DOD ADNI
PROCEDURES MANUAL

Version 3.0 August 28, 2017

CHAPTER 1

OVERVIEW

San Francisco Veteran Affairs Medical Center (SFVAMC) will be responsible for the mail effort, recruitment, the telephone screeners, and clinical interviews. There will be NO participants seen on the SFVAMC campus. Subjects may also be referred to SFVAMC by local clinic sites for the initial telephone pre-screens (eligibility and clinical interviews (SCID CAPS)). Sites are permitted to advertise to potential participants and refer interested parties to SFVAMC for pre-screening.

Study participants will have two separate prescreening phone visits up to four months prior to the first DOD ADNI clinic visit. After initial mail contact and telephone screening, all eligible participants will undergo a clinical psychological interview using the Structured Diagnostic Interview SCID-I for DSM IV-TR, and the Clinician Administered PTSD Scale (CAPS) by telephone, conducted by the PTSD Core at the San Francisco VA Medical Center.

Participants who continue to meet eligibility criteria and live within 150 miles of the closest ADNI clinic, will be referred to their local site for an in-clinic Screening Visit.

If the participant meets all inclusion/exclusion criteria after the in-clinic Screen Visit, the study participant will proceed to a Baseline Visit and have clinical/cognitive assessments, biomarker and genetic sample collection, and imaging. If participant continues to meet eligibility criteria after the in-clinic screen/baseline visit, he/she will have a six month interim phone check (by SFVAMC), followed by a 12 month phone check by SFVAMC who will refer the subject to the site for the 12-month in-clinic visit. Any changes and/or SAE's reported by the subject during the six and 12-month phone checks will be promptly reported to the sites for follow-up.

After the participant's original Baseline Visit, a reduced battery of tests is allowable if the subject is not able/willing to complete the full battery.

All MRI and PET scans will be rapidly assessed for quality so that subjects may be rescanned if necessary. All raw and processed image data will be archived at USC's Laboratory of Neuro Imaging (LONI). All clinical data will be monitored by the Coordinating Center at the University of Southern California (USC). The University of Pennsylvania (UPENN) will receive and process biomarker samples, and the National Cell Repository of Alzheimer's Disease (NCRAD) will receive and process genetic samples.

Tau PET imaging is also offered as an addendum to the main protocol. Please see the DOD ADNI tau PET addendum for further details.

CHAPTER 2

GENERAL INFORMATION & CERTIFICATIONS

PERSONNEL REQUIREMENTS

The following roles must be assigned, in order to conduct the Department of Defense Alzheimer's Disease Neuroimaging Initiative (DOD ADNI) Study.

DELEGATION AND SIGNATURE LOG

The Delegation and Signature Log details study staff to whom significant study-related tasks have been delegated as well as each individual's dates of involvement in the trial. The log will also document that the PI is responsible for, accountable for, and has approved such delegation of duties. In addition, the full legal signature and initials of all study personnel authorized to make entries and corrections on CRFs and source documents will be captured.

The Delegation and Signature Log should be completed prior to beginning trial-related activities and updated as needed to reflect changes in staff, role assignments and/or the delegation of responsibilities. Any changes to the log must be documented using a blue or black ink pen.

The Study Coordinator can complete the log; however, the PI must review and acknowledge approval of the duties being delegated by providing his/her initials and the date next to each personnel. Similarly, if any changes are made to the Delegation and Signature Log during the course of the study the PI must review and acknowledge approval of the changes by providing his/her initials and the date next to the changes.

For detailed instructions on how to complete the log, refer to the "Delegation and Signature Log Instructions" posted in the DOD ADNI study portal document repository.

SITE PROTOCOL PRINCIPAL INVESTIGATOR (PI)

The PI should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial.

Responsibilities include, but not limited to:

- Protect the rights and well-being of study participants.
- Conduct appropriate informed consent of study participants.
- Medical care of study participants.
- Personally conduct or supervise the described study.
- Maintain appropriate staff qualifications including study specific training.
- Adequate staffing resources.
- Supervision of study personnel, including:
    - Delegation of roles and duties to appropriately qualified study personnel.
    - Ensuring that all study personnel are informed about the protocol and their delegated duties.
    - Ensuring that clinical raters maintain a high level of skill and accuracy.

Conduct the study in accordance with Federal Regulations, Internal Conference on Harmonization (ICH) and Good Clinical Practices (GCP).

Approved protocol (as indicated by signed 1572).

Communications with IRB.

Compliance with study protocol.

Maintenance of adequate and accurate source documents, study records and other study related reports (this includes data entered into the online DOD ADNI EDC system).

Safety Reporting

The Site PI may also serve as the Study Physician / Site Clinician.

STUDY PHYSICIAN/SITE CLINICIAN
This person must possess certain credentials – MD, DO, NP, or PA-C.

Responsibilities include, but not limited to:

Conducting or supervising the clinical evaluation of all participants including physical and neurological exams, reviewing adverse events, and interpreting lab results at each study visit.

Ensuring that biological samples (CSF, blood) are correctly processed.

Performing lumbar punctures (if applicable) unless another accredited individual is qualified to do so.

STUDY COORDINATOR
Responsibilities include, but not limited to:

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

Ensuring accurate administration of all instruments at the site.

Supervising accurate data collection and maintaining case report forms.

Preparing, handling, and processing of all laboratory samples.

Coordinating clinic visits.

Scheduling visits at MRI and PET centers and schedule assessments and LP procedures.

Serving as a liaison with the ATRI Clinical Monitor/ATRI Clinical Operations Group.

REGULATORY
Responsibilities include, but are not limited to:

Managing all regulatory related documents for the duration of the trial, including submitting all required regulatory documents to ATRI Regulatory Affairs.

Ensuring that all safety reports, protocol deviations, continuing review documents, protocol amendments and consent form modifications are submitted to the IRB in a timely manner and per the IRB's SOPs.

Serving as the liaison between the site IRB and ATRI Regulatory Affairs.

BILLING - REMITTANCE
Responsibilities include, but are not limited to:

Accepting and processing payments from the ATRI.

BILLING - STATEMENT
Responsibilities include, but are not limited to:

Reviewing and verifying payments from the ATRI are in alignment with procedures completed.

MRI CONTACT
Responsibilities include, but are not limited to:

Conducting phantom and human volunteer scans per protocol for site qualification purposes and as needed to assess for drift.

Conducting participant MRI scans per protocol.

Uploading MRI scans to LONI in a timely manner.

Ensuring that all MRI data is archived according to protocol.

PROJECT INTERVIEWER/PSYCHOMETRIST
Responsibilities include, but are not limited to:

Have at least a bachelor's degree in healthcare psychology, social work or a related field, and/or well-documented experience in administering interviews and neuropsychological tests.

Administration of the ADAS-Cog and/or the CDR; however the same person may not administer both the ADAS-Cog and CDR for the same subject.

The Study Coordinator may server as the interviewer/psychometrician as long as he/she is properly trained.

SIGNATURES

"Wet" signatures on hard copy worksheets and electronic signatures on eCRFs serve to acknowledge that a clinician has reviewed each study visit and that the visit was conducted to his/her satisfaction.

ONLY STUDY PERSONNEL WITH CERTAIN CREDENTIALS (MD, PA, DO, OR NP) ARE ALLOWED TO PROVIDE HARD COPY AND ELECTRONIC SIGNATURES.

Hard Copy ('Wet') Signatures

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

- Neurological Exam
- Physical Exam
- Adverse Events and Hospitalizations
- MRI/CT Clinical Read
- Lab Results
- ECG reports (specific to tau-PET addendum)

STUDY COORDINATORS WITH THE CREDENTIALS MD, PA, DO, AND NP ARE ALSO ALLOWED TO PERFORM AND SIGN OFF ON THESE ASSESSMENTS

CERTIFICATIONS

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

ADAS administration, scoring, and guidelines can be accessed in the Cognitive Assessments Chapter of this Procedures Manual.

THE ADAS QUESTIONNAIRE CAN BE ACCESSED VIA THE FOLLOWING LINK: HTTPS://DOCS.GOOGLE.COM/FORMS/D/E/1FAIPQLSEJ14GM47C3MMHQXF2PP9YXJZFJ3UPSFXNUO9I4RPOF1TXA6Q/VIEWFORM

AFTER BEING SCORED, THE RATER WILL RECEIVE ADAS CERTIFICATION BY EMAIL FROM THE ATRI. CERTIFICATION IS VALID FOR 5 YEARS; AFTER THIS TIME THE RATER MUST RECERTIFY.

CDR Rater
All individuals administering the CDR for DOD ADNI must be certified through Washington University. Depending on previous CDR certification there are two separate requirements:

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

CDR Certified: For those raters who have been previously certified over 5 years ago will require a refresher training. This refresher includes five (5) reliability tapes. The ratings/scores are compared to the Gold Standard and, if the rater passes, Washington University will issue a certificate

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

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

IT IS IMPORTANT FOR THE CDR RATER TO REMAIN BLINDED TO THE ADAS-COG DATA. IF THE CDR RATER IS ALSO THE PI, THE CDR MUST BE COMPLETED BEFORE VIEWING AND APPROVING THE STUDY DATA COLLECTED DURING THE VISIT.

MRI Scan Certification
All participating sites for DOD ADNI must complete the scanner certification process, as the MRI protocol sequence for DOD ADNI is different from ADNI.

Site MRI qualification requires a phantom scan and a volunteer scan. **Volunteer scanning can be done only AFTER IRB approval**. See MRI section in the Procedures Manual, along with the MRI Technical Manual for further details.

PET Scan Certification
Any new participating sites for DOD ADNI must complete the PET scanner certification process. Sites that have been certified previously for ADNI2 do NOT require recertification unless there has been a change in PET scanner or change in software platform. For more details, refer to the PET Technical Manual.

SUMMARY OF CERTIFICATION AND OTHER ADMINISTRATIVE REQUIREMENTS:

- Delegation and Signature Log (see section above for more details)
- Contact Information Form(s) for new personnel
- Current ADAS-Cog Certification (through ATRI)
- Current CDR Certification (through Washington University, St. Louis)
- MRI Certification
- PET Certification (if applicable)
- Trained Psychometrist and Raters for Neuropsychometric Testing Battery and other assessments

SUPPLIES

The ADNI Coordinating Center at the ATRI will provide the following laboratory supplies for the DOD ADNI study:

DNA, APOE and RNA Collection, Labels and Shipping Supplies.

Biomarker Collection, Labels and Shipping Supplies.

Buffy Coat supplies

CSF Collection and Shipping Supplies (including Sprotte Needles and LP Trays).

Other Supplies Provided by the ATRI:

Subject binder inserts/tabs, spine and covers. (The cost of the actual subject binders has been factored into the startup fund distributed at the beginning of DOD ADNI; therefore, actual subject binders will NOT be provided by the ATRI).

The Procedures Manual and Source Document Worksheets are posted in the document repository and are to be printed by site staff. Hard copies will not be printed and sent by ATRI.

Blank Self-Report Questionnaires are posted in the document repository. If the study participant forgets to bring the completed questionnaires to the screening visit, ensure to provide the blank self-report questionnaires for completion while in clinic.

Neuropsychometric Testing Supplies (ADAS Kits, Boston Naming Testing Booklet).

ADAS KITS AND BOSTON NAMING TESTING BOOKLET ARE THE SAME SUPPLIES PROVIDED AND USED IN ADNI2. NEUROPSYCHOMETRIC SUPPLIES WILL NOT ROUTINELY BE PROVIDED TO EACH SITE AS IT IS EXPECTED TO USE ONE SET ACROSS ADNI2 AND DOD ADNI.

- Hard copies of the MMSE Worksheet.
  - Due to copyright restrictions, the MMSE will no longer be included in the source document packets posted in the document repository. The number of hard copies of the MMSE included in the initial shipment from the ATRI will be based on the number of potential participants prescreened in your area from SFVAMC. The order form posted in the document repository will need to be used to order additional copies of the MMSE.
  - DO NOT make photocopies of the MMSE worksheet at any time. Hard copies should be ordered directly from the ATRI.
- Hard copies of the SCL-90R Worksheet.
  - Due to copyright restrictions, hard copies of the SCL-90R are available, if needed. Participants will be mailed the SCL-90R for completion prior to the DOD screening visit. If the participant fails to bring the completed SCL-90R with them to the clinic, they should complete while on site. Backup copies of the SCL-90R will be provided to each site with the initial set of ATRI supplies at start up and are listed in the supply order form.

SPANISH TESTING SUPPLIES WILL NOT BE OFFERED FOR THIS STUDY, AS ALL PARTICIPANTS MUST BE FLUENT IN ENGLISH.

Screening Laboratory Supplies Provided by University of Rochester Medical Center (URMC)

URMC Labs will provide screening specimen collection kits, which includes blood chemistry, TSH, Vitamin B12, and urinalysis. Additionally, homocysteine and methylmalonic acid kits, as well as pregnancy tests are available should it be needed.

Each site will receive 5 screening specimen collection kits, 1 homocysteine and methylmalonic acid kit, and 1 urine pregnancy test as an initial set of supplies once the site is close to obtaining approval to begin receiving referrals. **There are no auto shipments after the initial set of supplies are shipped. To request additional specimen collection kits, use the URMC supply order form posted in the document repository**.

URMC Labs Clinical Trials Central Laboratory Manual is available in the document repository and contains more information about the initial supply distribution, clinical lab supplies, lab reports, specimen collection, packaging, and shipping.

URMC and ATRI Resupply

The URMC request form is available on the document repository under 'forms'. Request additional Screening Laboratory Kits from URMC by

Fax: 585-486-1375

Or

Email: LabSRSS@urmc.rochester.edu

ATRI supplies can be requested from the ATRI using the online supply order form (link can also be referced in memo #25_20160331): http://goo.gl/forms/K6cptHDeOb

USE OF MULTIPLE LOCATIONS AT A SINGLE CENTER

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

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 into the DOD ADNI EDC from any location. The ATRI Coordinating Center should be immediately notified if the study coordinator changes.

Monitoring visits must be carried out at a single location.

All source documents must be at a single location in order to avoid the expenses associated with additional travel by the clinical monitors.

PARTICIPANT TRANSFERS

Sites should immediately notify their Clinical Monitor when a potential transfer situation has been identified, including the following information:

- Participant ID
- Reason for transfer
- Date / Timing of transfer
- Last visit complete at home site
- Whether an alternate site has been identified and/or contacted
    - The home site will communicate with the proposed transfer site regarding the potential transfer to confirm that the transfer site is willing and able to accept the participant transfer. If not, consult with ATRI regarding other possible transfer sites or alternative strategies for managing the participant.

Documentation and Consent

The participant should sign a medical release allowing the home site to share medical records with the transfer site.

Original source documents are retained at the site where the source was created. The home site should share a copy of any regulatory documentation (if required by transfer site), source documents, research records, and medical records that are needed by the transfer site to provide adequate medical oversight of the participant. Each site will retain ICFs signed at that site. It is recommended that the study teams at each site conduct transition coordination meeting (s) prior to the participant's first visit at the transfer site to ensure each site has what is needed (source documents, medical records, research records, etc.) and to discuss any participant-specific issues that may impact conduct or management of study procedures or participant medical issues.

The transfer site must consent the participant using their site-specific, IRB approved consent form (and HIPAA authorization) prior to conducting any protocol specific procedures.

Data Entry, Queries, and Monitoring

Data and queries will be "moved" to be accessible under the transfer site at which time they will not be accessible to the home site. ATRI will conduct data review and cleaning for the transferring participant (for example, performing monitor review, running post-entry edit checks, and reviewing protocol deviations) to the extent possible at the time of the transfer.

IN ORDER TO REDUCE BURDEN ON THE TRANSFER SITE, THE HOME SITE SHOULD MAKE EVERY EFFORT TO COMPLETE DATA ENTRY AND QUERY RESOLUTION ON EXISTING DATA IN ADVANCE OF "MOVING" THE DATA. THIS WILL REQUIRE CLOSE COORDINATION WITH YOUR CLINICAL MONITOR.

Once the data from the home site is transferred to the transfer site in the EDC, the following will be required:

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

Adverse Event (AE) and Serious Adverse Event (SAE) Reporting
The home site will provide documentation to the transfer site that should include up-to-date information on concurrent medications, medical history, initial health status and study entry, and any adverse events experienced in the study. Normal SAE reporting process must always be followed - SAEs must be reported within 24 hours of becoming aware of the event.

CHAPTER 3

CLINICAL MONITORING

OVERVIEW

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

The purposes of monitoring is to ensure that:

The rights and well-being of human participants are protected

The reported trial data are accurate, complete, and verifiable from source documents

The conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with the applicable regulatory requirement(s).

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

MONITORING FREQUENCY

On-site monitoring visits will be conducted approximately annually with the initial on-site monitoring visit occurring ***within 2 months of the first successful baseline visit*** at your site.

The frequency of on-site visits may increase based on the discretion of the Clinical Monitor Manager and/or Monitor.

MONITORING RESPONSIBILITY

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

Be the primary contact person for the sites and main line of communication between ATRI and DOD ADNI participating sites.

Verify that the Investigator has the appropriate qualifications, resources and facilities including laboratories, equipment and staff, to safety and properly conduct the trial, and that these remain adequate throughout the study.

Conduct ongoing training of site personnel as needed.

Confirm all participants screened signed the appropriate ICF and that no study related procedure was conducted prior to obtaining consent.

