembering Test Instructions) should not include the prompts given for the first two words.

Word Recognition Task Scoring: On the CRF, the examiner should check the "yes" or "no" response made by the subject for each of the target and distractor items.

ADAS Word List to use for the Recall and Recognition Tasks at each ADNI visit by subject group

	BL	M6	M12	M18	M24	M30	M36
NL	1	2	3	--	2	--	3
MCI	1	2	3	1	2	--	3
AD	1	2	3	--	2	--	--

Remembering Test Instructions

This item evaluates the subject's ability to remember instructions and is based **ONLY** on observations during the Word Recognition task (Question 8). If the subject fails to respond with "yes" or "no" on the recognition trial, this signifies that the task instructions have been forgotten and the instructions are repeated. Each instance of this memory failure, beyond the first two items, is noted.

On the online CRF, check level of impairment:
- ❏ None - subject 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 subject's ability to understand speech. To rate this item the examiner should consider how well the subject was able to understand the examiner's speech during the opening discussion and throughout the test session. **DO NOT** include the subject's responses on the formal Commands task in making this evaluation.

On the online CRF, check the level of impairment.
- ❏ None - no evidence of poor comprehension
- ❏ Very Mild - one or two instances of poor misunderstanding
- ❏ Mild - 3-5 instances of misunderstanding
- ❏ Moderate - requires several repetitions and rephrasing
- ❏ Moderately Severe - subject only occasionally responds correctly; i.e., yes/no questions
- ❏ Severe - subject rarely responds to questions appropriately, not due to poverty of speech

Word Finding Difficulty

This item rates impairment in expressive speech. The examiner rates the level of difficulty the subject had in finding the desired word in spontaneous speech during the interview and test session. **Note: the subject may attempt to mask word finding difficulty by circumlocution (i.e., giving explanatory phrases or nearly satisfactory synonyms). DO NOT** include the subject's responses on the formal object and finger naming tasks in this rating.

On the online CRF, 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 the subject's speech and their ability to communicate verbally (i.e., clarity, difficulty in making oneself understood). In rating this item the tester should consider all of the speech produced by the subject during the test session. Quantity of speech and word-finding difficulty are not rated on this item (i.e., circumlocutions would not be rated/evaluated on this item). It should be noted that the higher scores (4-5) on this item are reserved for subjects whose expressive language abilities are impaired to such an extent that they seldom communicate without difficulty.

On the online CRF, check level of impairment:

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

Number Cancellation

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

Discontinue the example after 30 seconds.

Instructions for Task: Place the form face up in front of the subject and say: **"On the top of this page are two numbers. Throughout this page you will find these numbers mixed in with other numbers. I'd like you to begin here..."** (point to the beginning of the first line), **"...and going across line by line, cross off the numbers that match the numbers at the top of the page. Please work as quickly as you can."** If the first cancellation done by the subject is incorrect, say: **"These are the correct numbers to cross out,"** and point to the target numbers at the top of the page. If the subject becomes confused or stops while doing the test, repeat the standard instructions as needed.

Discontinue the test after 45 seconds.

The following information should be entered on the online CRF:

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 subject needed to be reminded of the task or re-directed back to the task.

There are multiple versions of the number cancellation task. Prior to each visit, the Study Coordinator should go online and print out the correct version of the stimuli for the task for that visit.

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 ADCS 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 following Standardization/Certification Questionnaire.

To request an ADAS Certification Packet please email: support@adni.ucsd.edu

MINI-MENTAL STATE EXAM (MMSE)

Orientation

Items 1 – 10: Each item should be asked separately as indicated on the online CRF. When a year or season is near transition the correct answer can be prompted with **"are you sure?"**

Scoring: Each item is worth one point. No partial credit is given. If a subject gives the date when prompted for the day, he/she should be given credit for date if the response is correct. For the hospital item, any correct name is acceptable except generic names such as "medical center" or "hospital". All other items require exact answers.

If the subject gives only the last two digits of the year, he/she should be prompted, "**What is the full year?"**

Immediate Recall

Use the instructions on the form.

Scoring: One point is given for each correct response for a total of three points.

Attention

The examiner should give the instructions as follows: **"The word WORLD is spelled W-O-R-L-D. Spell WORLD backwards."** Repeat the instructions if the subject asks for a repetition or appears confused. As clarification, the examiner may say, **"Start from the end and go to the beginning."** Allow additional trials if the subject requests them.

Scoring: Record the actual letters of the subject's final response. Score one point for each correct letter as indicated on the score sheet. For example, "D-L-O-W" would receive two points for the correct placement of the "D" and the "L".

Delayed Recall

After a 3 minute delay from Immediate Recall, ask the subject, **"Now what were those three objects I asked you to remember?"** If needed, explain the source of these three objects with: **"I asked you to repeat three words earlier and to remember them. Can you recall them now?"** If the subject is unable to recall an item, the item should be scored as "Incorrect." If the intervening attention task is completed in less than 3 minutes, perform remaining non-verbal parts of the MMSE (e.g., Questions 25, 26, 27 and 30) until 3 minutes have elapsed, and then return to the delayed recall task.

Scoring: Score one point for each correct response.

Language Naming

Show the subject a wristwatch and say, **"What is this?"** If subject gives a function say, **"Yes, but what is this called?"** or **"What's its name?"** Repeat for pencil. No other clues should be provided.

Scoring: Score one point for each correct response.

Command

Present a piece of paper at the subject's mid-line and say, **"Take the paper in your right hand, fold it in half and put it on the floor."** One repetition is permitted at the subject's request, but the entire command must be repeated. The subject is allowed to fold the paper using both hands.

Scoring: One point is scored for each of the three segments - (1) take in right hand; (2) fold in half; and (3) place on floor - for a total of three points.

Repetition

Engage the subject's attention and clearly say **"Repeat after me: no ifs, ands, or buts."**
Scoring: One point is given for an exact repetition of the phrase.