Review and approve all potential participants for enrollment in the trial.

Confirm that all assessments are conducted per protocol.

Verify the proper handling and storage of lab specimens.

Review all serious and non-serious adverse events for completeness and accuracy. Please note this includes AE/SAE information during the prescreening phase collected by San Francisco Veterans' Affairs Medical Center (SFVAMC) that is transferred to the DOD ADNI site at the point of referral.

Ensure that participant enrollment, data verification, and query resolution are taking place on schedule.

Verify that all regulatory documents are accurate, current, properly stored and maintained; confirm all required communication with the IRB is on file and are current.

Verify the Delegation of Duties and Signature log at every on-site visit to ensure the appropriate personnel are performing assessments as delegated.

Follow-up on requests made by project management as needed.

CLOSE-OUT VISIT

The CM will conduct a site close-out visit after all participants at the site have completed all study visits and all data queries have been resolved. Generally the close-out visit should occur within 45 days of the last participant last study visit.

Close-Out Visit Activities Include:

- A final review of the regulatory binder.

    - CAP/CLIA accreditations are verified.
    - Current and signed CV for the PI and all co-investigators are verified.
    - FDA form 1572 is verified to ensure it lists all current staff and is signed by the PI (if applicable).
    - Delegation of Duties and Signature Log is verified as complete and signed by all site personnel, with a final signature and date by PI.
    - Financial disclosure forms are verified as complete for the PI and all co-investigators.
    - All IRB submissions, notifications, and correspondence are verified as present and organized.
    - All study memos from the ATRI are verified as present and organized.
    - Training records (i.e., ADAS Rater, CDR rater) are verified.
    - All other significant study related documents are reviewed for completeness.
- A final review of AEs/SAEs is conducted to ensure no issues remain.
- Confirmation that all issues/actions from previous monitoring visits are closed.
- Confirmation that all queries have been addressed and are closed.
- Remind the Principal Investigator of his/her financial disclosure obligations for one year post-study. If there are any changes to the PI's equity interest, they must be reported to the Project Director, Dr. Michael Weiner.
- Inform the investigator that if he/she becomes unable to maintain the study records that he/she should notify ATRI of the location of the records and the person responsible for retention.

IMPORTANT NOTE:

THE CLOSING OUT OF A SITE IS A PROCESS AND NOT MERELY A FINAL AND/OR ROUTINE MONITORING VISIT. YOUR SITE'S PARTICIPATION MAY CONCLUDE MONTHS BEFORE THE LAST VISIT IS CONDUCTED AT OTHER SITES, AND YOUR CLINICAL MONITOR MAY CONDUCT A FINAL MONITORING VISIT SOME TIME BEFORE THE ENTIRE TRIAL IS OVER, HOWEVER, DO NOT CLOSE OUT ANY STUDY WITH YOUR IRB UNTIL YOU ARE OFFICIALLY NOTIFIED BY THE ATRI THAT THE TRIAL HAS BEEN COMPLETED AND IT IS APPROPRIATE TO DO SO. UNTIL SUCH TIME, IT IS ESSENTIAL THAT ALL STUDY DOCUMENTS AND INFORMATION ARE EASILY RETRIEVABLE AND CONTINUE TO BE STORED IN A SECURE LOCATIO

CHAPTER 4

CENTRAL RECRUITMENT BY THE SAN FRANCISCO VETERANS AFFAIRS MEDICAL CENTER (SFVAMC)

SUMMARY

This new Department of Defense (DOD) funded project, the *"Effects of TBI and PTSD on Alzheimer's Disease in Veterans Using ADNI",* will differ from the ADNI2 and ADNI3 projects, in that all recruitment will be done centrally at the San Francisco VA Medical Center (SFVAMC).

SFVAMC will be identifying possible participants by utilizing VA Compensation and Pension (C&P) records where the appropriate diagnostic codes for Traumatic Brain Injury (TBI) (or other potential head or face injuries) or Post Traumatic Stress Disorder (PTSD) is indicated, as well as Veterans Affairs Health records, and/or response to advertisements. A sample of subjects with service connection for injuries not related to TBI or PTSD was also obtained from the VA (C&P) and will also be contacted and screened for possible controls. We will not attempt to enroll control subjects until approximately 25% of the TBI and PTSD ***subjects have been enrolled***.

Once potential participants are identified, SFVAMC will be responsible for the mail effort to the potential participants, conducting a prescreening telephone interview, as well as clinical interviews over the phone to confirm eligibility. ***There will be NO study participants seen on the SFVAMC campus***.

Mail Efforts by SFVAMC

Those who will be contacted by mail will meet the following criteria:

- Vietnam War veterans aged 50-90 *(*subjects between 60-80 years of age will be enrolled first; Subjects between 50-59 years of age, as well as those over 80 years will only be contacted should the preferred age prove difficult to enroll)
- Documented history of moderate/severe TBI, (or self report of loss of consciousness of ≥ 5 minutes and/or dizziness, confusion, amnesia >24 hours), and/ or PTSD
- Are neuropsychiatrically healthy

The mail effort will consist of an informational letter, brochure, and response post card. Letters will be sent out to those participants who reside within 150 miles of a DOD ADNI site who have received both local and DOD approval.

Subjects may also be recruited from newspaper advertisement/article, craigslist, veterans magazine, flyer, or referred by local clinic sites. A study brochure, containing study information and contact info, can be found in the DOD ADNI document repository.

Local clinic sites may post flyers, hand out brochures, advertise in local newspapers, veterans magazine, craigslist, or contact potential subjects on their own lists, to help recruit potential subjects in their area. If potential subjects express interest, the subject will be provided

SFVAMC contact information.

Phone Prescreen by SFVAMC

After the initial mailing, participants will be contacted by telephone by SFVAMC staff to explain the study. After the study explanation, verbal consent for the screening interview will be obtained and then the screening questions will be administered. If after the screening interview, the participant is eligible, the SFVAMC staff will mail a written consent form for a telephone clinical interview, as well as a form for consent to audio-record the clinical telephone interview. In addition, three self-report questionnaires on MRI safety, medical history, and concomitant medications will be mailed to the participant with the clinical interview consent.

SFVAMC study staff will call the participant a few days later to review the written consent forms, answer any questions the participant has, and assist with the self-report questionnaires as necessary. If participant is interested in continuing, staff will ask subject to sign the consent form(s) and return them along with the completed self-report questionnaires by fax or mail (in the stamped addressed envelope).

Clinical Interview by SFVAMC

After self-report questionnaires and written/consent form is received and reviewed for eligibility, participants will be called and told of their eligibility status. Eligible participants will be referred to the PTSD core for comprehensive psychiatric assessment, which involves a telephone administration of the SCID I for DSM-IV TR and Clinician Administered PTSD scale (CAPS). If the signed consent form to audio-record the clinical telephone interview is also received, the interview will be audio recorded.

Once the SCID/CAPS is entered and reviewed for eligibility criteria, SFVAMC staff will call the participant to let him/her know of the eligibility status. If participant is eligible, they will be subsequently referred to a nearby approved DOD ADNI site. SFVAMC staff will give the participant the contact information of the selected clinic, and ***will send a secur email to the clinic to give the clinic site the participant contact information.***

Those participants referred to the clinic, will be mailed a packet of self-report questionnaires and will be asked to bring them to the DOD ADNI clinic on their first clinic appointment. Eligible participants will be referred to the DOD ADNI site based on their zip code; if the participant is within range of more than one zip code, they will be referred to the DOD ADNI site of their choice.

ALL PATIENT DATA AND TELEPHONE CALLS CONDUCTED BY SFVAMC TEAM WILL NOT BE ACCESSIBLE TO THE DOD CLINIC SITES. PERTINENT DATA (I.E. MEDICAL HISTORY, SAFETY EVENTS AND CONCOMITANT MEDICATIONS) WILL BE SHARED WITH THE REFERRED DOD SITE VIA AN ONLINE REPORT INTERFACE.

SFVAMC TEAM IS RESPONSIBLE TO ENTER ONLINE THE SELF-REPORT QUESTIONNAIRES RETURNED BY THE PARTICIPANT DURING THE DOD CLINIC SCREENING VISIT. ENSURE TO UPLOAD THE SELF-REPORT QUESTIONNAIRES THROUGH THE STUDY FILE UPLOAD ECRF IN ORDER FOR SFVAMC TO HAVE ACCESS TO THE ORIGINAL SOURCE DOCUMENTS.

SELF REPORT QUESTIONNAIRE PACKET

Combat Exposure Scale

Keane, T.M., J.A. Fairbank, J.M. Caddell, R.T. Zimering, K.L. Taylor, and C. Mora, Clinical evaluation of a measure to assess combat exposure. J of Consulting and Clinical Psychology, 1989. 1: p. 53-55

A brief but reliable and valid 7-item Combat Exposure Scale to quantify the subjective report of wartime traumatic stressors experienced by combatants in the Vietnam War.

Pittsburgh Sleep Quality Index

Buysse, D.J., C.F. Reynolds, 3rd, T.H. Monk, S.R. Berman, and D.J. Kupfer, The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res, 1989. 28(2): p. 193-213.

This self-report measure provides a subjective assessment of sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances (including nightmares), use of sedative-hypnotics, and daytime energy.

SF-12 Health Survey

Ware, J.E., M. Kosinski, and S.D. Keller, A 12-Item Short-Form Health Survey - Construction of Scales and Preliminary Tests of Reliability and Validity. Medical Care, 1996. 34(3): p. 220-233.

This is a brief inventory measuring functional status in 6 domains and measuring global daily functioning. Published normative age-adjusted means for each domain and a global functioning score were derived from US residents.

Smoking/Lifetime Smoking

The smoking history questionnaire used for this study is based on a modified Fagerström nicotine dependence scale, designed to obtain an estimate of both dose exposure and duration of smoking history

Symptom Checklist-90 Revised

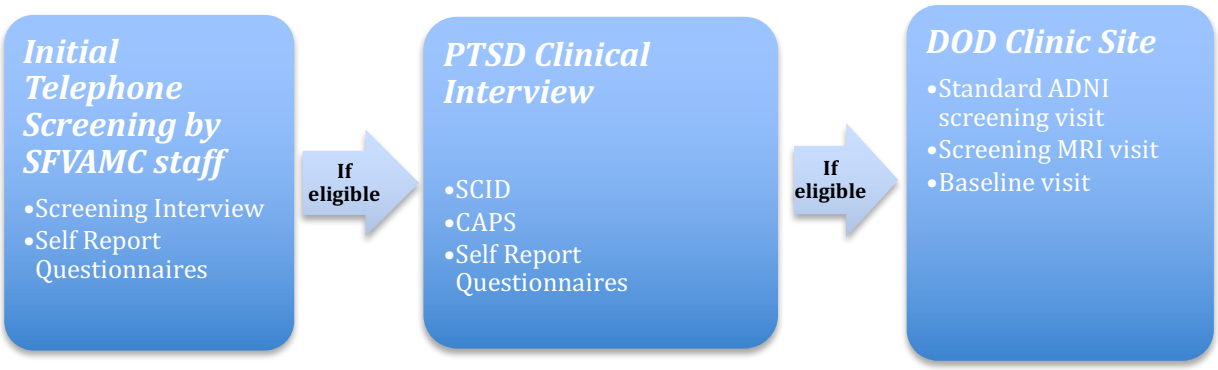
Derogatis, L. and L. Lazarus, SCL-90--R, Brief symptom inventory, and matching clinical rating scales, in The use of psychological testing for treatment planning and outcome assessment, M.E. Maruish, Editor. 1994, Lawrence Erlbaum Associates, Inc.: Hillsdale, NJ. p. 217-248

The SCL-90-R is a standard self-report measure of general psychopathology. Extra copies of this test will be mailed to the site in case a participant does not bring the completed SCL-90-R.

In the event that a participant fails to bring the complete self-report questionnaire packet to the DOD clinic screening visit, blank copies of the Self-Report Questionnaires are available in the document repository and should be provided to the participant to complete while in clinic for screening.

DUE TO COPYRIGHT REQUIREMENTS, BLANK COPIES OF THE SCL-90R WILL NOT BE AVAILABLE IN THE DOCUMENT REPOSITORY. HARD COPIES ARE AVAILABLE BY REQUESTING VIA THE ONLINE SUPPLY ORDER FORM.

SFVAMC TO DOD ADNI SITE REFERRAL FLOW DIAGRAM



SCREEN/BASELINE DOD ADNI SITE VISIT - WITHIN 30 DAYS TO 4 MONTHS OF REFERRAL, IF POSSIBLE.

CHAPTER 5

DOD ADNI CLINIC SCREENING PROCEDURES

SUMMARY

All study participants who pass the pre-screen evaluation conducted by SFVAMC, will be referred to a DOD clinic site within 150 miles of the participant's home. The purpose of the DOD ADNI screening visit is to determine eligibility and to collect measures that will be used as a reference to assess change. A standardized evaluation will be performed at each clinical site and must occur within four months of the date of referral.

Consent will be obtained before any portion of the screening visit is initiated. The MRI will be conducted only for participants who meet eligibility criteria for all other screening assessments as determined by both a site investigator and ATRI clinical monitor.

Eligibility will be determined according to the inclusion/exclusion criteria outlined in the protocol and confirmed by an ATRI clinical monitor before the participant can be brought back for Baseline.

KEY REMINDERS

Sites must complete data entry within 3 business days of the screening visit, including uploading laboratory reports to the study file upload eCRF.

Monitor approval is required prior to conducting the Screening 3T MRI scan.

Scan must be approved before proceeding to Baseline.

PARTICIPANT IDENTIFIERS

The DOD ADNI Participant ID (PTID) consists of a 7-digit numerical code assigned by SFVAMC at the beginning of their pre-screening process. Use the Participant ID for all study documents, source documents, MRI/PET scans and biologic samples. Phantom IDs are not assigned on the DOD ADNI Clinical Data Portal. Assign Phantom IDs following instructions in the MRI and PET Technical Manuals, while uploading to the LONI database.

PRE-SCREENING

Participants referred to sites will already have undergone a pre-screening process carried out by SFVAMC.

Safety, medical history, and concurrent medications information will be collected by SFVAMC during the pre-screening process. These data are made available to sites in the reports tab located in the DODADNI study portal. It is recommended that these reports be referred to during the DOD screening visit in order to ensure complete and accurate information is collected. Any discrepancy between the interview conducted with the participant at the DOD site and the data

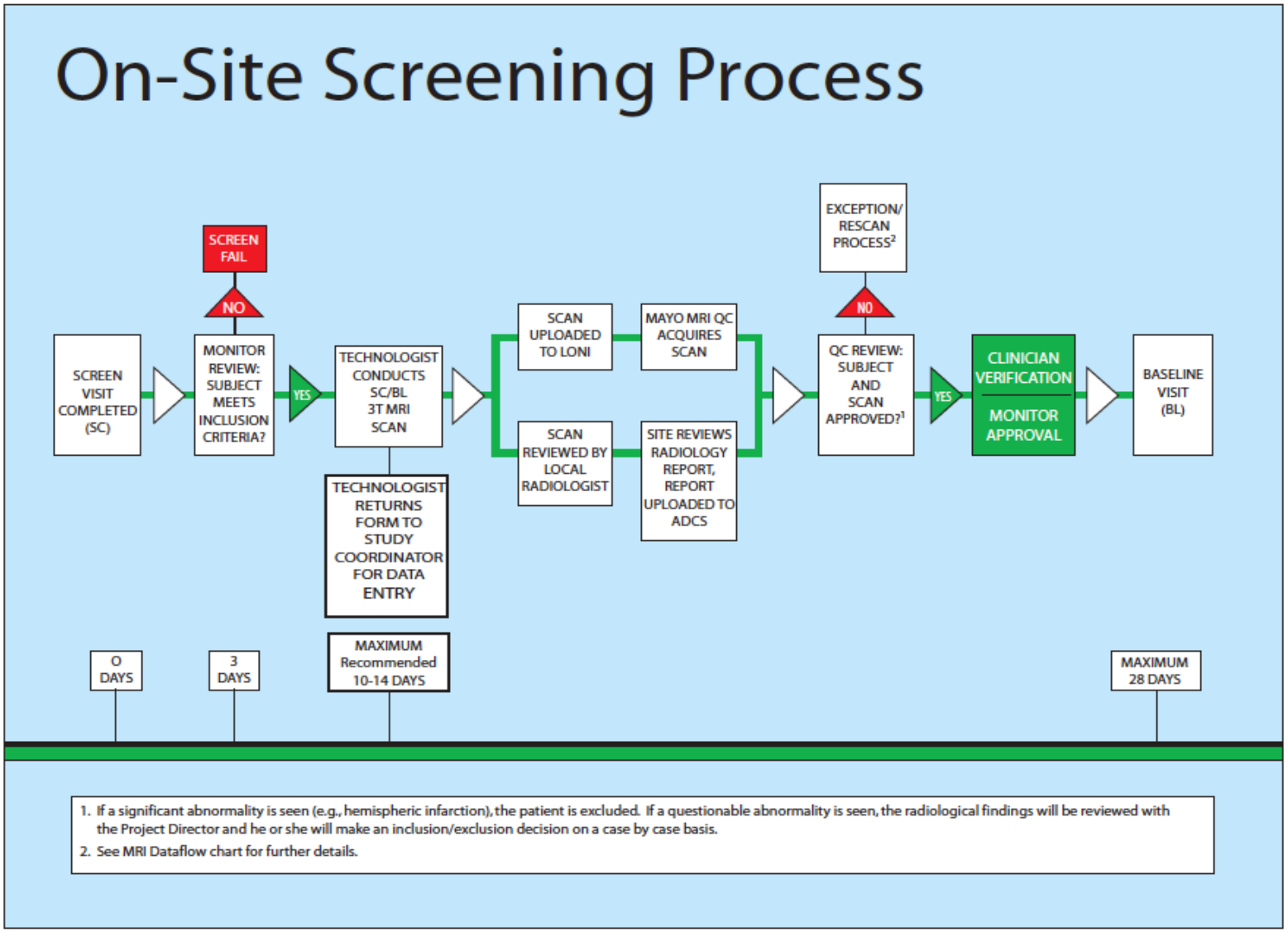
collected by SFVAMC during the pre-screen phase should be addressed at the point of screen to ensure the participant meets eligibility criteria.

ADDING A NEW PARTICIPANT TO YOUR SITE

- Participants are assigned a 7-digit PTID number during the SFVAMC pre-screening.
- Sites will be notified that a participant has completed pre-screening and is eligible to continue to the on-site screening visit.
- To add the new participant to your site:
    - Click the "Add a new participant" button on the Participant Menu page of the DOD ADNI Clinical Data Portal.
    - Select the appropriate 7-digit PTID from the drop-down menu.
    - Double-check that the selected PTID is an exact match to the PTID provided to you by SFVAMC.
    - If the PTID matches the one you have been given, click the green "Register" button to add that participant to your site.

SINCE THE DROP DOWN WILL CONTAIN ALL PARTICIPANTS ELIGIBLE TO CONTINUE TO CLINIC VISITS, THERE MAY BE MULTIPLE PTIDS AVAILABLE IN THE DROP-DOWN MENU, IT IS VITAL THAT YOU ONLY SELECT THE PARTICIPANT(S) MATCHING THE PTID PROVIDED TO YOU.

Additional instructions related to data entry can be refereced in the Data Entry Manual posted to study documents in the DOD ADNI study portal.


On-Site Screening Process
SCREEN VISIT COMPLETED (SC)
MONITOR REVIEW: SUBJECT MEETS INCLUSION CRITERIA?
SCREEN FAIL
NO
YES
TECHNOLOGIST CONDUCTS SC/BL 3T MRI SCAN
TECHNOLOGIST RETURNS FORM TO STUDY COORDINATOR FOR DATA ENTRY
SCAN UPLOADED TO LONI
SCAN REVIEWED BY LOCAL RADIOLOGIST
MAYO MRI QC ACQUIRES SCAN
SITE REVIEWS RADIOLOGY REPORT, REPORT UPLOADED TO ADCS
QC REVIEW: SUBJECT AND SCAN APPROVED?1
EXCEPTION/ RESCAN PROCESS2
NO
YES
CLINICIAN VERIFICATION
MONITOR APPROVAL
BASELINE VISIT (BL)
0 DAYS
3 DAYS
MAXIMUM Recommended 10-14 DAYS
MAXIMUM 28 DAYS
1. If a significant abnormality is seen (e.g., hemispheric infarction), the patient is excluded. If a questionable abnormality is seen, the radiological findings will be reviewed with the Project Director and he or she will make an inclusion/exclusion decision on a case by case basis.
2. See MRI Dataflow chart for further details.

Screening Visit

Consent must be obtained prior to beginning screening procedures.

Conduct screening visit within four months from the point of referral.

Enter all data in the DOD ADNI Clinical Data Portal within 3 business days of screen.

Upload worksheets via the Study Document Upload eCRF.

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

Monitor Review

Clinical Monitor will review all data entered in the EDC and uploaded study documents.

Clinical Monitor enters all queries in the DOD ADNI EDC system.

Site is to resolve or reply to all queries in a timely fashion.

Upon satisfactory resolution of queries, clinical Monitor approves screen and participant may proceed to the 3T MRI visit.

3T MRI Scan

Tentatively schedule a MRI scan date with the participant and MRI center once the screening visit has been conducted.

Proceed with the 3T MRI scan, once the screening visit is approved by the ATRI Clinical Monitor. If the participants ends up failing the initial screening visit, the MRI scan cannot be conducted and will need to be cancelled with the MRI center.

Ensure Participant and Study Partner (if applicable) have the MRI Pamphlet with Appointment Reminder and Directions.

Ensure MRI Center has current MRI Technologist manual and MRI Scan Information Form for this participant.

Upload Scan to LONI day of scan (see MRI Technologist Manual for details).

Enter MRI Scan Information eCRF.

Email monitor that scan has been conducted and entered in the EDC system.

Upload copy of de-identified Radiology Report/Clinical Read as soon as it has been reviewed/signed off by Study Clinician via the Study Document Upload eCRF.

MRI QC Review

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

Clinician Verification

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

Monitor Approval

The Clinical Monitor completes the Monitor Eligibility only after confirming:

Site Clinician approval

MRI QC Approval

Important Reminders

3T MRI may **NOT** be conducted until screen approved by both clinician and monitor

Baseline may **NOT** be conducted until 3T MRI approved by Mayo MRI QC group, clinician and monitor.

Baseline visit (in-clinic assessment) must start within 28 days of screening visit. An additional 2 weeks are allowed to complete other Baseline procedures (e.g., Florbetapir F 18 PET, LP, etc.).

DO NOT CONTINUE TO BASELINE UNTIL MONITOR ELIGIBILITY IS CONFIRMED

SCREEN FAILURES AND RE-SCREENS

Indicate whether a participant is a screen fail on the Clinician Verification form. Enter all data collected for screen fails. At a minimum, these forms are required:

Registry (Reminder: For all participants, even those who screen fail, the participant status should be 'active,' and visit type as 'standard').

Participant Demographics

Clinician Verification

Before scheduling a rescreen, contact ATRI Clinical Operations and your clinical monitor for approval. Rescreens must be assigned a new DOD ADNI Participant ID (PTID) that is generated solely by the SFVAMC team. Ensure Clinician Verification for initial screen is entered as 'screen fail'.

IF 4 MONTHS HAS PASSED SINCE A PARTICIPANT WAS REFERRED TO YOUR SITE AND A SCREENING VISIT HAS NOT BEEN CONDUCTED, THE PARTICIPANT MAY REQUIRE A RE-EVALUATION AT THE PRE-SCREEN PHASE. CONTACT ATRI CLINICAL OPERATIONS AND YOUR CLINICAL MONITOR FOR GUIDANCE.

INCLUSION/EXCLUSION CRITERIA

Please refer to the current protocol for detailed eligibility criteria.

HISTORY OF CANCER FIVE YEARS PRIOR TO SCREENING MAY BE EXCLUSIONARY IF NOT MEDICALLY STABLE (HISTORY OF NON-MELANOMA SKIN CANCER IS NOT EXCLUSIONARY)

EXCLUDED MEDICATIONS:

- Anti-coagulant drugs include, but not limited to: Coumarin (Warfarin), Pradaxa (Dabigatran) and Heparin for the MAIN study.
    - If previously baselined subject is only being referred for the tau PET addendum, there is no need for an LP; anti-coagulants may be taken if needed in this circumstance.
- Drugs used to enhance cognitition (e.g. memantine) are exclusionary for non-MCI particiapnts.
- Tau PET addendum, please refer to separate listing of prohibited medications (Listing posted to studydocs>proceduresmanuals, and by clicking here).
- 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.

MEDICATION EXCEPTIONS / CASE-BY-CASE BASIS

- In general, centrally acting anticholinergic agents include (but not limited to): Seroquel (Quetiapine), Zyprexa (Olanzapine), Elavil* (Amitriptyline), Benadryl (Diphenhydramine), Compazine (perchlorperazine) and atropine or scopolamine containing medications are exclusionary, however, because many subjects with PTSD are prescribed these medications for nightmares, sleep issues, and other PTSD symptoms, the study will allow on a case by case basis.
- Drugs used to enhance cognition (e.g. memantine), are NOT exclusionary for the MCI cohort. Any subject prescribed these types of medications will be allowed, and will be automatically placed in the MCI cohort.
- Subjects who are prescribed drugs on the “discouraged” list for the tau PET addendum, may be enrolled if approval is obtained (Listing posted to studydocs>proceduresmanuals, and by clicking here).

CONTACT YOUR SITE MONITOR FOR QUESTIONS RELATED TO MEDICATIONS

Investigational Drugs

Individuals may not participate in any drug study while participating in this protocol. Additionally, no Investigational drugs may be taken within 4 weeks of screening.

PERMITTED MEDICATIONS

- Peripheral acting anticholinergic agents and other medications are allowed, if at a stable dose for at least 4 weeks prior to prescreen and DOD screening visit.
- Use of estrogen and estrogen-like compounds is allowed if the dose has been stable for 4 weeks prior to screening.

- Use of vitamin E is allowed if the dose has been stable for 4 weeks prior to screening (no cap on amount allowed).

Change in Medication Use After Enrollment

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

THIS IS NOT A COMPLETE LIST OF ALL MEDICATIONS. FOR ANY MEDICATION THAT MAY FALL INTO ONE OF THESE CATEGORIES OR IF YOU ARE UNSURE, PLEASE RAISE TO YOUR MONITOR FOR REVIEW BEFORE ENROLLING THE SUBJECT IN DOD ADNI.

SCREENING ASSESSMENTS

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

SCREENING BLOOD DRAWS

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

Laboratory reports must be reviewed, signed and uploaded for monitor review.

PRIMARY CARE PROVIDER NOTIFICATION

ATRI will provide a study involvement letter that can be shared with the participant's primary care provided. The letter template is posted to the document repository. Consent from the participant is required before sending information to their primary care provider. Each site should include in the letter to the provider the name and telephone number of a site physician who is available to answer any questions about DOD ADNI.

CHAPTER 6

DOD CLINIC BASELINE PROCEDURES

Key Reminders

The window from Screening visit to the start of Baseline is 28 days.

Participants must meet all inclusion/exclusion criteria before proceeding to Baseline

Once the Baseline visit begins, you have 2 weeks to complete all baseline procedures.

Complete Data Entry within 5 business days of the visit.

Data Flow

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

Local Radiologist

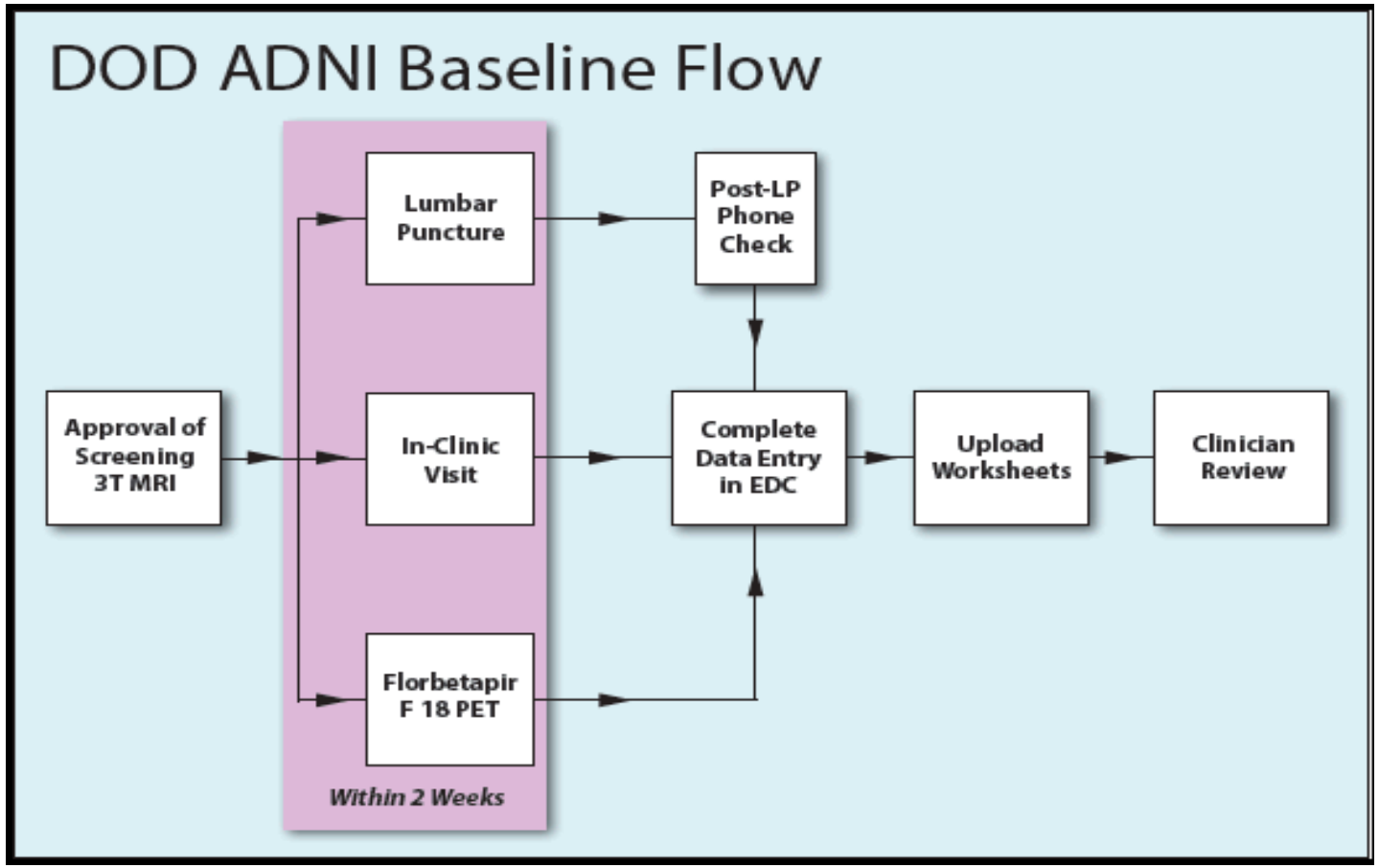
ADNI MRI QC (MRI Inclusion eCRF)

Site Principal Investigator

Clinical Monitor

IMPORTANT:

IF BASELINE ASSESSMENTS ARE CONDUCTED PRIOR TO OBTAINING FULL APPROVAL, THE SITE MAY NOT BE COMPENSATED FOR THESE.



Once the Baseline Visit begins, you have 2 weeks to complete all baseline procedures. Please refer to the Sample Visit Schedule below for rules on scheduling Lumbar Puncture and Florbetapir F 18 PET scan in relation to the Baseline in-clinic visit.

Keep in mind that the CSF, Plasma and Serum collected for Biomarker analysis are after an overnight or 8-hour fast. Buffy Coat is extracted from Plasma tubes and shipped ambient to NCRAD. **Cognitive assessments should NOT be scheduled while the participant is fasting, or immediately after an LP or imaging session.**

Complete Data entry within 5 business days of the Baseline visit. Scan and Upload worksheets via the Study Document Upload eCRF.

BASELINE ASSESSMENTS

Plasma and Serum Biomarker Collection (fasting)
CSF Collection*
Genetic Sample Collection (DNA, RNA, Cell Immortalization)
Neuropsychological Battery (follow order of assessments on worksheets)
MoCA
ADAS-Cog 13
Everyday Cognition - Participant and Study Partner Self-Report
Neuropsychiatric Inventory
Functional Assessment Questionnaire
Vital Signs
Concurrent Medications Review / Key Background Medication Review
Diagnostic Summary / Clinical Status Form
Adverse Event
Florbetapir F 18 PET Scan
Post LP phone call
Armed Forces Qualification Test (AFQT)
Clinician Review
Autopsy consent discussion

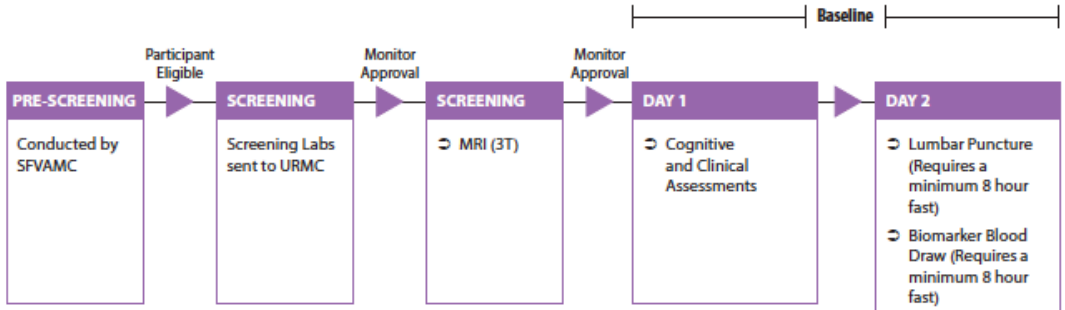
PRE AND POST FLORBETAPIR F 18 INJECTION VITALS WERE REQUIRED UNDER THE ORIGINAL PROTOCOL BUT ARE NO LONGER A REQUIREMENT AS OF AMENDMENT DATED MARCH 2013.