Reading

Show the Close Your Eyes stimulus card to the subject and say, **"Read this and do what it says."** The subject can be reminded not just to read the sentence, but to obey it. If the subject is unable to read, read the sentence out loud to him/her.
Scoring: One point is given if the instructions are completely and correctly followed.

Writing

Give the subject a pencil (or pen) and a blank sheet of paper and say, **"Write a sentence."** If needed, prompt the subject with **"Write a sentence about the weather."**
Scoring: One point is given for any complete sentence (even if not about weather). Grammar, spelling, and punctuation are not scored, but the subject must write a sensible sentence that contains a subject and a verb. A sentence with an implied subject (e.g., close the door) is acceptable. If the sentence is illegible, ask the subject to read it aloud for scoring.

Construction

Give the subject a pencil (or pen) and the paper with the overlapping pentagons figure and say, **"Copy this design."**. Do not allow erasures. If the subject appears dissatisfied with his/her drawing, or requests a second attempt, allow the subject to re-draw the figure. Clearly label the first and second attempt. The best drawing should be scored.
Scoring: To receive one point, the drawn design should be two intersecting pentagons (i.e., five-sided designs), the intersection should result in a four-sided figure, and all ten angles must be present with two intersecting.

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

Present the subject with the laminated 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 subject 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 subject 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 subject begins having difficulty pronouncing them.

Scoring

On the CRF, record the number of errors committed (i.e. the number of words mispronounced).
Note: Some words have multiple correct pronunciations. Be familiar with these, so as to score accurately!

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 subject draws a clock to verbal instructions, and a **copy condition** in which the subject 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 subject 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 subject to work without feedback; interrupt only if the patient starts to scratch out or destroy any of their drawing. If the subject 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 subject 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 patient 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 subject undo anxiety or frustration when they are unable to perform the clock drawing task.

Clock Copying Administration

Immediately after the Clock drawing to command condition is completed, present the subject 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 subject to work without feedback; interrupt only if the patient starts to scratch out or destroy any of their drawing. If the subject 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 patient 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 subject undo anxiety or frustration when they are unable to perform the clock copying task.

Scoring

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

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, subjects will draw an "old fashioned" mantle clock or grandfather clock (i.e., with a square clock face). If this occurs, ask the subject to draw a "regular clock."

2. Symmetry of number placement. One method to assist the examiner in determining if the numbers are symmetrical is to visually "line up" the opposing numbers, e.g., 3-9, 12-6, 4-10. If there are any obvious gaps or misalignments, then the numbers may be considered asymmetrical.

3. Correctness of numbers. All numbers must be present and in the correct order, and inside the face of the clock. If a subject draws the numbers outside the circle, this item would be INCORRECT.

4. Presence of two hands. Two hands (and only two hands) must be present on the clock face to receive credit for this item.

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

See the below examples of scored clock drawings.

5 points

3 points
- approximately circular face
- presence of 2 hands
- presence of 2 hands, set to 10 after eleven
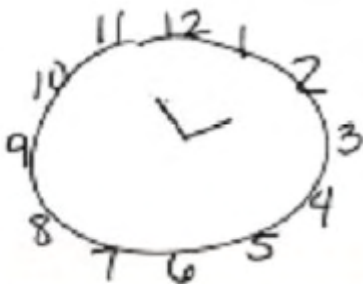
3 points
- circular face
- symmetry of number placement
- presence of 2 hands

3 points
- approximately circular face
- correct numbers
- presence of 2 hands
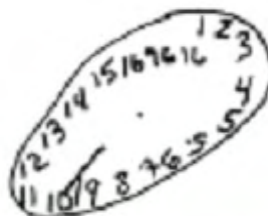
0 points

REY AUDITORY VERBAL LEARNING TEST (AVLT)

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

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

Trial I Administration

After engaging the subject'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 subject 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 subject 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 subject 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 subject 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, 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 subject 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.**

Recognition Administration

Present the subject 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."**

LOGICAL MEMORY TEST I – IMMEDIATE RECALL (Story "A" only)

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 subject in a clear voice. Immediately after hearing the story, the subject is asked to retell the story from memory. The story should be read with adequate volume and clarity for the subject to understand during the presentation. No repetitions are permitted. It is important for the examiner to get a sense of the subject'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 subject, rather down "into" their clipboard.

Administration

The following standard instructions are printed on each case report form 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 subject, "**Now what did I read to you? Tell me everything and begin at the beginning."**
Always permit the subject to include additional information by prompting with "**Anything else?**". Record any additional "bits of information" and score appropriately.
After the subject 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."** Logical Memory II - Delayed Recall is administered at least 30 minutes, and no more than 40 minutes, after this immediate recall condition. The examiner should 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.**

Recording

Record the subject'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 subject's response, and then transcribe any words they may have missed after the session. This is acceptable if appropriate consent has been obtained.

Scoring

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

DIGIT SPAN FORWARD

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

Description
This is a widely-used test of working memory (or attention) in which the subject is read number sequences of increasing length and asked to repeat them. The total score is the number of sequences correctly repeated.

Administration
Begin with item Ia and read aloud the following instructions, **"I am going to say some numbers. Listen carefully, and when I am through, say them right after me. Ready?"** Read digits clearly at the rate of one per second, letting voice pitch drop on last digit. If the subject begins saying the numbers before you've said them all, say "**I'll be saying several numbers. I'd like you to wait until I've finished saying them all before you respond."** Record the subject's response verbatim. Then proceed to the next item.

Subsequent items are preceded by "**Here is another**." Again, read digits clearly at the rate of one per second, letting voice pitch drop on last digit. On each item, record the subject's response verbatim.

Each digit sequence is presented only once. If the subject asks for a repetition, say, "**Just tell me what you can remember**". The examiner may <u>not</u> repeat a number sequence for the subject. If the subject cannot respond, say, "**Let's try another one**." Spontaneous changes of the response are permitted. The procedure is discontinued after two consecutive errors at the same item length.

Scoring is deferred until after the examination and is done from the written record, which must be written in a legible, decipherable manner.