DOD ADNI SAMPLE VISIT SCHEDULE

GENERAL GUIDELINES:

- LP and Biomarker Blood Draws require a minimum 8 hour fast.
- MRI should occur prior to LP, otherwise the MRI must occur at least 3 days after LP
- If all blood draws are completed at the same time, the RNA sample should not be taken first
- If RNA Blood Draw occurs separate from the other blood draws, the red topped evacuation tube should be used to capture the initial blood flow and discarded
- Buffy Coat extracted from Biomarker Plasma Sample and shipped to NCRAD
- Cognitive assessments should not be done immediately after a blood draw or LP, as this may affect the results
- If LP and PET scan are done on the same day, LP should be completed prior to the Florbetapir F 18 PET scan; otherwise there should be at least 12 hours between the LP and the scan.

DOD ADNI SAMPLE VISIT SCHEDULE (SCREENING AND BASELINE)



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

CHAPTER 7

MONTH 6 PROCEDURES

SFVAMC will contact the subject about 4-6 months after the baseline clinic visit to administer a brief interview. The SFVAMC team will ask participants a few questions over the phone to ascertain if there has been any change in memory or thinking, changes in overall health, activity levels, physical ability, or any adverse health events.

If a change in medication, condition or subject's well-being is identified during the brief interview by SFVAMC, the outcome of this call will be reported to the clinic site. **The clinic site will be responsible to follow up with the study participant and record the change in medication on the concurrent medication log and/or capture any new conditions/symptoms as adverse events both in the research chart and in the online DODADNI study portal.**

If no changes are found at the month 6 follow-up call by SFVAMC, the Registry form for the month 6 visit by DOD clinic is to be entered as "Not done" and select "Visit not required" as the reason why the standard visit was not conducted.

CHAPTER 8

MONTH 12 FOLLOW UP PHONE VISIT BY SFVAMC

SFVAMC will conduct a follow up phone visit approximately 12 months after their initial pre-screen. Participants who are eligible for the 12 month follow up screener by SFVAMC are those who completed the DOD Screen and Baseline clinic visits. The 12 month follow up interview will be identical to the pre-screen interview by SFVAMC, but will reference any change in the past year. The follow-up screener will NOT be screening anyone out of the study, but will help determine whether anything has changed since the last clinic visit that may make a particular procedure unsafe, and to determine that the participant is still willing and able to participate. After SFVAMC completes the 12-month telephone interview, the subject will be referred via secure email to the clinic site.

CHAPTER 9

MONTH 12 FOLLOW UP DOD CLINIC VISIT PROCEDURES

Key Reminders

The Month 12 Follow Up visit is scheduled 12 months from baseline visit day 1.

SFVAMC phone follow up should be completed before scheduling the in-clinic visit.

Plasma and Serum collected for Biomarker analysis are after an overnight or 8-hour fast. Buffy Coat is extracted from Plasma tubes and shipped ambient to NCRAD.

There is **NO** LP or Florbetapir F18 scan conducted at the month 12 visit

Complete Data entry within 5 business days of the visit. Scan and Upload worksheets to the study portal via the Study Document Upload eCRF.

COGNITIVE ASSESSMENTS SHOULD NOT BE SCHEDULED WHILE THE PARTICIPANT IS FASTING.

MONTH 12 FOLLOW UP IN-CLINIC VISIT ASSESSMENTS

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

CHAPTER 10

ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

ADVERSE EVENT (AE)

An adverse event is any adverse change from the subject's 'enrollment' condition at point of verbal consent during the prescreening interview.

A causal relationship with study procedures is **not** necessary to qualify as an AE. The event can include any abnormal sign (e.g., abnormal physical exam or laboratory finding, that is Clinically Significant), symptom, or disease that occurs during the participants' involvement in the research.

Example:

> "New confusional episodes" would qualify as "Clinically significant adverse changes in clinical status, neurological and physical exams."
>
> "Headache related to elevated systolic blood pressure" is a complaint associated with an abnormal finding, but the site clinician should help decide whether this warrants 2 related AEs (elevated SBP and headache) or just 1 AE = elevated SBP, with "headache accompanied finding" in the Comment section on the one AE's eCRF.
>
> Pre-existing symptoms that have worsened or changed in nature, severity, or frequency of conditions or symptoms, even if the event was not caused by a study procedure, would include worsening of a cataract that then led to cataract removal. Whenever possible, the AE should not be listed as the procedure itself.
>
> An example of a recurrence of a previously resolved condition might be "poison ivy exposure."

Please refer to the Code of Federal Regulation Title 21 Part 312.32

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32

Collection and Documentation of Adverse Events

Adverse events that occur during the prescreen phase (prior to referral to a DOD clinic site) will be recorded by the SFVAMC team and assessed by Dr. Weiner, but all safety data collected by the SFVAMC team will need to be entered online in the EDC system within the Pre-existing Symptoms log and/or Medical History by the referring DOD site at the point of referral. An online report will be accessible to the DOD site staff in order to obtain original safety data during the prescreen phase to enable the completion of the AE/Hospitalization Log eCRF. The DOD site will also be responsible for assessing and recording all adverse events that occur from the point of informed consent at the DOD site and up to 30 days after the last study visit.

Diagnosis/Medical Event Term

The Event Diagnosis field should always contain a diagnosis or the medical term for the event, if a diagnosis is known. Symptoms associated with the diagnosis (or medical term) should be recorded in the Comments/Narrative section of the Adverse Events worksheet and not as separate AEs. When a diagnosis cannot be made, symptoms should be reported as separate AEs unless your site clinician can link them together as a syndrome (e.g., headache, cough, myalgia, and chills could be summed up as “influenza”). The admitting diagnosis may suffice if a participant goes to hospital and is still undergoing workup at the time you complete the AE eCRF. You may be asked to update the AE or SAE verbatim term once a discharge summary is available.

An attempt should be made to establish a diagnosis based on signs/symptoms and/or other clinical information. If a diagnosis is suspected but not yet established, state this in the Comments/Narrative section and indicate whether a workup is underway.

Remember to Provide Follow-up Information as it Becomes Available.

If signs/symptoms initially reported as AE(s) are later determined to be the result of an ongoing or pre-existing condition, then document this history within the Comments/ Narrative section of the AE eCRF. The AE report(s) about the initial signs/symptoms should also reference the condition AE and then be closed out.

Adverse events must be described in appropriate medical terminology with sufficient information to ensure the event is accurately recorded so it can be matched against a coding dictionary such as MedDRA (Medical Dictionary for Regulatory Activities).

Pre-Existing Symptoms:

Any pre-existing symptom present at the point of enrollment must be entered into the Pre-Existing Symptoms Log. If any of the pre-existing symptoms worsen in frequency or severity after the initial report then this should be reported as an AE. The report for the worsened pre-existing symptom should indicate that the AE was recorded previously as a pre-existing symptom but has worsened in chronicity or severity. The symptom number(s) from the Pre-Existing Symptoms Log should also be provided in the AE report.

Abnormal Test Findings

An abnormal test finding should be reported as an AE if one or more of the following criteria are met:

- Test result is associated with accompanying symptoms
- Test result requires additional diagnostic testing or medical/surgical intervention
- Test result leads to discontinuation from the study, significant additional concomitant drug treatment, or other therapy
- Test result is considered to be clinically significant by the PI

An abnormal test finding should **NOT** be reported as an AE if one or more of the following criteria are met:

- Abnormal test results do not meet the above criteria.
- Test result is determined to be an error

If an abnormal test finding is the result of an underlying medical condition, then the condition should be documented as an AE. As with other signs/symptoms initially reported as AE(s) in the absence of a diagnosis, once a diagnosis has been made then the diagnosis/condition should be documented as an AE and the initial signs/symptoms should be referenced in the Comments/ Narrative section. The AE report(s) about the initial signs/symptoms should be updated to also reference the condition AE and then be closed out.

Compound Events

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

Participant experiences:

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

Identifying Adverse Events

In addition to a thorough review of the medical records, the following questions may help identify an adverse event:

Has your previous AE (if any) continued unchanged, worsened, or resolved since the last visit?

Have you taken any new medication since the last study visit? (If so, it could be for an AE.)

Have you stopped or changed the dosage or frequency of any medications you were taking at the last study visit?

Has your health changed in any way through illness or injury since the last study visit?

Have you had any surgeries or hospitalizations since the last study visit?

Question any missed study visits (reason for missing the visit, may be considered an AE).

AE Reporting Process

1. Record in the Adverse Events /Hospitalization -Log eCRF all AEs that were noted during the prescreen phase
2. Screen for potential new AEs at every DOD study visit
3. Confirm that any potential AEs should be documented as AEs based on the following criteria:
    - The condition is new

- The condition has worsened from what was recorded in the Pre-Existing Symptoms Log
- The condition has worsened since the last study visit

4. Document the AE **within 24 hours of becoming aware of the event**
    - Both the Adverse Events worksheet and the Adverse Events/Hospitalizations - Log eCRF must be completed.
    - Complete the worksheet and eCRF with as much information as is available at the time of the report.
    - Be sure to use medical terminology. Don't hesitate to get your site clinician involved in choosing the terminology and in creating a brief synopsis of the event.
5. Fulfill local IRB requirements

SERIOUS ADVERSE EVENT (SAE)

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

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

The event does not need to have a causal relationship with study procedures to be considered a Serious Adverse Event.

Death

Death is an **OUTCOME** of an event, not an event term or diagnosis. It is necessary to find out the cause of death. If the cause of death is unknown at first reporting, then this should be updated in a follow up report once the cause is known. Death can only be documented as the event if death is the only information available for reporting. In this case, be sure to include a comment explaining that no qualifying information is available. There should only be one SAE with an outcome of death for each participant.

Example: "Death due to myocardial infarction" is reported

Event: Myocardial infarction

Outcome: Death

Life-Threatening Event

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

Examples:

Pacemaker failure
Hepatitis - resolved without hepatic failure
Bone marrow suppression

Hospitalization or Prolongation of Existing Hospitalization

Hospitalization is any event resulting in admission to a healthcare facility that requires an overnight stay. Prolongation of existing hospitalization would be any event that extends a hospital stay beyond the normal expected time. Any hospitalization or prolongation of hospitalization is considered serious. Hospitalization or prolongation is used when admission to the hospital was a result of the event and should not be used as the event term itself.

Hospitalization does NOT include:

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

The following hospitalizations are NOT considered serious:

Social admission (i.e., participant has no place to sleep)
Administrative admission (i.e., yearly physical exam)
Admission for an elective or cosmetic procedure
Protocol-specified admission (i.e., for a procedure required by the study protocol)

Disability or Permanent Damage

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

Congenital Anomaly/Birth Defect

Congenital anomaly/birth defect(s) are considered SAE(s) if it is suspected that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the participant's child.

Important Medical Events

A medically important event is any event that the investigator regards as potentially jeopardize the participant and may require medical or surgical intervention/treatment in order to prevent one of the other serious outcomes.

Examples:

Allergic bronchospasm that required treatment in an emergency room

Seizures/convulsions that do not result in hospitalization

Additionally any experience which the investigator regards as serious, or which would suggest significant hazard, contraindication, side effect, or precaution associated with participation in the study should be reported as a serious adverse event.

Please refer to the Code of Federal Regulation Title 21 Part 312.32

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32

Collection and Documentation of Serious Adverse Events

Any such experience due to any cause, which occurs after verbal consent and up to 30 days after the last study visit, must be reported to the Project Director within 24 hours after learning of the event.

Serious Adverse Events that occur during the prescreen phase will be recorded by the SFVAMC team and assessed by Dr. Weiner, however all safety data collected by the SFVAMC team will need to be entered online in the EDC system by the referring DOD site at the point of referral.

At the point of referral to the DOD site, the site clinician is responsible to follow the event to resolution or to when it is considered stable.

The same guidelines for collecting and documenting AEs should be followed when collecting and documenting SAEs. An event is considered serious if it resulted in one of the outcomes described earlier in this section of the procedures manual (i.e., death, life-threatening, hospitalization or prolongation of existing hospitalization, disability or permanent damage, congenital anomaly/birth defect, important medical events).

The reporting Investigator must follow all SAEs to resolution based upon the information that is available and approved via the Informed Consent. Resolution of an event occurs when one of the following criteria are met:

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

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

Over time some events may resolve such that the original symptoms are no longer present. In these circumstances the outcome would probably best be described as “resolved”.

By contrast some events may resolve such that the original symptoms are no longer present, but other related symptoms may be present. In these circumstances the outcome would probably best be described as “resolved with sequelae”..

Comments/Narrative

Use the Comments/Narrative section on the last page of the Adverse Events worksheet to provide a clear, concise, chronological, and comprehensive description of the event. The information provided should be detailed and descriptive enough to assess the event remotely. You do not need to repeat information in the Comments/Narrative section that was previously reported on the Adverse Events worksheet.

A detailed, descriptive and relevant history may include, but is not limited to, the following:

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

It is most helpful if you review your entry with your site clinician before submitting. S/he can help consolidate the medical records into the most appropriate verbatim event term and a relevant summary. All entries should begin with the date and the initials of the person writing the narrative. For example, if the Adverse Event worksheet was being completed on June 15, 2013 by a Study Coordinator then the Comments/Narrative section might begin with something like, “(06-15- 2013) SC:”

Other Relevant History

Provide a description of relevant medical history or pre-existing symptoms in the Other Relevant History section on the last page of the Adverse Events worksheet. This section is not for details of the hospitalization for the current AE. If applicable, also comment on how the event might be related to other AEs/SAEs.

Concurrent Medications

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

Follow-Up Reports

The site is responsible for following up on events that occurred during the prescreen phase and were ongoing at the point of referral, as well as any event that occurred after consent has been signed at the DOD clinic. Whenever new information is obtained for an event that is the responsibility of the DOD site investigator to follow up on, it must be reported to the ATRI as soon as it becomes available. Examples of reports that may require follow up:

An SAE for which complete information was not available at the time of the report.

Updates or new information related to an event that was previously reported.

Resolution of a previously unresolved event.

Once the initial SAE has been reported any new information or changes to previously reported information must be submitted in a follow-up report using the Supplemental Narrative page, which is available as a stand-alone worksheet in the document repository. New information should be documented in the narrative using the lines provided and, if applicable, also captured on the initial Adverse Event worksheet. Any changes made to information previously reported should also be documented in the narrative.

Be sure to include the Adverse Event Number from the initial SAE report on the Supplemental Narrative page and assign a follow up report number (i.e. check the "F/U1" box for the first follow up report, the "F/U2" box for the second follow up report and so on).

As with the initial report, begin all follow up narratives with the date and the initials of the person writing the narrative.

Note: In the Adverse Event/Hospitalization Log eCRF, there is NOT a separate supplemental narrative page. Instead, capture the information on the supplemental narrative worksheet onto the initial comments/narrative field as appended. **Please ensure to email your monitor once an update is made in order to ensure our Medical and Safety Core is apprised of the update and a follow up SAE report is created by the ATRI Medical and Safety Core**.

IMPORTANT: WHILE YOU MAY CHANGE THE VERBATIM EVENT TERM WHEN YOU RECEIVE MORE MEDICAL RECORDS, PLEASE DO NOT DELETE PREVIOUS ENTRIES IN THE NARRATIVE FIELD. NEW ENTRIES AND/OR UPDATES TO THE NARRATIVE SHOULD BE APPENDED.

SAE Reporting Process

6. Screen for potential AEs at every study visit
7. Confirm that any potential AEs should be documented as AEs based on the following criteria:
    - The condition is new
    - The condition has worsened from what was recorded in pre-existing symptoms
    - The condition has worsened since the last study visit
8. Confirm that the event should be considered serious based on the fact that the event results in one of the following outcomes:
    - Death
    - Immediately life-threatening
    - Hospitalization or prolongation of existing hospitalization
    - Disability or permanent damage
    - Congenital anomaly/birth defect
    - Important medical event
9. Document the SAE within 24 hours of becoming aware of the event
    - Both the Adverse Events worksheet and the Adverse Events/Hospitalizations – Log eCRF must be completed

- Complete the worksheet and eCRF with as much information as is available at the time of the report
- Be sure to use medical terminology

IN THE EVENT THAT AN SAE OCCURS AND THE ATRI EDC SYSTEM IS UNAVAILABLE, FILL OUT THE AE/HOSPITALIZATION WORKSHEET BY HAND AND EMAIL A SCANNED COPY TO THE ATRI MEDICAL AND SAFETY CORE AT ATRI-MEDOPS-L@USC.EDU IN ORDER TO MEET FDA REPORTING REQUIREMENTS. ONCE YOU HAVE ACCESS TO THE EDC, THE SAE WILL ALSO NEED TO BE ENTERED ONLINE USING THE ECRF.

10. Notify your Clinical Monitor via email whenever initially completing or updating any SAE
11. Fulfill local IRB requirements
12. Promptly respond to any inquiries regarding the event

THE ENTIRE SAE REVIEW AND REPORTING PROCESS MUST BE COMPLETED BY THE SITE WITHIN 4 CALENDAR DAYS.

Severity

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

> **Mild:** Awareness of signs or symptoms but no disruption of normal daily activity. Signs and symptoms are transient. Event resolved without intervention.
>
> **Moderate:** Discomfort sufficient to reduce or affect normal daily activity.
>
> **Severe:** Incapacitating with inability to perform normal daily activity.

Reporting a Change in Severity
If a previously reported AE increases in severity or frequency, note this in the original worksheet and eCRF and report as a new AE at the higher severity grade (i.e. worsening of osteoarthritis). The onset date will be the date that the severity or frequency increased. A decrease in severity should **not** be reported as a new AE.

Relatedness

The investigator is responsible for determining whether or not an event is related to imaging, lumbar puncture, or other study procedure(s).

Note: Other study procedure(s) refers to any procedure other than imaging or LP that may be deemed a causal relationship to the adverse event (e.g. depression related to neurocognitive testing).

> **Not related:** There is no evidence of a causal relationship and a causal relationship cannot be reasonably attributed to study procedures.
>
> **Possibly Related:** A relationship cannot be ruled out with certainty and the event may be related. There is some evidence to suggest a causal relationship but the influence of other factors may have contributed to the event, such as the participant's clinical condition or concomitant treatments.
>
> **Probably Related:** The event is likely related to the study. There is evidence to suggest a causal relationship, such as a reasonable temporal sequence from procedure. The influence of other factors is unlikely.
>
> **Definitely Related:** The event is clearly related to the study and there is clear evidence to suggest a causal relationship. The influence of other factors can be ruled out.

Event Outcome

Event outcome is captured in order to provide a complete picture of each event that occurred during the trial. Outcome must be answered for each individual event. For example, if there is a compound event (stroke, hip fracture, pneumonia) in which death occurred as a direct result of one of those events (pneumonia), only that event (pneumonia) should have an outcome of

Fatal. The other related events (stroke, hip fracture) cannot have Fatal as an event outcome nor can they have Recovering/Resolving as an outcome.

Events that are not resolved prior to death or by the end of the study cannot be Recovering/Resolving; they must be either Not Resolved/Not Recovered or Unknown. The cease date must be the same as the date of death or the same as the last study visit date. Again, each participant should only have one SAE with an outcome of Fatal.

Adverse Event Checklist

The Adverse Event Checklist should be used at each DOD study visit after screening in order to query the participant about any new symptoms and capture any AEs that may have occurred since the last visit. If the participant presents with a new symptom that was not previously reported and is not on the Medical History, then this should be reported as an AE. If a symptom has improved (but not resolved), no documentation is necessary. Only record new or worsening of symptoms.

Downgrading or Correcting an SAE to an AE

If it is determined that an event initially recorded as an SAE does not meet the criteria to be considered serious, then complete a follow-up report and, in the Comments/Narrative field, explain why the event was determined not to be serious and ensure to uncheck the "serious" box on the AE eCRF.

If a symptom has improved in frequency or severity, do not create a new entry. If there is complete resolution, do enter an end or resolution date. Only record new or worsening of symptoms.

CHAPTER 11

MRI PROCEDURES

SUMMARY

Magnetic Resonance Imaging (MRI) is a principle component of the Department of Defense Alzheimer's Disease Neuroimaging Initiative (DOD ADNI) study. All participants enrolled in DOD ADNI will be scanned using protocol sequences specific to the DOD ADNI study. **The protocol sequences installed for ADNI 1 or ADNI GO / 2 should NOT be used for this study.** The study participants will be scanned at Screening and at the Month 12 Follow Up Visit.

The collection of these images is central to meeting the DOD ADNI objective of developing biomarkers to track both the progression of Alzheimer's Disease and change in underlying pathology in Vietnam Veterans with either PTSD or TBI.

For detailed instructions and MRI protocol, please reference the DOD ADNI MRI technologist manual posted to the study document repository.

MRI SCANNER CERTIFICATION

Since the DOD ADNI protocol is different from that of the ADNIGO/2 clinical trial, each site will be required to be qualified for DOD ADNI MRI.

Site qualification includes two different exams.

The first, being the quality control phantom scans on the specially designed ADNI phantom using the DOD ADNI Phantom QC sequences loaded by your local service engineer.

Secondly, your site will be asked to scan a human volunteer with the approved DOD ADNI human sequences loaded by your local service engineer, **AFTER your site has received IRB approval for the DOD ADNI protocol.** In terms of human scanning, each site will image a volunteer subject with the protocol and send the images to LONI. Each parameter in each of the pulse sequences in the protocol will be checked at Mayo.

In the event that the protocol has NOT been performed according to protocol, the site will be asked to perform another human volunteer scan. This will be repeated as many times as necessary until the site has demonstrated exact execution of the MR protocol in a volunteer subject, at which point they will have passed the human scanning portion of MR site qualification. The volunteers do not need to be elderly controls; in fact scanning for site qualification may be more easily performed with normal younger volunteers. In the event that repeat attempts are needed, repeat scans need not be on the same volunteer subject. Once a site has demonstrated perfect execution of the protocol, the protocol will be stored permanently on the scanner at that site that will be used in the study.

ANTICIPATION OF HARDWARE UPGRADES: THE MAYO QC TEAM REQUIRES NOTIFICATION PRIOR TO ANY SOFTWARE AND/OR HARDWARE UPGRADES FOR ANY SCANNER INVOLVED IN THE DOD ADNI IMAGING STUDY.

ADNIMRI@MAYO.EDU

DEPENDING ON THE IMPACT OF THE UPGRADE THE SITE MAY BE REQUIRED TO SCAN A PHANTOM AND/OR VOLUNTEER PRIOR TO CONTINUED SCANNING.

For more information on the MRI scanner certification process and the phantom and human scan protocols to be used, refer to the DOD ADNI MRI technologist manual posted to the document repository.

MRI PRE-SCREENING

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

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

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

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

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

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

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

SEDATION DURING THE SCREENING MRI SCAN IS NOT OFFERED FOR THIS PROTOCOL. EXCEPTIONS MAY BE GRANTED ON A CASE-BY-CASE BASIS BY THE CLINICAL CORE TO ALLOW THE USE OF SEDATIVES FOR MR SCANS AT VISITS AFTER SCREENING.

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

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

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

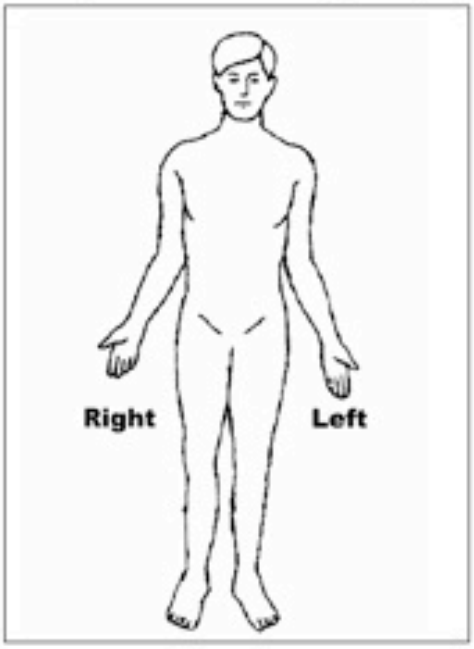
Please Inform MRI Center:

☐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



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 _____/_____/_____

DATA FLOW

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

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

After the scan is uploaded into LONI, the MRI core will complete their QC. In DOD ADNI the Screening MRI done at the DOD ADNI Clinic will determine whether the participant meets eligibility requirements. If the participant requires a rescan, it must be completed within 4 weeks of the original scan.

Each MRI scan requires a local radiologist interpretation. The clinical read should follow standard practice. The site clinician is responsible to review the local radiological interpretation of the MRI scan, as well as upload the local read to the DODADNI study portal via the Study Document Upload eCRF.

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

QUALITY REVIEW OF SCANS

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

1. CLINICALLY SIGNIFICANT FINDINGS

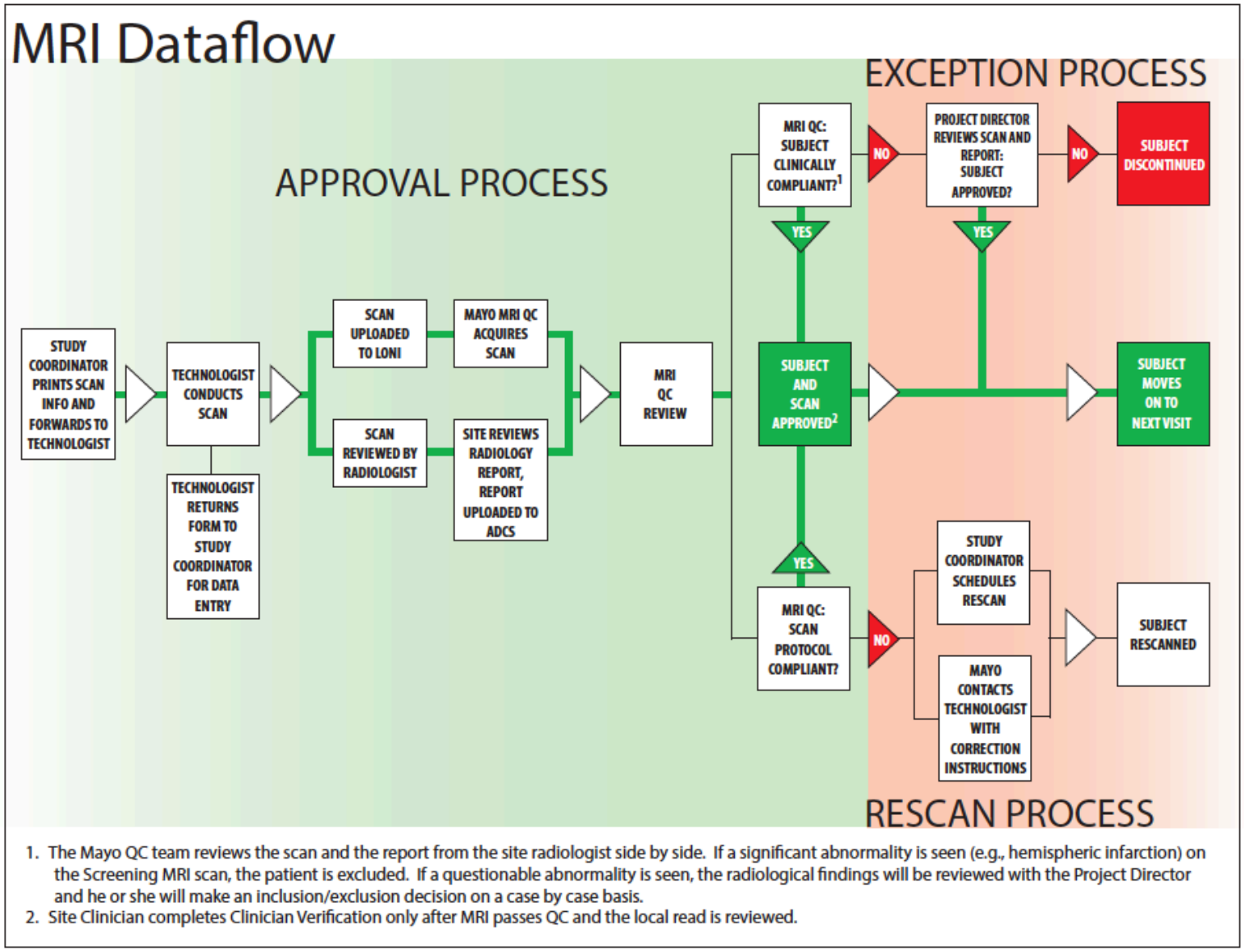
If a significant abnormality is seen (e.g. hemispheric infarction) on the screening MRI scan, the participant is excluded. In the event that a radiological finding that is not normal for age is identified by MRI QC, the site will be informed of this result by email. If a participant must be screen failed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

2. PROTOCOL COMPLIANCE OF SCAN

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

FOR TECHNICAL QUESTIONS OR CONCERNS ABOUT MRI SCANNING RELATED ISSUES OR SITE QUALIFICATION SCANS EMAIL: ADNIMRI@MAYO.EDU

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



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

GENERAL REMINDERS

It is mandatory that the DOD ADNI acquisition protocol electronically imported to your MRI be used for all sequences at the Screening MRI exam and for the month 12 follow-up MRI scan, unless otherwise directed by the coordinating center.

Failure to use the same sequence at the time of Screening and the month 12 follow-up visit will result in the request for a rescan of the participant.

It is mandatory that the DOD ADNI qualified scanner be used for all participants in the DOD ADNI study.

Failure to use the DOD ADNI qualified scanner for all participants in the DOD ADNI study will result in a request for a rescan of the participant.

GUIDELINES FOR SCHEDULING MRI SCANS

Screening

The screening MRI cannot be conducted until after completion of the DOD ADNI screening clinic visit. Both the clinician and monitor must indicate that the participant meets inclusion/exclusion criteria for DOD ADNI via the clinician verification eCRF and monitor eligibility eCRF. Once both confirm the participant meets eligibility criteria the participant may proceed to have their screening MRI conducted.

MOST SITES WILL NEED MORE THAN 2 WEEKS IN ORDER TO OBTAIN AN IMAGING SLOT AT THEIR LOCAL MRI CENTER. ENSURE TO UPLOAD ALL SOURCE DOCUMENT WORKSHEETS IN A TIMELY MANNER TO THE STUDY PORTAL IN ORDER FOR YOUR MONITOR TO REVIEW THE DOD ADNI SCREENING CLINIC VISIT. IT IS RECOMMENDED THAT A TENTATIVELY SCHEDULED SCAN DATE WITH THE MRI CENTER BE SCHEDULED 10-14 DAYS AFTER THE CLINIC SCREENING VISIT. IF THE PARTICIPANT DOES NOT MEET CLINICIAN AND MONITOR APPROVAL TO PROCEED TO THE SCREENING MRI, THE SCREENING MRI MUST BE CANCELLED.

Month 12 Follow-Up Scan

MRI Scan for the month 12 Follow-Up visit should be scheduled as far in advance as possible, taking the participant's availability into account. Scans for visits after screening should be scheduled as close to the visit date as possible. Keep in mind that scans must take place within 2 weeks before or 2 weeks after the in-clinic visit, and rescans must be scheduled within 4 weeks of the original scan date. If a scan or rescan is conducted outside of the allotted window a protocol deviation will need to be documented in the EDC system and in the subject's research chart.

THE MONTH 12 SCAN WILL BE BASED 12 MONTHS FROM BASELINE VISIT DAY 1.

Checklist for Scheduling MRI Scanning Appointments:

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

ON THE DAY OF EACH APPOINTMENT THE STUDY COORDINATOR SHOULD PHONE THE RADIOLOGY CENTER, CONFIRM THE APPOINTMENT, AND REMIND THE RADIOLOGIST WHICH ADNI MRI PROTOCOL SHOULD BE USED IN SCANNING THIS PARTICIPANT (I.E. DOD ADNI SEQUENCE).

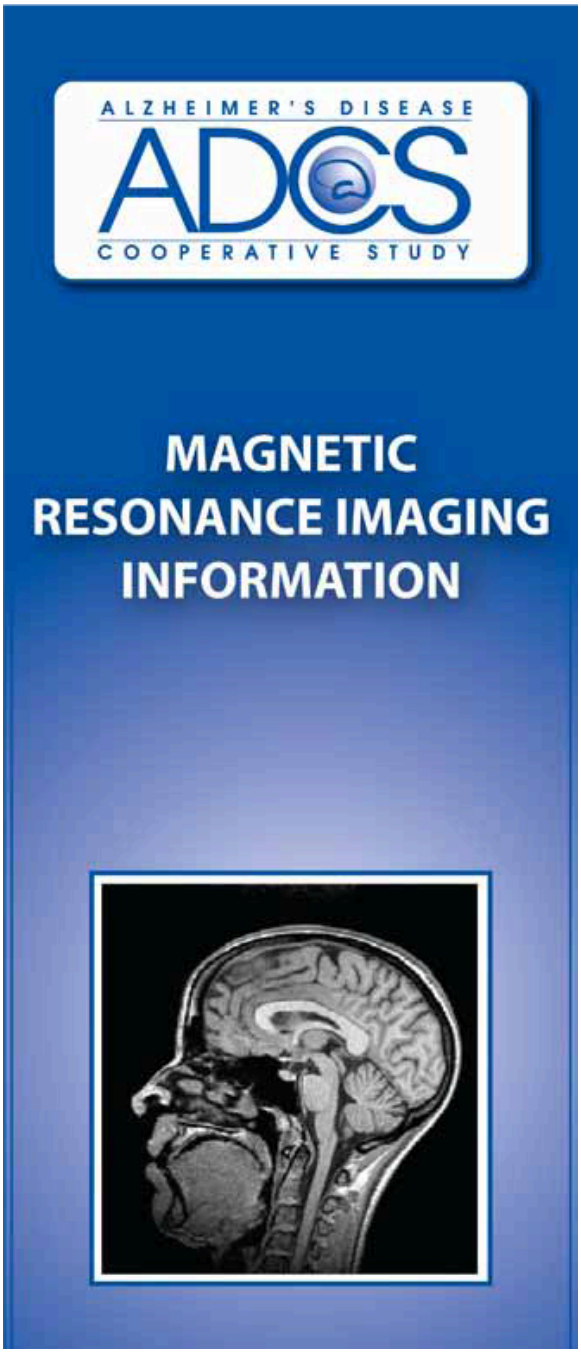
ARCHIVE PROCEDURES

Every MRI (both human and phantom) for the DOD ADNI Study must be archived locally at the MRI facility following standard local practice in addition to the data transfer to LONI immediately after the MRI scan. Additional data transfers or copies will be requested by the coordinating center in the event that a data transfer is interrupted or incomplete. Possible MRI archive mediums include:

Optical Disk
PACS
CD or DVD
USB

MRI PAMPHLET

The MRI pamphlet should be distributed to participants in the DOD ADNI study. The MRI pamphlet includes basic information regarding the details of a MRI scan. It briefly describes how participants can best prepare for their MRI and outlines ways participants can reduce anxiety during the procedure.