Scoring
Each response is scored as an error (0) or correct (I) in the space provided on the *Worksheet for Digit Span Forward* . The Total Correct score is the number of correct responses prior to two consecutive errors at the same digit length.

The Digit Span Forward Length is the length of the highest digit sequence the subject was able to repeat correctly.

DIGIT SPAN BACKWARD

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

Description
This is a widely used measure of working memory (or attention) in which the subject is read number sequences of increasing length and then asked to repeat each sequence backward. The primary measure of performance is the number of digit sequences correctly reversed.

Administration
The task immediately follows Digit Span Forward and begins with practice to orient the subject to the task. Read aloud the initial instruction, **"I am going to say some more numbers. When I stop, I want you to say them backwards. Ready?"**
Present practice item PI on the *Worksheet for Digit Span Backward* by saying, **"Try this one: 2-8-3."**

Pause for the subject to respond, and encourage a guess if need be. Record the response code (0 = error; 1 = correct) for PI in the space provided on the *Worksheet for Digit Span Backward.*

>   If the subject is <u>correct</u>, read the appropriate instruction branch:
> [SAY]: "**That's right. Now I have some more numbers. Remember, you are to say them backward."** Proceed to the first test item (trial Ia).

>   If the subject is <u>incorrect</u>, read the appropriate instruction branch:
> [SAY]: "**No, I said 2-8-3, so to say these backward, you would need to say 3-8-2**. **Now try these numbers: Remember, you are to say them backwards. Ready? I-5-8.** Pause for the subject to respond, and encourage a guess if need be. Record the response code (0 = error; 1 = correct) for P2 in the space provided on the *Worksheet for Digit Span Backward.* Whether the subject passes or fails practice item 2, proceed to the first test item (trial Ia).

For the first test item (Ia) say, "**I am going to say some more numbers. When I stop, I want you to say them backwards.**"
Make sure you have the subject's attention before presenting each item. Do this by saying "**Ready?**" before each item. Subsequent items are preceded by "**Here is another.**" Read digits clearly at the rate of one per second, letting voice pitch drop on last digit. Each digit sequence is presented only once. If the subject asks for a repetition, say "**Just tell me what you can remember.**" Spontaneous changes of the response are permitted. The procedure is discontinued after two consecutive errors <u>at the same item length</u>. If the subject asks for reinstruction, say, "**After I say the numbers, you try to say them backward.**"

If the subject repeats digits in the forward order on either of the first two test trials, you may cue them to say the numbers in the backwards order, but do not repeat number sequence. Reinstruct the subject by saying, "**Remember, after I say the numbers, you are to say them backward. Ready**?". Score correct if the subject is able to give the correct backward order. Only one unrequested reinstruction is permitted (so subsequent forward orders are simply scored as errors). Do not cue for any of the remaining backward sequences.

Scoring

Each response is scored as an error (0) or correct (1) in the space provided on the *Worksheet for Digit Span Backward.* The Total Correct score is the number of correct responses prior to two consecutive errors at the same digit length.

The Digit Span Backward Length is the highest digit sequence the subject was able to reverse.

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 subject 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 subject'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 response, 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 subject 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 subject specifically requests it.

Next, read the instructions for the Vegetables category:

[SAY] "**Now I want you to name things that belong to another category: Vegetables. You will have one minute. I want you to tell me all the vegetables 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–Vegetables.* Stop the procedure at 60 seconds. One prompt ("Tell me all the vegetables 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.

Scoring
Defer scoring until after all test administration is finished.

The <u>Animal Total </u>score on the *Worksheet for Category Fluency–Animals* is the number of correct unique animal names produced within the one-minute time limit.

- 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.

The <u>Vegetable Total </u>score on the *Worksheet for Category Fluency–Vegetables* is the total number of correct unique names of vegetables produced within the one-minute time limit.

- CREDIT: Both superordinate and subordinate responses (e.g., peppers and jalapenos are credited); less specific names (e.g., greens); nuts (e.g., peanuts, acorns); and grains such as corn or rice.

  - ⇨ Names of vegetables found in other cultures but perhaps unfamiliar to you (e.g., Jicama) are acceptable only if they can be verified in the dictionary. After completion of the task, ask the subject to spell the word if you are unsure of the correct spelling.

  - ⇨ Grains (e.g. rice, wheat, oats, etc.), gourds, sugarcane, herbs and seaweed are counted as acceptable 'vegetable' responses.

  - ⇨ Tomato, avocado and pumpkin are acceptable responses.

  - ⇨ Prepared vegetable products are not acceptable responses (e.g. pickles, tomato sauce, ketchup, etc.).

- DO NOT CREDIT: Repetitions.

TRAIL MAKING TEST

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

Description

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

Part A consists of 25 circles numbered 1 through 25 distributed over a white sheet of 81/2" x 11" paper. The subject 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 subject 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 subject'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 subject 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 subject's response and say "**Please start here and continue.**"

If the subject 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 subject when maximum time is reached. Allow a maximum of 150 seconds for the test.

Part B: Place the form for Part B sample practice side up, in front of the subject. 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 subject 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 subject's response and say "**Please start here and continue**."

If the subject 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 subject 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 subject failed to draw a connecting line to a given circle in the correct sequence. This only occurs when the subject 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 subject 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 subject intended to touch a circle but barely missed it, do not count it as an omission. However, caution the subject to touch circles when you first observe this.

⇨ If the subject 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 subject 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 visit of the subject.

DIGIT SYMBOL SUBSTITUTION TEST

Wechsler, D. Wechsler Adult Intelligence Scale-Revised. The Psychological Corporation, 1981.