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

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

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

IRB approval is required for the pamphlet and is posted to the DOD ADNI document repository.

CHPATER 12

PET PROCEDURES

SUMMARY

Evidence suggests that both traumatic brain injury (TBI) and post-traumatic stress disorder (PTSD) increase risk for cognitive decline, AD, and dementia. TBI and PTSD are common problems resulting from military service. Thus far, there have been no prospective studies using imaging and biomarkers, which directly measure changes in the brain and AD pathology to study the effects of TBI and PTSD. The DOD ADNI study will provide novel data to test these hypotheses.

Florbetapir F18 imaging will be performed on all enrolled participants during the baseline DOD ADNI clinic visit and must be completed within 2 weeks before or 2 weeks after the in-clinic assessments at Baseline. Currently, the Florbetapir F18 PET scan is only conducted at baseline and NOT at the month 12 follow-up visit.

Tau PET imaging is offered as an optional addendum to the main DOD ADNI protocol. Optimally, tau PET scans will be performed once at baseline and again at the month 12 follow-up visit, however, can performed at any point in the study. If a tau PET scan is conducted +/- 6 months from a baseline or month 12 follow-up visit, an In-clinic Visit should also be conducted. See DOD-ADNI tau PET addendum for more details on assessment/procedures and scheduling.

For detailed instructions and PET protocol, please reference the DOD ADNI PET technologist manual posted to the study document repository.

SITE QUALIFICATION

PET Scanner

It is preferable for sites to use existing qualified ADNI scanners for the Florbetapir F18 imaging. If a new scanner must be introduced it will need to be qualified using standard ADNI scanner qualification before imaging can be performed for DOD ADNI.

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

CONTACT ADNI-PET-L@USC.EDU PRIOR TO IMAGING IF A NEW SCANNER WILL BE USED FOR DOD ADNI OR IF HARDWARE/SOFTWARE UPGRADES HAVE OCCURRED OR IF HARDWARE/SOFTWARE UPGRADES HAVE OCCURRED.

Regulatory

Sites must be appropriately licensed through appropriate state or federal agencies to receive and use Florbetapir F18 prior to imaging (i.e. Radioactive Materials License).

Sites must also receive IRB approval, DOD approval and radiation safety committee (RSC) or the equivalent approval, before scanning any participants for the DOD ADNI study.

For more information on the PET scanner certification process and the continued quality monitoring expected throughout the study, refer to the DOD ADNI PET Technical Manual posted in the document repository.

EXCLUSIONARY TO PET SCANS

All participants who consented to receive PET scans must be queried to assure that they do not have specific exclusions to PET.

These are:

- received an investigational medication within 30 days of the scheduled Florbetapir F18 scan;
- received a radiopharmaceutical for imaging or therapy within the past 24 hours prior to the imaging session for DOD ADNI;
- pregnancy or risk of pregnancy;
- a history of radiation therapy within the past year, or a history of receiving radiation for research purposes within the past year that would exceed the limits of annual and total dose commitment set forth in the US Code of Federal Regulations (CFR) Title 21 Section 361.1.;
- participants taking a prohibited medication (i.e. immunotherapy, secretase inhibitor, selective amyloid lowering agents, experimental study with an amyloid targeting therapy)

For exclusionary criteria specific to tau PET imaging, please refer to the DODADNI tau PET addendum.

All enrolled participants will have had a screening MRI as part of DOD 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 the participant's records. If the answer to any of these is 'Yes' consult with a technologist before consenting the participant to PET imaging for DOD ADNI.

☐ Yes ☐ No Is there a history of radiation therapy in the past year?

☐ Yes ☐ No Is there a history of having radiation for research in the past year?

☐ Yes ☐ No Is the participant taking any prohibited medications?

☐ Yes ☐ No Is the participant pregnant or of child bearing potential?

(if yes, a pregnancy test would need to be conducted to confirm/rule out pregnancy)

☐ Yes ☐ No Would there be a problem with the participant's abiity to cooperate with the scan?

REMINDER: IF LUMBAR PUNCTURE AND PET SCAN ARE DONE ON THE SAME DAY, LP SHOULD BE COMPLETED PRIOR TO THE FLORBETAPIR F18 SCAN; OTHERWISE THERE SHOULD BE AT LEAST 12 HOURS BETWEEN THE LP AND THE SCAN. RESEARCH INTO WHETHER THE BINDING LIGAND TO ABETA HAS ANY EFFECT ON CSF ABETA MEASURES OR PLASMA LEVELS IS ONGOING.

DATA FLOW: FLORBETAPIR F18

Please refer to the PET Data Flow Charts below for an illustration of this process. Study coordinators are responsible for collecting some basic information on each PET scan from the PET center conducting the scan. In general, this will involve interacting with the PET Technologist who will usually be the individual conducting the PET Scans. The study coordinator must ensure the PET Technologist has a copy of the Florbetapir F18 PET Scan Information Forms prior to each scan session and that the metadata sheet is completed ***as the study is being acquired***. The study coordinator should ensure a process has been worked out with the radiology center on how to transfer this information immediately after the scan is completed. The study coordinator is responsible for entering scan data in the DOD ADNI EDC system **within 24 hours of the scan**. All PET scans will be uploaded by your radiology center to the Laboratory of Neuroimaging (LONI). These procedures are outlined in the DOD ADNI PET Technical Manual posted in the document repository. If your radiology center is unable to upload scans to LONI, request training for uploading by emailing: adni@loni.ucla.edu.

IMPORTANT: DATA UPLOADS TO LONI SHOULD BE PERFORMED AS SOON AS THE IMAGES HAVE BEEN ACQUIRED & RECONSTRUCTED AS IT WILL BE IMPORTANT TO PROMPTLY QC THE DATA TO IDENTIFY IF THE SCAN NEEDS TO BE REPEATED. THE TIMEFRAME SHOULD BE 1-2 BUSINESS DAYS FROM ACQUISITION.

QUALITY REVIEW OF FLORBETAPIR F18 PET SCANS

Every Florbetapir F18 PET scan will be reviewed for protocol compliance by the DOD ADNI PET QC team.

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

If the problem with the scan is not fixable, the PET QC team will provide the PET technologist with protocol guidance to apply to future PET scans.

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

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

QUESTIONS ON PET TECHNICAL ISSUES SHOULD BE DIRECTED TO: ADNI-PET-L@USC.EDU

GUIDELINES FOR SCHEDULING FLORBETAPIR F18 PET SCANS

Most sites will need more than 2 weeks in order to obtain an imaging slot at their local radiology center. For DOD ADNI, the Florbetapir F18 scan should be scheduled after the Screening MRI scan is reviewed and final approval has been sent to the site PI and study coordinator; whereby allowing the participant to proceed to baseline.

The Florbetapir F18 PET Scan must be completed within a 2-week window before or after the DOD ADNI baseline clinic visit. If scans take place outside of the allowed window, request a deviation by providing the date of imaging and reason for deviation on the protocol deviation log.

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

FLORBETAPIR F18 DELIVERY

Study coordinators and PET technologists will need to reference the Avid Radiopharmaceuticals, Inc. Clinical Supplies Guidance Document (CSGD) for all relevant documents regarding ordering, shipping and receiving Florbetapir F18 for injection. Study coordinators will coordinate Florbetapir F 18 ordering with the PET imaging facility using the Florbetapir F 18 drug request form (DRF).

AVID TYPICALLY REQUIRE A 5 DAY NOTIFICATION PRIOR TO THE DESIRED DAY OF IMAGING TO COORDINATE PRODUCTION AND DELIVERY.

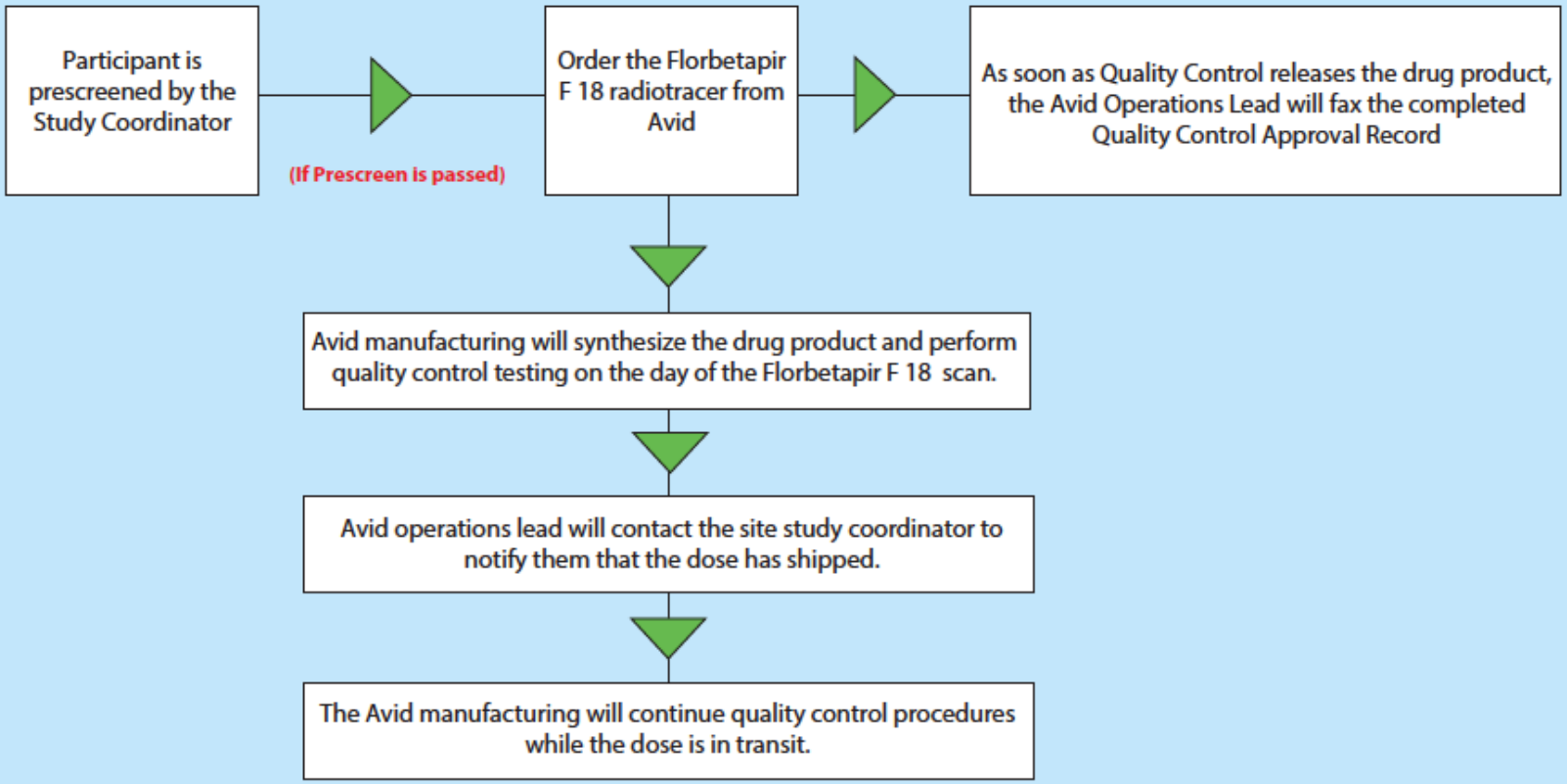
Changes to the scheduling or deviations from the Avid Clinical Supplies Guidance Document may be possible (e.g. scheduling a participant with only 3 days' notice), but if they are required, the site should contact Avid as soon as possible to work with the manufacturing team on the logistics.

Checklist for Scheduling PET Scanning Appointments

- ❑ PET pre-screening checklist completed/reviewed for changes.
- ❑ Participant is given pamphlet with appointment information.
- ❑ Participant and Study Partner (if applicable) have Directions and Information for Parking.
- ❑ PET Technologist has copy of appropriate PET Scan Information Form (Florbetapir F18).
- ❑ Scan uploaded to LONI (by technologist if possible).
- ❑ Appropriate PET Scan Information form (Florbetapir F18) received and data entered in ADCS EDC system within 24 hours of scan.

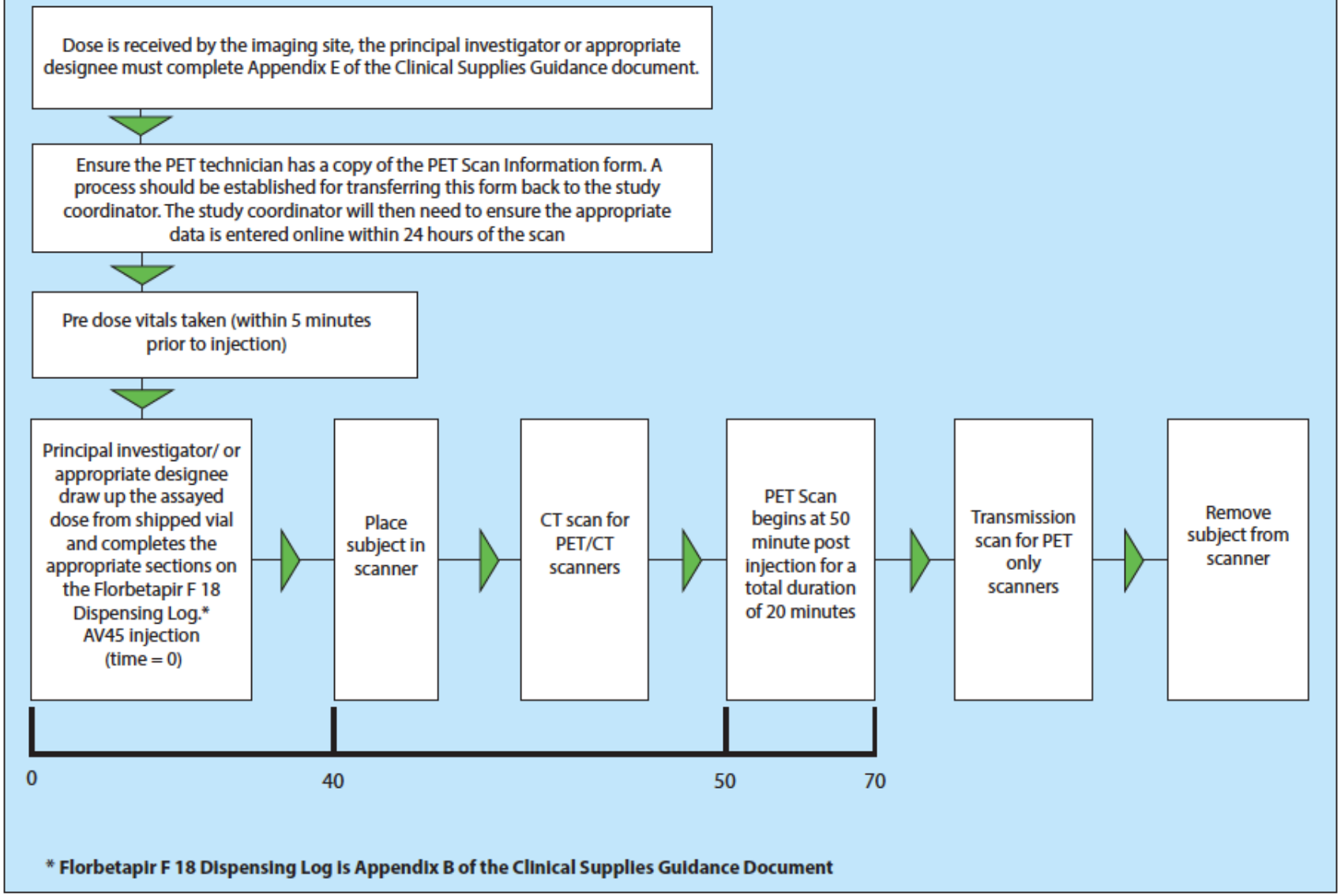
ON THE DAY OF EACH APPOINTMENT THE STUDY COORDINATOR SHOULD PHONE THE RADIOLOGY CENTER, CONFIRM THE APPOINTMENT, AND REMIND THE RADIOLOGIST TO UPLOAD THE PET SCAN TO LONI WITHIN 24 HOURS OF THE SCAN.