Administration

Place the response form before the subject and say, **"Look at these boxes. Notice that each has a number in the upper part and a special mark in the lower part. Each number has its own mark. Now look down here where the boxes have numbers in the top part but the squares at the bottom are empty** *[point to the sample items].*

You are to put in each of the empty squares the mark that should go there, like this: Here is a 2; the 2 has this mark, so I put it in this square like this. Here is a 1; the 1 has this mark, so I put it in this square. This number is 3; the 3 has this mark, so I put it in this square *[Examiner fills in first three boxes to demonstrate].* **Now you fill in the squares up to this heavy line.** *[If S makes errors, continue to help until all sample items are filled in correctly].* **Yes, now you know how to do them.**

When I tell you to start, you do the rest of them. Begin here and fill in as many squares as you can, one after the other, without skipping any. Keep working until I tell you to stop. Work as quickly as you can without making any mistakes. When you finish this line, go on to this one. Ready? Begin." *[Allow 90 secs.]*

⇨ If the subject skips an item, immediately give a reminder to go in order and not skip over any, point out the skipped item, and direct them to continue from the last item completed successfully in order.

⇨ Do not intervene if the subject fills in a wrong symbol, but if the subject has clearly lost set as to what to do (e.g. starts filling in something other than symbols), you may give the following reminder, "Remember, you are to fill in the symbol that goes below each number, as indicated in the key up above."

⇨ If the subject pauses at the end of a row, say "Good, keep going", and point to the beginning of the next row, if necessary.

Scoring

Credit 1 point for each item filled in correctly within the 90 sec. time limit. The seven sample items are not included in the score. Calculate total number of points received (Maximum possible = 93).

LOGICAL MEMORY TEST II – DELAYED RECALL (Story "A" only)

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

Administration
Administer this test at least 30 minutes and no more than 40 minutes after Logical Memory I - Immediate Recall. The following standard instructions are printed on each case report form 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 subject does not recall the story, it is permissible to offer the following reminder which is also printed on the case report form. Say, **"The story was about a woman who was robbed."** Do not give any further help other than general encouragement. Note on the CRF if the reminder was given and do not then give a point for that item (i.e., "robbed") when scoring. After the subject 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 subject'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 subject'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 listed in the Weschler Memory Scale-Revised manual.

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

BOSTON NAMING TEST

Kaplan, E., Goodglass, H., Weintraub, S. <u>The Boston Naming Test.</u> 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., abacus). This test is sensitive to aphasia and also to object recognition deficits. For the purposes of the ADNI, only the odd-numbered items from the full test will be administered.

Administration

Begin at item 1 and present all 30 items in order. Place the test booklet in front of the subject 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 subject 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 subject 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 subject 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 subject'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). If the subject succeeds with a phonemic cue, place a check mark in the column "correct with phonemic cue". If the subject 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).

Scoring

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

- ⇨ Record the subject's responses verbatim if incorrect or circumlocutory, and write in 'DK' only if the subject actually says she or he doesn't know.

- ⇨ Mispronunciations are treated as incorrect unless they clearly reflect a regional or dialect-specific pronunciation (e.g. someone from the Boston area may omit the 'r' sound in 'dart'). If a mispronunciation does not reflect such a regionalism (e.g. 'esculator'), the answer is incorrect and cueing proceeds as appropriate.

- ⇨ If the subject 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 subject gives a more specific response (e.g. 'daisy' for 'flower'), say **"Can you think of a more general name for it?"**

- ⇨ If the subject 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.

Global, Functional, and Behavioral Assessments

All worksheets required for administering the global, functional and behavioral assessments are available at https://adni.ucsd.edu under 'Document Repository'.

Please refer to the Schedule of Assessments for each subject group (under the ADNI Protocol section of this manual) for a listing of when each assessment will be administered.

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 each subject group (NL, MCI, AD). The CDR is conducted at screening and at every in-clinic from the Month 6 visit.

CDR Rater

CDR certification is required prior to administering the CDR for ADNI. Please refer to the Start-Up Certification section of this manual for more details.

> The same person cannot administer both the CDR and ADAS during a single clinic visit.

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 subject's visit throughout the study.

Instructions

Worksheets have been created with a semi-structured interview for the informant and subject. A certified CDR Rater must complete the interview and 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 PI's 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.

Determining Global CDR Score

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 subject 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.

Quality control checks verifying the Global Score entered will be used on the CDR online form.
To verify the global CDR, you may also access the Washington University CDR web page:
www.biostat.wustl.edu/~jack/cdr/

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. The form should be completed by a clinician familiar with the subject.

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 or characteristic* of the subject by circling the appropriate value.

GERIATRIC DEPRESSION SCALE (GDS)

Sheikh JI, Yesavage JA, Geriatric Depression Scale (GDS): Recent evidence and development of a shorter version. Clinical Gerontology: a Guide to Assessment and Intervention 165-173, NY: The Haworth Press, 1986.

The GDS is should be administered by site staff as a direct interview with the subject, as a part of the screening process and every 12 months while in the study. 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 and at every subsequent in-clinic visit.

Instructions
The study partner should be queried based on the subject's level of difficulty on each item in the past four weeks.

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.

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 the following questions to the study partner based upon changes in the ADNI subject. 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, the sub-question on Severity must also be completed.

Completion of Online Forms

DEMOGRAPHIC INFORMATION

Education

Use the following guidelines to determine the number of years of education completed:

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

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

Degree	Years
GED	12
High School Diploma	12
AA	14
BA/BS	16
MA/MS	18
Law Degree	19
MD, PhD, or both	20

Occupation

- **a)** Enter the one occupation that the subject performed during most of his/her adult life (paid or volunteer work).
  If the subject had multiple occupations, select the one with the longest time of service. "Homemaker" is an acceptable entry for occupation.
- **b)** Enter subject's most recent occupation. If it is the same as (a), enter, **"same as above."**

For MCI and AD subjects, Year of Onset of Alzheimer's Disease Symptoms

Ask the study partner to give his/her best estimate of when the subject's disease began.

- ➪ This refers to the onset of symptoms, not the year of diagnosis.

Ethnic Categories

Hispanic or **Latino**: A person of Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture or origin, regardless of race. The term, " Spanish origin," can be used in addition to "Hispanic or Latino."

Racial Categories

American Indian or **Alaska Native**: A person having origins in any of the original peoples of North, Central, or South America and maintains tribal affiliation or community.

Asian: A person having origins in any of the original peoples of the Far East, Southern Asia, or the Indian subcontinent including for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Phillipine Islands, Thailand, and Vietnam.

Black or **African American**: A person having origins in any of the black racial groups of Africa.

Native Hawaiian or **Other Pacific Islanders**: A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White: A person having origins in any of the original peoples of Europe, North Africa, or the Middle East.

VITAL SIGNS
Units of Measure
Units used to report temperature and weight must be consistent across all visits for each subject . For example: A subject's temperature reported in fahrenheit at the Screening Visit must be reported in fahrenheit at all subsequent visits.

Rounding Decimals: For weight, the decimal should reflect a single digit, not a fraction (e.g., if weight is 178.75, enter 178.8, not 178 3/4). Round up or down, to the nearest number.

Measuring Blood Pressure and Pulse
Every effort should be made by the investigator to see individual subjects at approximately the same time of day throughout the study. Mental activity, especially talking, causes the blood pressure to rise. Therefore, the subject should not engage in conversation either during or shortly before blood pressures are recorded. The subject should be kept as calm and undisturbed as possible.

Measurement of blood pressure and pulse will be according to the following procedures:
1. All arterial blood pressure measurements should be taken consistently in the same arm, preferably by the same person, using the same calibrated mercury sphygmomanometer and blood pressure cuff.
2. When possible, the subject's dominant arm should be used for measuring blood pressure.
3. When recording sitting pressure, position the forearm at the horizontal level of the fourth intercostal space at the sternum (the level of the heart).
4. Pulse will be counted for 30 seconds. The **per minute** rate will be entered on the online case report form.

CONCURRENT MEDICATIONS LOG
At the Screening Visit, enter all medications online (prescription and over-the-counter, including vitamins and herbal supplements) taken within the past three months.

The amount **AND** unit of the dose **MUST BOTH BE LISTED** for all medications.
Example: 250 mg, 250 = amount of dose, mg = unit of dose
1. For use of topical medication, it will be acceptable to enter percentage (if known) or number of applications for dose.
2. For multivitamin (or any medications that have several active ingredients, such as Premarin, Bactrin, etc.), it will be acceptable to enter one tab or one cap for dose.
3. For use of inhalers, it will be acceptable to enter number of puffs for dose.
    ⇨ Please see the end of this section for acceptable abbreviations for units, frequency, and route.

Example of notation: "Digoxin, 0.25 mg., QD, PO"
   ⇨ This online form will serve as an ongoing record of concurrent medications for the entire study period. The "continuing at end of study" box should be checked, if appropriate, at the conclusion of the protocol for each subject. At each study visit, the concurrent medications list should be reviewed with the subject and study partner, and appropriate changes made.
   ⇨ If there are any changes in dose, frequency, or route of a continuing medication, the date ended must be entered for the original entry and a new entry made to record the new dose, frequency or route.
   ⇨ If the subject does not know the exact day and/or month a medication began or ended, select "ND/UNK" for the appropriate boxes. If the subject does not know the year a medication began, ask for his/her best guess and enter the year in the appropriate box.

MEDICAL HISTORY

Review each system listed on the online form. Indicate whether or not the subject has a clinically significant history of problems in that area.

Check:

"NO" - if the subject has no clinically significant history of problems in the system.
"YES" - if the subject has a clinically significant history of problems in the system.

This includes medical problems that are episodic but not currently active.

For each system checked "yes" click on the "Details" button to provide detailed information about specific problems in the system.

Each problem within a system should be entered as a separate record. The following should be provided for each record:

❏ Enter the system name and number from the drop-down menu.
❏ Enter a detailed description of the problem including date of onset (best estimate of year is acceptable).
❏ Indicate whether the problem is current. If the problem is current, indicate whether it is medically stable (this applies to all systems except Alcohol Abuse, Drug Abuse, and Smoking).

REMINDER: On Question 19, if the subject has no other problems that need to be recorded, please remember to check "NO" for this Question.

⇨ All conditions requiring medication must be entered on this online form (i.e., if the subject takes a thyroid supplement, then hyper- or hypo- thyroidism must be listed on the Medical History form).
⇨ If the subject is currently taking medication for a condition, the condition should be entered on the Medical History and marked as both "YES" and "CURRENT."

NEUROLOGICAL EXAMINATION

The Neurological Examination must be performed by an appropriately trained clinician.

Items 1-3 have two possible responses of either "Absent" or "Present."

⇨ Any item checked "Present" must be accompanied by a description or comment.

Items 4 - 11 have two possible responses of either "Normal" or "Abnormal."

⇨ Any item checked "Abnormal" must be accompanied by a description or comment. If there are no other findings, please check Item #12 ("Other") as "Normal" and leave the comment section blank.

The Neurological Examination online form must be signed off in the Signature Log by a clinician trained in the administration of a neurological exam (MD, PA, DO, NP). Only clinicians with these credentials are allowed to perform and sign off on the neurological examination. If this is not possible due to staffing issues, contact the Project Director.

Individuals with any new abnormal clinically significant finding after Baseline should be recorded on an Adverse Events online CRF.

PHYSICAL EXAMINATION

The Physical Examination must be completed by an appropriately trained clinician.
There are two possible responses to the questions on the Physical Examination:

Normal - Any finding that is considered to be within normal limits.
Abnormal - Any finding that is considered to be outside the range of normal or a finding that is considered to be notable upon examination (for example, scar). When any finding is considered "abnormal," there must be an accompanying comment, describing the finding.

If there are no other findings, please check Item #12 ("Other") as "Normal" and leave the comment section blank.

The Physical Examination online form must be signed off in the Signature Log by a clinician trained in the administration and assessment of physical exams (MD, PA, DO, NP). Only clinicians with these credentials are allowed to perform and sign off on the physical examination. If this is not possible due to staffing issues, contact the Project Director. Individuals with any new abnormal clinically significant finding after Baseline should be recorded on an Adverse Events online CRF.