Prior to Florbetapir F 18 Scan



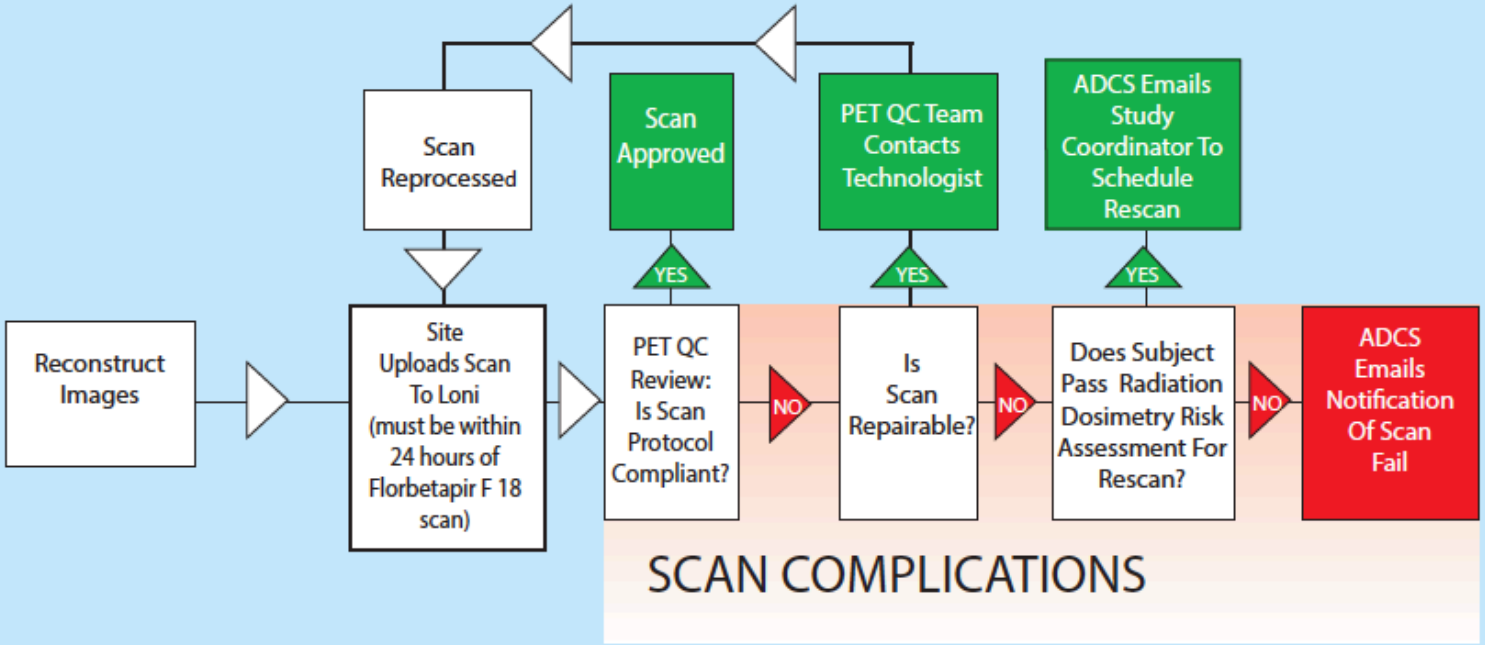
NOTE: Complete Appendix A (Avid Dose Request Form) of the Clinical Supplies Guidance Document located in the document repository when ordering the Florbetapir F 18 radiotracer.

Conducting the Florbetapir F 18 Scan



*** Florbetapir F 18 Dispensing Log is Appendix B of the Clinical Supplies Guidance Document**

Post Florbetapir F 18 Scan



PET PAMPHLET

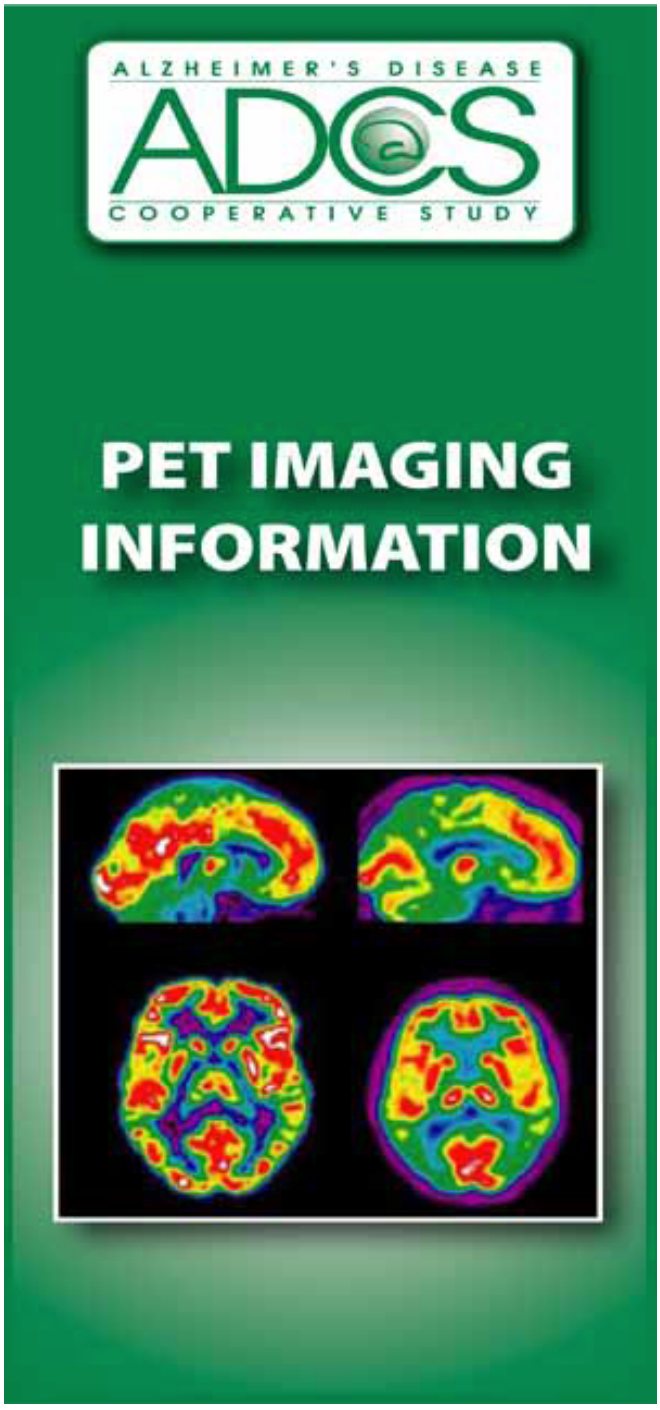
The PET pamphlet should be distributed to any participant undergoing a PET scan for the DOD ADNI study.

The PET pamphlet includes basic information regarding the details of the Florbetapir F18 PET scans. It briefly describes how participants can best prepare for their PET scans and outlines ways participants can reduce anxiety during the procedure.

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

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

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



IRB approval is required for the pamphlet and is posted to the DOD ADNI document repository.

CHAPTER 13

BIOFLUIDS: COLLECTION, PROCESSING AND SHIPMENT

BIOFLUIDS GLOSSARY

DOD ADNI	Department of Defense Alzheimer's Disease Neuroimaging Initiative
AD	Alzheimer's disease subject
NC	Normal Control 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
CELL-I	Cell Immortalization Sample
GWAS	Genome Wide Association Study
LP	Lumbar Puncture
NCRAD	National Cell Repository for Alzheimer's Disease

SUMMARY

The collection of biofluids is central to Department of Defense Alzheimer's Disease Neuroimaging Initiative goals:

Determine the prevalence of brain AD pathology (measured by CSF Aβ and tau), after accounting for effects of age and ApoE

Examine group difference for each biomarker measurement

And more globally to:

Aid in the recognition of the illness at its earliest clinically recognizable stages

Detect the disease before dementia or other symptoms appear

Distinguish AD from other causes of dementia

Biomarkers, together with imaging tests, will be especially valuable in obtaining the long-term goal of the field, which is to prevent the development of cognitive impairment or dementia by treatment of normal subjects.

Promising biomarkers that will be measured in DOD ADNI fluids:

Tau in CSF

Amyloid beta in CSF

CSF BACE levels and enzyme activity

CSF sAPPβ levels

Aβ 40 and Aβ 42 in Plasma

ApoE genotyping-blood

DNA from blood cells

RNA from blood cells

Other promising CSF and plasma biomarkers may be added based on ongoing multiplex immunoassay studies and mass spectrometry MRM studies

BIOFLUIDS COLLECTION SCHEDULE

	URMC Screening Labs	CSF	Buffy Coat	Plasma	Serum	RNA	ApoE/ GWAS	Cell Immort.
Screening	✓							
Baseline		✓	✓	✓	✓	✓	✓	✓
Month 12 Follow-Up			✓	✓	✓	✓		

SAMPLE AMOUNTS OBTAINED AT EACH VISIT (ML)

Sample	Volume at BL	Volume at M12	Total for study
CSF	20 mL	N/A	20 mL
Buffy Coat	1-2 mL	1-2 mL	2 – 4mL
Plasma from blood	20 mL	20 mL	40 mL
Serum from blood	20 mL	20 mL	40 mL
Blood for RNA Genotyping	3 x 2.5 mL	3 x 2.5 mL	15 mL
Blood for ApoE/GWAS	10 mL	N/A	10 mL
Blood for Cell Immortalization	2 x 8.5 mL	N/A	17 mL

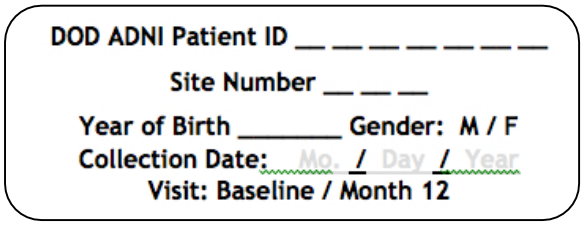
Please see URMC lab manual for sample amounts obtained with clinical labs at screening.

SAMPLE IDENTIFICATION AND TRACKING

Clinical Laboratory Samples obtained during the DOD ADNI clinic visit will be done through screening kits provided by URMC. Laboratory samples at screen will use URMC's barcode system. Please refer to the URMC lab manual for more detail on screening labs.

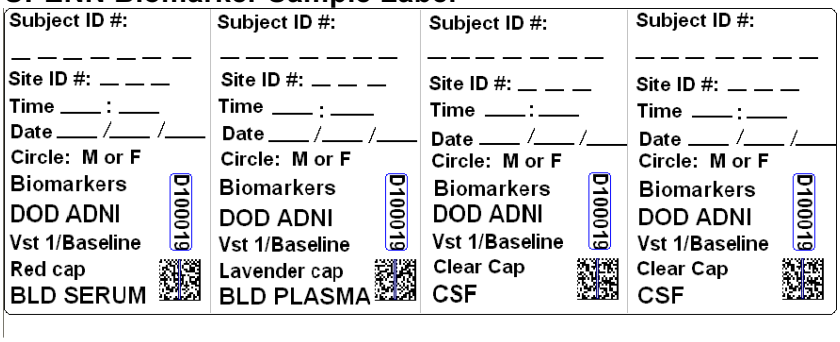
All genetic samples (ApoE, GWAS, RNA, Cell Immortalization, and Buffy Coat) must be identified using the NCRAD Sample Identification label provided by the ATRI.

NCRAD Sample Label



All biomarker samples (plasma, serum and CSF) must be identified using the UPENN biomarker identification label provided by ATRI.

UPENN Biomarker Sample Label



THERE ARE DIFFERENT UPENN LABELS BASED ON THE VISIT. ENSURE YOU USE THE APPROPRIATE UPENN LABEL THAT CORRESPONDS TO THE CORRECT VISIT.

Sample Tracking

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

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

The Genetic sample collection worksheet and Biomarker sample collection worksheet (located in the Worksheet Packets posted in the Document Repository) must be completed **on the day of each visit**. These forms include information used to track the sample, confirm receipt of the

sample, and information essential to processing and analysis. Additionally, the corresponding eCRF in the DOD ADNI web portal must be completed on the day of each visit.

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

NCRAD email: alzstudy@iupui.edu
NCRAD fax: 317-278-1100

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

Sample Quality Checks

In addition to being tracked online in the DOD ADNI web portal, the condition and amount of samples received will be tracked by the Biomarker Core (UPENN) and Genetic Core (NCRAD).

Sites are responsible to ensure the requested amounts of each fluid are collected, to the best of their ability.

If a sample is not obtained at a particular visit, this should be recorded on the appropriate sample collection form in the worksheet packet and eCRF in the DOD ADNI web portal. Please ensure the reason why the sample was not obtained is provided.

IMPORTANT: ENSURE YOU ARE USING THE APPROPRIATE SAMPLE LABELS FOR EACH SAMPLE TYPE. NCRAD LABELS FOR: CELL IMMORTALIZATION SAMPLE, APOE/GWAS SAMPLE, RNA SAMPLE AND BUFFY COAT SAMPLE. UPENN LABEL FOR: PLASMA BIOMARKER SAMPLE, SERUM BIOMARKER SAMPLE AND CSF.

UPENN LABELS ARE VISIT SPECIFIC AND DIFFER BY SAMPLE TYPE (I.E., BASELINE / BLD SER (SERUM)). IT IS VITAL THAT THE CORRECT UPENN SPECIMEN LABEL MATCHES THE VISIT AND SAMPLE COLLECTED.

CLINICAL LABORATORY SAMPLES AT SCREENING

Clinical Laboratory Kits

Screening laboratory kits are being provided by URMC, all other laboratory supplies are provided by the ATRI. Please note that URMC will not handle the management of any labs beyond the DOD ADNI screening clinic visit.

An initial shipment of screening kits will be shipped once your site is close to receiving full approval to begin enrolling in the DOD ADNI Study. After the initial shipment there are no auto shipments. To order additional screening kits complete the Supply Order Form located in the document repository and ***fax the form to URMC Labs at 585-486-1375 or email LabSRSS@urmc.rochester.edu***.

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

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

SEE URMC LAB MANUAL FOR DETAILS OF KIT CONTENTS AND SPECIMEN COLLECTION/SHIPPING. INSTRUCTIONS ON HOW TO COLLECT, PROCESS AND PACKAGE SCREENING LABORATORY SPECIMENS ARE OUTLINED IN THE URMC LAB MANUAL LOCATED IN THE DOCUMENT REPOSITORY. INSTRUCTIONS ARE ALSO INCLUDED ON THE LABORATORY REQUISITION FORM INCLUDED IN THE SCREENING KITS.

ALL CLINICAL LABORATORY SPECIMENS MUST BE SHIPPED ON THE DAY OF COLLECTION. FOR SPECIMENS MAILED ON A FRIDAY, BE SURE TO CHECK "SATURDAY DELIVERY" ON THE SHIPPING LABEL

Clinical Laboratory Reports

Lab Reports will be faxed to each site to the attention of the Investigator. Testing will be completed and results reported within 48 hours of specimen receipt at URMC Labs.

To order additional clinical laboratory screening kits, or if you have any questions about how to use the clinical laboratory screening kits, complete the requisition forms, ship supplies, or need to contact URMC for any other reason, email **LabSRSS@urmc.rochester.edu**

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

SUPPLIES FOR BIOMARKER SAMPLES FROM ATRI:

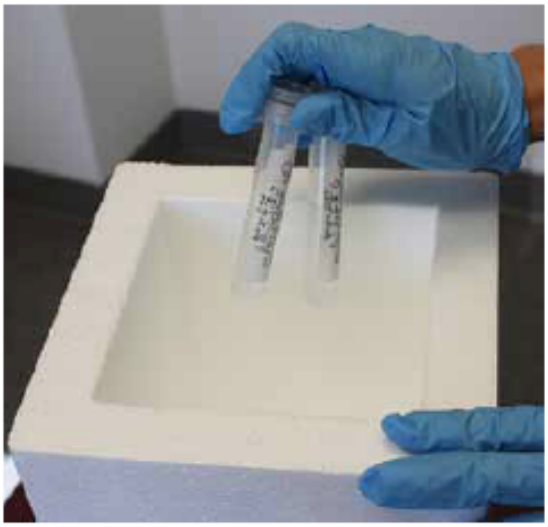
1. 13-mL polypropylene transfer tubes with colored screw caps (red screw-capped for transfer of serum; lavender screw-capped for transfer of plasma)
2. 10-mL, lavender top plastic Vacutainer blood tubes (for collection of blood for plasma samples)
3. 10-mL, plain red top plastic Vacutainer blood tubes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

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

To order additional Biomarker kits, fill out the supply order using this link:
http://goo.gl/forms/K6cptHDeOb

PACKAGING PROCEDURES FOR BIOMARKER SAMPLES

1. Biomarker samples shipping supplies.



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

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

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

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

6. Cover styrofoam box and place into card board box.

7. Seal cardboard box firmly with packing tape.

8. Affix FedEx label and call for pickup.

BIOMARKERS: BLOOD SAMPLES

Plasma and serum for biomarkers will be collected at Baseline and Month 12 Follow Up visit for all study participants.

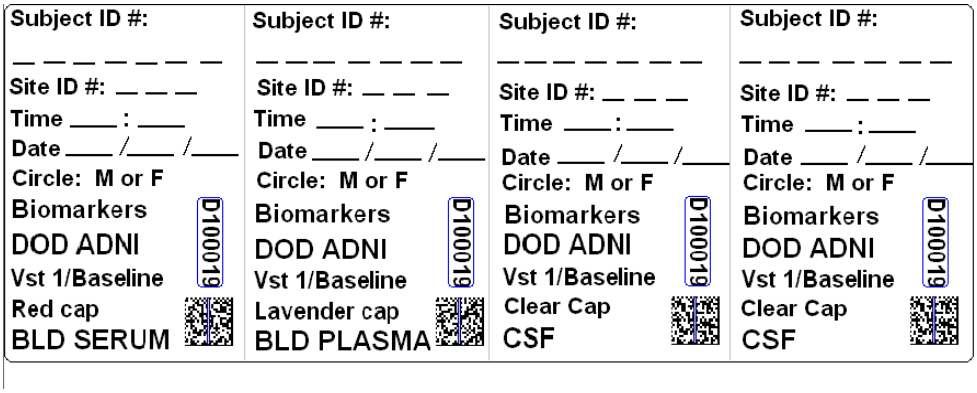
FASTING OVERNIGHT (MINIMUM 8 HOURS) IS REQUIRED FOR PLASMA, SERUM, AND CSF SAMPLE COLLECTION.