ELIGIBILITY CONFIRMATION

Status of Subject at this Visit - Screening Visit

Check the appropiate box to indicate if the subject is eligible or excluded. If the subject is excluded, enter the reason for Screen fail in the space provided.

Principal Investigator/Study Clinician Signature

Ideally, the Principal Investigator should sign off in the online Signature Log to confirm the subject's eligibility status. If this is not possible, a Study Physician may sign off on eligibility.

BASELINE DIAGNOSES AND SYMPTOMS

Baseline Diagnoses and Symptoms Checklist

The Baseline Diagnoses and Symptoms Checklist is completed at the Baseline Visit. This online form should be completed with information from both the subject and study partner.

Episodic medical conditions listed on the online Medical History form should also be recorded on the online Baseline Symptoms form if these occurred within the three months prior to the Baseline Visit.

> Baseline Diagnoses and Symptoms should not be recorded in the subject's or study partner's own words.

If the subject and/or study partner reports a symptom(s) after the baseline visit was clearly in existence prior to the Baseline visit this diagnosis/symptom should be recorded as a Baseline Diagnosis or Symptom.

The following online forms should be updated:
1. Baseline Diagnoses and Symptoms Checklist - the symptom(s) previously recorded as "absent" should be checked as "present".
2. Documentation of Baseline Diagnoses and Symptoms Log - the missed symptom(s) should be added to this form with all the necessary information, such as symptom number, description, severity, chronicity, date of onset and date ceased (if applicable).

Remember to update source documentation to reflect changes to online forms.

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.

Symptoms of Potential Concern

Abdominal Describe discomfort: epigastric burning; lower abdominal fullness; Discomfort cramping, etc.

Dizziness: If you can determine that the subject is actually experiencing lightheadedness, vertigo, drowsiness, palpitations, confusion, poor concentration, etc., report the more specific symptom. If you cannot obtain a betterunderstanding 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.

Documentation of Baseline Diagnoses and Symptoms Log

All Diagnosis and Symptoms entered as "present" on the Baseline Symptoms Checklist must be entered into this log. At each subsequent visit, subjects should be queried about the status of each ongoing baseline symptom.

- ⇨ Enter both the symptom number and name.
- ⇨ Specific information about the symptom should be entered in the space provided.
  Example: If subject reports pain, elaborate on location of pain – "Pain in right foot".
- ⇨ If the symptom has ceased or has worsened in chronicity or severity, enter the date in the "Date Ceased" boxes.
- ⇨ Any symptom that worsens in chronicity or severity MUST be recorded as an AE.
- ⇨ If the symptom is still present at the end of the study, check the "Continuing at End of Study" box.

> Do NOT record new Adverse Events on the Baseline Symptoms Log.

24-HOUR CLOCK CONVERSION TABLE

The Huperzine A protocol requires that all times be given as military time (24-hour clock). The following table shows the military equivalent of conventional time.

Documenting the minutes is the same for both military and conventional time.

For example: 3:15 am would be documented as 0315 in military time, and 3:15 pm would be documented as 1515 in military time.

Conventional	Military Time	Conventional	Military Time
Midnight (12:00 am)	2400	Noon (12:00 pm)	1200
1:00 am	0100	1:00 pm	1300
2:00 am	0200	2:00 pm	1400
3:00 am	0300	3:00 pm	1500
4:00 am	0400	4:00 pm	1600
5:00 am	0500	5:00 pm	1700
6:00 am	0600	6:00 pm	1800
7:00 am	0700	7:00 pm	1900
8:00 am	0800	8:00 pm	2000
9:00 am	0900	9:00 pm	2100
10:00 am	1000	10:00 pm	2200
11:00 am	1100	11:00 pm	2300

MEDICATION CODES

UNITS	
app = Applicatorful	mg/l = Milligram/liter
ampules = Ampules	mg/min = Milligram/minute
Au/ml = Gold/milliliter	mg/ml = Milligram/milliliter
cap = Capsule	mg/m^2 = Milligram/square meter
cc = Cubic centimeter	mg/m^2/hr = Milligram/square meter/hour
cc/hr = Cubic centimeter/hour	mg/m^2/day = Milligram/square meter/day
cm = Centimeter	ml = Milliliter
cpm/ml = Counts per minute/milliliter	ml/hr = Milliliter/hour
gm = Gram	ml/sq m = Milliliter/square meter
gm/d = Gram/day	mm = Millimeter
gm/dl = Gram/deciliter	mmol/L = Millimole/liter
gr = Grains	MU = Million Units
gtt = Drop	ng = Nanogram
in = Inch	ng/min = Nanogram/minute
IU = International Units	ng/ml = Nanogram/milliliter
kg = Kilogram	nl/min = nanoliter/minute
kg/m^2 = Kilogram/square meter	nl/ml = nanoliter/milliliter
kU = Thousand Units	O or OT = Other
L = Liters	oz = Ounce
lb = Pound	pg/ml = picogram/milliliter
L/min = Liters per minute	ppm = parts per million
mcg = Microgram	puffs = Puffs
mcg/gm = Microgram/gram	Sachet = Sachet
mcg/hr = Microgram/hour	sniffs = Sniffs
mcg/kg = Microgram/kilogram	spray = Spray
mcg/kg/min = Microgram/kilogram/minute	supp = Suppository
mcg/kg/hr = Microgram/kilogram/hour	tab = tablet
mcg/min = Microgram/minute	tbsp = tablespoon
mcg/ml = Microgram/milliliter	tsp = teaspoon
mcgE = Microequivalent	U = Units
mcgE/ml = Microequivalent/milliliter	U/ml = Unit/milliliter
meq = Milliequivalent	Unk = Unknown
meq/dl = Milliequivalent/deciliter	mcCI = Microcurie
meq/ml = Milliequivalent/milliliter	mcCI/min = Microcurie/minute
meq/l = Milliequivalent/liter	mcl = Microliter
mg = Milligram	mcU = Micro-units
mg/dl = Milligram/deciliter	mcU/min = Microunit/minute
mg/gm = Milligram/gram	% = Percent
mg/kg = Milligram/kilogram	% solution = Percent solution

MEDICATION CODES

FREQUENCY		
IV = Continuous infusion	QH = Every hour
QD = Every day	Q2H = Every 2 hours
QOD = Every other day	Q3H = Every 3 hours
BID = 2 times a day	Q4H = Every 4 hours
TID = 3 times a day	Q6H = Every 6 hours
QID = 4 times a day	Q8H = Every 8 hours
HS = Every night/Bedtime	QI2H = Every I2 hours
PRN = As needed	Q2D = Every 2 days
QAM = Every morning	Q3D = Every 3 days
BSD = Before study drug	Q2W = Every 2 weeks
O or OT = Other	Q3W = Every 3 weeks
QW = Every week	Q4W = Every 4 weeks
BIW = Twice weekly	Q5W = Every 5 weeks
QHS = Every Hour of Sleep/Bedtime	Q6W = Every 6 weeks
	Q8W = Every 8 weeks

IX = One dose
2X = Two doses
3X = Three doses
5XD = Five times a day
6XD = Six times a day
IXW = Once a week
2XW = 2 times a week
3XW = 3 times a week
4XW = 4 times a week
5XW = 5 times a week
IXM = Once a month
2XM = 2 times a month
3XM = 3 times a month

MEDICATION CODES

ROUTE					
ART	=	Arterial	IV	=	Intravenous
BUC	=	Buccal (mouth/gums)	IVCV	=	IV central venous
CBV	=	Cerebroventricular	IVPV	=	IV peripheral venous
EAR	=	Ear	NAS	=	Nasal
ED	=	Epidural	NEB	=	Nebulizer
ET	=	Endotracheal	NG	=	Nasogastric tube
IA	=	Intra-articular	O or OT	=	Other
IAO	=	Intra-aorta	OD	=	Right eye
IBL	=	Intra-biliary	OS	=	Left eye
IC	=	Intracoronary	OU	=	Both eyes
ID	=	Intradermal	PER	=	Percutaneous
IDRM	=	Intra-dermal	PITP	=	Pump-intraperitoneal
IM	=	Intramuscular	PITV	=	Pump-intravenous
INF	=	Infusion	PO	=	Oral
INH	=	Inhalation	PSUB	=	Pump-subcutaneous
INP	=	Intra-penile	PV or VAG	=	Vaginal
IP	=	Intraperitoneal	R or PR	=	Rectal
IPCD	=	Intra-pericardial	SC or SQ	=	Subcutaneous
IPL	=	Intra-pleural	SIRG	=	Sinus irrigation
IPR	=	Intra-corporal	SUBLING or SL	=	Sublingual
ISP	=	intra-spinal	T or TOP	=	Topical
IT	=	Intrathecal	TD or TDRM	=	Transdermal
ITCH	=	Intra-tracheal	URETH	=	Urethral
ITV	=	Intravesical			

ADNI DISTRIBUTED DATA ENTRY

*Note: *Following instructions reference the Database in an Internet Explorer 6.0 online environment. If you are using another browser, there may be some slight adjustments you would need to make.*

1 System Requirements

The following are minimum system requirements

1.1 Internet Access

1.2 Current web browser installed on your computer.
- ❏ Internet Explorer 6.0 or higher (IE is not supported for Macintosh users.)
- ❏ Netscape Navigator 7.0 or higher
- ❏ Current versions of Safari

1.3 Adobe Acrobat Reader 5.0 or higher

Important! Any older versions of the above browsers may not be compatible with the secure ADNI web page applications. Because of this, your access to the applications cannot be guaranteed or supported by ADNI staff. You are <u>strongly</u> advised to upgrade your browser software to one of the above versions.

2 Getting Started.

2.1 Initial Login Process for users with temporary password

2.1.1   Open an internet browser.

2.1.2   In the URL Address box, type in
https://adni.ucsd.edu

2.1.3   Enter User Name and temporary Password and Click OK. The temporary password is randomly generated and emailed to you.
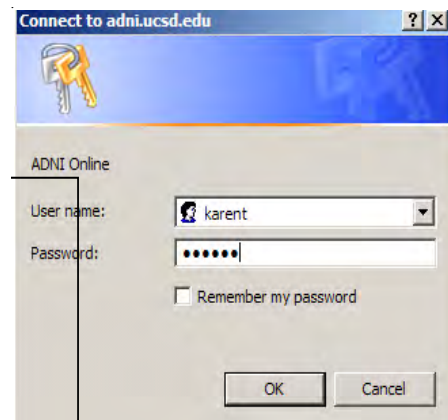
Important! DO NOT check **Remember my password** box.

2.1.4   Follow the instructions on the next page. Provide a new password and retype it. Click on **Change Password**. You are asked to log in with new password. You are then taken to the ADNI Online Home page.

If you forget your password, another user can request a replacement under 'Help'. You may also request another temporary password by emailing support@adni.ucsd.edu.

WELCOME TO ADNI ONLINE

Good afternoon, Karen.

- To continue, you must provide a new password of your choice.
- The password must be at least 5 characters in length (letters and numbers only).
- Please write down your password and keep it in a safe place for future reference.

NOTE: Passwords are case sensitive. Characters that are upper or lower case here must always be upper or lower case when you type in your password in the future.

Please provide a new password:

Please retype your new password:

Change Password

Note: Once you have successfully updated your password, you will be asked to log back in using your <u>new</u> password

## 2.2 Login Process for users with permanent passwords

2.2.1 Open an internet browser.
2.2.2 In the URL Address box, type in https://adni.ucsd.edu/ Enter User Name: and Password: in corresponding boxes and Click OK.

IMPORTANT! You should never give your User Name and permanent Password to anyone. Giving out your User Name and Password is essentially giving someone your signature. Account privileges and electronic signatures are determined by those two identifiers. You are held accountable for all entries and updates made.

2.2.3 ADNI Online Home Page opens. The Date and User Name are displayed at the upper right hand corner.

2.3 ADNI Online
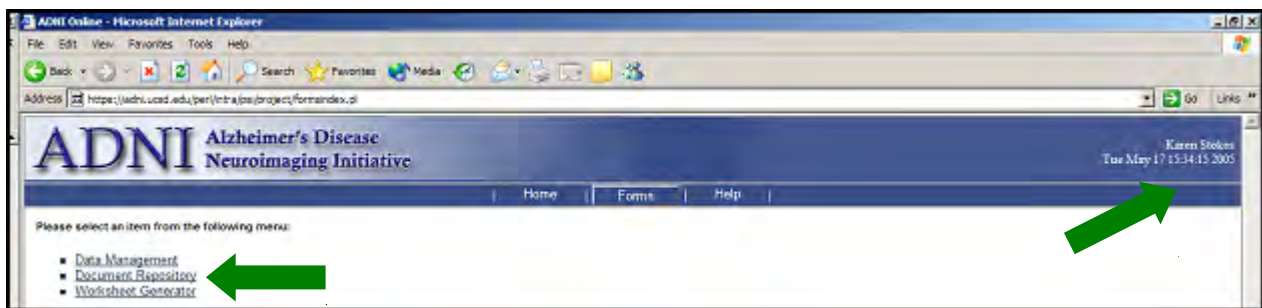
2.3.1 All active links are Underlined
2.3.2 Home displays "Welcome to ADNI Online" and a greeting to the User
2.3.3 Forms display links for:

❏ Exceptions Review- Location for reviewing and approving Inclusion and Exclusion Exception requests. This is available only to the Project Director.

❏ Data Management- Location for data processing and printing out CRFs w/ data populated.

❏ Document Repository- Location for printing out blank Stimuli forms, logs and administrative forms. The full Data Entry Manaul is also located here.

❏ Participant Enrollment- Location for Adding a new participant, Failing and Rescreening.

❏ Quality Assurance- Location for viewing and updating errors, as well as managing discussion regarding errors.

❏ SAE Reporting- Location for SAE Reporting. This is available only to the Project Director.

❏ Signature Log- Location for signature sign-off on required forms. This is available only to users who are designated as signers.

❏ Worksheet Generator- Location for printing out blank CRFs.

❏ Account Request- Location for requesting new accounts or updating current accounts. This is available only to the Site P.I.

2.3.4 Reports display links for various reports that summarizes protocol activities.
2.3.5 Help displays links to Help Desk and Typical Questions.

3　Document Repository

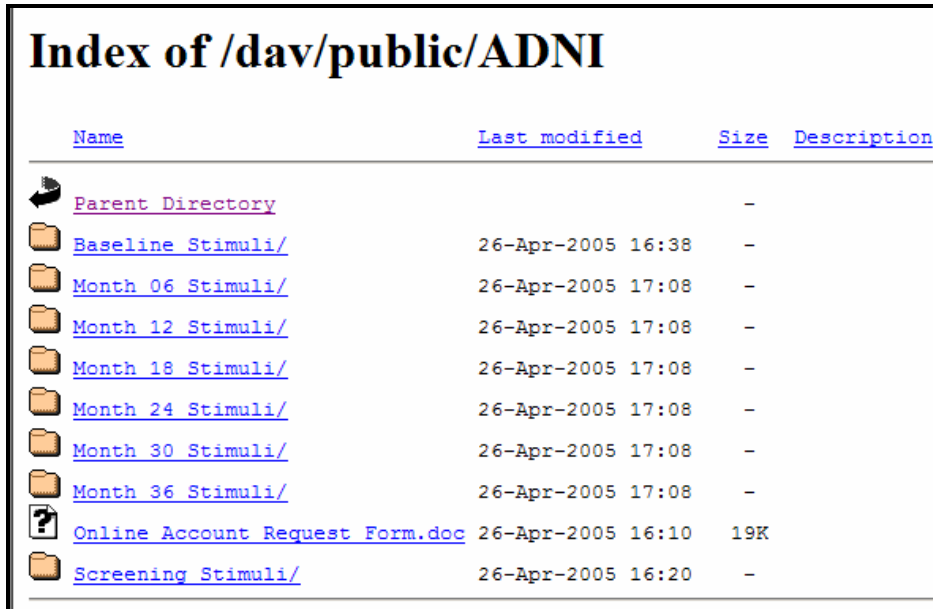3.1 All Project Documentation and Procedures are available online for view and download. Blank Stimuli forms, logs and administrative forms would be printed from here.

3.2 From Forms, click on Document Repository.

3.3 Select public/ link

3.4 Select the next desired folders.

3.5 Word Document files will ask you if you would like to Open or Save the file. Powerpoint and PDF files will open directly. You may download the file to your computer by saving the files.

Index of /dav/public/ADNI

Name	Last modified	Size	Description
Parent Directory		–	
Baseline Stimuli/	26-Apr-2005 16:38	–	
Month 06 Stimuli/	26-Apr-2005 17:08	–	
Month 12 Stimuli/	26-Apr-2005 17:08	–	
Month 18 Stimuli/	26-Apr-2005 17:08	–	
Month 24 Stimuli/	26-Apr-2005 17:08	–	
Month 30 Stimuli/	26-Apr-2005 17:08	–	
Month 36 Stimuli/	26-Apr-2005 17:08	–	
Online Account Request Form.doc	26-Apr-2005 16:10	19K	
Screening Stimuli/	26-Apr-2005 16:20	–	

4　Account Request

4.1 As the Site Principle Investigator is accountable for all data entered at the site, only the Site PI has the access to account request.

4.2 From Forms, click on Account Request.

4.3 The site's current accounts will be listed.

4.4 From here the Site PI can add a new account or update an existing account.

4.5 The Account Request Form requires the individual's name, degrees, protocol role, email address, and level of access. Click on 'Submit' and allow up to 24 hours for the request to be processed.

4.6 Email addresses should be unique. If an individual shares an email account with other people, the account information (user i.d. and password) will be sent by US Mail.