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

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

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

THE SAMPLE IDENTIFICATION LABEL MUST BE PLACED ON THE TRANSFER TUBE PRIOR TO FREEZING!



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

Blood Collection:

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

1. Write the Subject Identification Number on the side of the tubes prior to drawing blood.
2. Collect blood until each tube is full
3. Estimate blood volume and record on the DOD 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 SERUM and place this on one 13 mL plastic transfer tube (red screw cap) standing in a tube rack in the vertical position.

    - Please remember to use the correct UPENN Label specific to the visit (*i.e.*, visit 1/Baseline) and sample type (*i.e*., BLD SERUM). It is vital that this matches the sample and visit collected.

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

8. After the serum has been transferred to the plastic bar code labeled tube and capped, place the red screw-capped BLD SERUM-labeled tube upright in dry ice for at least 20 minutes to allow to completely freeze before being packaged.

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 DOD 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 PLASMA and place this on one 13 mL plastic transfer tube (lavender top screw cap) standing in a tube rack in the vertical position.

    - Please remember to use the correct UPENN Label specific to the visit (*i.e.*, visit 1/ Baseline) and sample type (*i.e.*, BLD PLASMA (plasma)). It is vital that this matches the sample and visit collected.

6. Using a **STERILE** pipette carefully transfer plasma from each of the two lavender top blood tubes into the bar code-labeled 13 mL plastic transfer tube, and firmly cap with the lavender screw cap.

7. After the plasma has been transferred to the plastic labeled tube and capped, place the lavender screw-capped BLD PLASMA labeled tube upright in dry ice for at least 20 minutes to allow to completely freeze before being packaged.

SUPPLIES FOR CSF COLLECTION VIA LUMBAR PUNCTURE

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

Lumbar Puncture Materials provided by ATRI:
Universal (VWR) Medical Lumbar Puncture Trays (all sterile components):

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

Each LP tray will have a Ziploc bag attached containing:

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

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

Sterile gloves in correct size for person performing the LP (one plus extras for backup)

Blue pad (one plus extras for backup)

Bottle of Betadine solution (not Betadine scrub)

Individually wrapped alcohol wipes

Attached needle is used for drawing up lidocaine, but NOT for injecting it

Sterile 4 x 4 gauze pads (extra)

Extra adhesive bandages (Band-Aid)

Clean washcloths and towels

Sharps container

Dry ice

BIOMARKERS: CEREBROSPINAL FLUID

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

For all participants, CSF will be collected only at the Baseline Visit

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

FILL IN THE LICENSE PLATE NUMBER ACCORDING TO THE LICENSE PLATE NUMBER ON THE BLOOD AND PLASMA BIOMARKER LABELS FOR THE PARTICIPANT.

Completion of Sample Collection – Biomarker Samples Worksheet:

Ensure all fields on the biomarker samples worksheet located in the visit packet are complete. Ensure the Bar Code License Plate and FedEx tracking number are included on the worksheet.

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

Temperature Requirements:

The CSF sample should be received by UPENN within 24 hours of collection. The CSF sample is shipped on dry ice.

DO NOT ALLOW SAMPLES TO BE THAWED AT ANY POINT AFTER BEING FROZEN

Shipping:

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

UPENN will *NOT* be able to receive any shipment on Saturday or Sunday.

Pre-Paid Federal Express air waybills and frozen shippers will be provided by ATRI. If your site needs additional UPENN air waybills or frozen shippers complete **the supply order using this link: http://goo.gl/forms/K6cptHDeOb**

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

For those instances in which a Friday study visit is necessary, CSF, plasma and serum samples should be placed in a -80 degree Celsius freezer until Monday and shipped on dry ice to UPENN. If a -80 degree Celsius freezer is not available, a -20 degree Celsius freezer is acceptable.

IMPORTANT: COMPLETE THE BIOMARKER SAMPLES ONLINE FORM BEFORE SHIPPING SAMPLES AND ENSURE A COPY OF THE SAMPLE COLLECTION WORKSHEET IS INCLUDED WITH THE SHIPMENT.

Sample Tracking:

- Enter the sample collection data on the Biomarker Samples electronic case report form located in the DOD ADNI web portal (www.adcs.org) immediately after sample collection.
- Make sure to enter the Bar Code License Plate (one per visit) and FedEx tracking number.
- Print a copy of the complete form and include it with the shipment.

General Reminders:

- CSF samples should be collected in the morning before breakfast and after an overnight fast.
- Only water is permitted until blood draws and the lumbar puncture are completed.

LUMBAR PUNCTURE SHOULD BE DONE *AFTER* ANY MRI SCAN FOR THAT SAME TIMEPOINT. IF THIS IS NOT POSSIBLE, PLEASE ENSURE THAT THERE IS AT LEAST A 3-DAY WINDOW BETWEEN THE LUMBAR PUNCTURE AND THE MRI APPOINTMENT.

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

Prevention of Post-Lumbar Puncture Headache:

1. Use of a Sprotte 22g atraumatic spinal needle using the gravity drip method and careful technique are optimal for reducing post-LP headache risk.

2. Having the subject refrain from exertion (e.g., exercise, housework, gardening, lifting, sexual activity or any other strenuous activities) for 24 hours after the LP is helpful.

3. Increasing fluid intake for 24 hours after LP is helpful.

Mild-to-Moderate Headache After a Lumbar Puncture:

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

Treatment of Mild to Moderate Headache:

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

Severe Headache After a Lumbar Puncture:

Severe headache which may be accompanied by nausea, vomiting, tinnitus, and/or visual disturbances and which is relieved by supine posture requires epidural blood patch to provide rapid relief. This type of headache most commonly occurs on the morning following LP, when the person arises from bed. Posturally-sensitive severe post-LP headache can last as long as a week even with bed rest 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.

Processing CSF:

1. Ensure that all necessary equipment and supplies are available ahead of time.

2. When gravity drip method is used for lumbar puncture, the CSF is drawn in four 7 mL collection tubes (or 5 mL syringes if using suction method).

3. Ensure to aliquot the first 2 mL of CSF for local laboratory testing (shipped ambient)

4. Transfer the remaining 18 mL of CSF into the 13 mL polypropylene clear capped transfer tubes.

5. Immediately freeze CSF samples upright on dry ice that will be shipped to UPENN for at least 20 minutes before being packaged.

SUPPLIES FOR BUFFY COAT SAMPLE COLLECTION & SHIPPING:

1. Buffy Coat sample shipping supplies

   1 small 95kPa canister
   Aqui-Pak segmented absorbent pouch
   Cushioning material
   List of contents card
   Shipping box

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

DOD ADNI Patient ID __ __ __ __ __ __ __

Site Number __ __ __

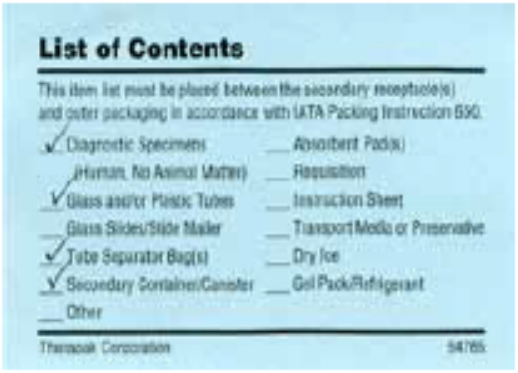
Year of Birth _____ Gender: M / F

Collection Date: Mo. / Day / Year

Visit: Baseline / Month 12

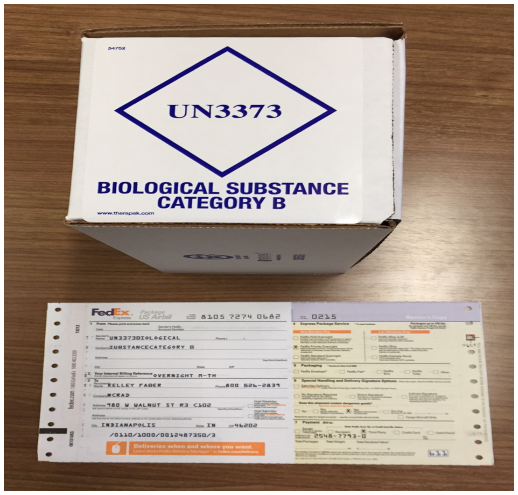
3. Insert cryogenic vials into tube sleeve

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



5. Fill out the list of contents card.

6. Place card and canister into shipping box

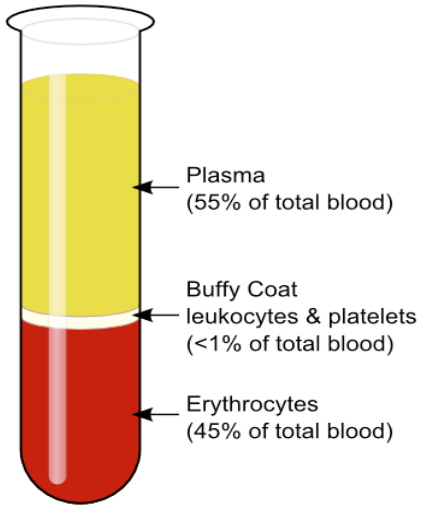


7. Fill out ***NCRAD*** FedEx airbill and attach to box

IN ORDER TO BE ABLE TO REUSE THE SHIPPING BOX, IT IS RECOMMENDED TO PLACE THE SHIPPING BOX INTO A FEDEX CLINICAL PAK AND AFFIX THE FEDEX AIR BILL TO CLINICAL PAK. FEDEX AIR BILLS CAN BE ORDERED FREE DIRECTLY FROM FEDEX AT WWW.FEDEX.COM/US

BUFFY COAT SAMPLE COLLECTION

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



Buffy coat extraction should follow each biomarker lab blood draw at Baseline and Month 12 Follow-Up Visit. Extract the buffy coat from the 2 lavender-top EDTA tubes that are used for the biomarker lab blood draw as follows:

1. After the lavender-top EDTA tubes have been centrifuged at 3000 rpm transfer the plasma into the 13mL plastic transfer tube, which will be sent to UPENN.
2. Using **sterile gloves and a sterile pipette**, extract the buffy coat from one of the lavender-top EDTA tubes and aliquot it into one of the 2mL cryogenic vials. Repeat this process for the second lavender-top EDTA tube and the remaining, empty 2mL cryogenic vial. ***It is very normal to get some of the red blood cells when pulling off the buffy coat. Generally, if you don't see red then you haven't gone far enough down the tube. After extracting the buffy coat, the remaining cells can be discarded.***
3. Complete the information on the genetic label. Ensure all fields on the label are complete using a ball-point pen or permanent marker. Securely place the label onto each cryogenic vial.
4. The label will be larger than the vial and should be dovetailed rather than wrapped around the tube in order to view all information on the label.

Completion of Sample Collection – Genetic Sample Worksheet:

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

Temperature Requirements:

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

Shipping:

The whole blood samples must be maintained at room temperature and shipped by Federal Express – **Priority Overnight** (Monday – Thursday) at ambient temperature to NCRAD. NCRAD will ***NOT*** be able to accept any shipment on Saturday or Sunday.

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

NCRAD Shipping Address:
Kelley Faber, National Cell Repository for AD
980 W Walnut St R3 C102 Indianapolis, IN 46202
NCRAD Helpdesk: alzstudy@iupui.edu
Tel: (800) 526-2839 Fax: 317-278-1100

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

Notifying the National Cell Repository for AD (NCRAD):

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

Sample Tracking:

Complete the Genetic Sample electronic case report form located in the DOD ADNI web portal immediately after the visit. Remember to include any issues that occurred during the extraction of the buffy coat, with packaging or temperature excursions on the visit comment electronic case report form.

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

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

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

1a. Tube types left to right: Single lavender-topped GWAS/ApoE, two gold-capped Cell immortalization tubes (only at Baseline), three red-capped RNA tubes, single red-capped discharge tube (only used if RNA is drawn first then discarded)

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

DOD ADNI Patient ID __ __ __ __ __ __ __ __

Site Number __ __ __

Year of Birth _____ Gender: M / F

Collection Date: Mo / Day / Year

Visit: Baseline / Month 12

2. Genetics samples shipping supplies

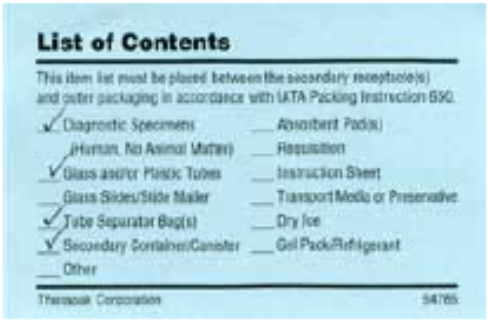
INCLUDES:

1 medium 95kPa canister,
Aqui-Pak segmented absorbent pouch
Cushioning material
List of contents card
Shipping box

3a. Insert all tubes into tube sleeve

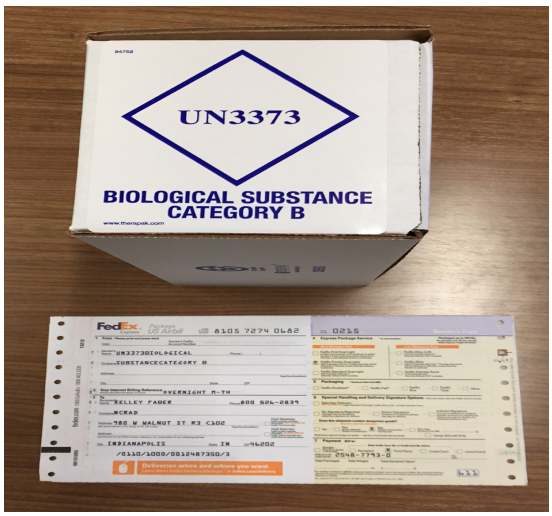
3b. ***NEVER INSERT DISCHARGE TUBE INTO TUBE SLEEVE.*** If used, the discharge tube should be discarded.

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



5. Fill out the list of contents card.

6. Place card and canister into shipping box



7. Fill out ***NCRAD*** FedEx airbill and attach to box

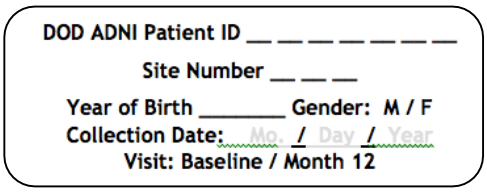
IN ORDER TO BE ABLE TO REUSE THE SHIPPING BOX, IT IS RECOMMENDED TO PLACE THE SHIPPING BOX INTO A FEDEX CLINICAL PAK AND AFFIX THE FEDEX AIRBILL TO CLINICAL PAK. FEDEX AIRBILLS CAN BE ORDERED FREE DIRECTLY FROM FEDEX AT WWW.FEDEX.COM/US

DNA SAMPLE COLLECTION FOR GWAS AND APOE GENOTYPING

Blood sample will be collected for DNA/GWAS at Baseline for all study participants after passing screening criteria for this study. Whole blood will be collected in a single 10 mL EDTA (lavender top) tube.

ApoE genotyping will be done using the same 10 mL whole blood sample.

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



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

Blood Collection:

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

Completion of Sample Collection – Genetic Sample Worksheet:

Ensure all fields on the sample collection worksheet located in the visit packet are complete. Pay particular attention to the questions regarding if the subject consented to DNA testing and sample storage. Ensure the name of the individual who packaged and shipped the blood specimen, along with their phone number and email is listed on the worksheet. Additionally, list in the comments section of the worksheet any issues that occurred during the blood draw, with packaging or any temperature excursions.

Temperature Requirements:

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

Shipping:

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

NCRAD will ***NOT*** be able to accept any shipment on Saturday or Sunday.
Pre-Paid Federal Express Air waybills and ambient shippers will be provided by ATRI. If your site needs additional air waybills or ambient shippers complete the Supply Order Form located in the document repository.

NCRAD Shipping Address:
Kelley Faber, National Cell Repository for AD
980 W Walnut St R3 C102 Indianapolis, IN 46202
NCRAD Helpdesk: alzstudy@iupui.edu
Tel: (800) 526-2839 Fax: 317-278-1100

For those instances in which a Friday study visit is necessary, the EDTA (lavender top) tube needs to be stored at room temperature (20-25 degrees Celsius) from Friday until Monday and must be shipped out no later than Monday to NCRAD. (EDTA tubes can be refrigerated from Friday until Monday, if needed. But if whole blood sample is refrigerated it must be shipped with ice packs to NCRAD).

Notifying the National Cell Repository for AD (NCRAD):

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

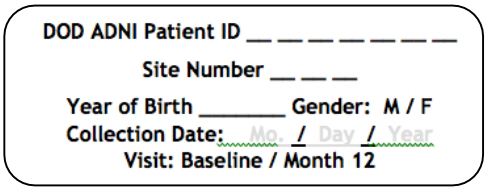
Sample Tracking:

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

CELLS FOR IMMORTALIZATION

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

Begin by confirming the participant consented to DNA testing and sample storage per their informed consent. **Next**, complete the information on the genetic label for each of the ACD-A (yellow top) tubes.



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

Blood Collection:

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

Completion of Sample Collection – Genetic Sample Worksheet

Ensure all fields on the sample collection worksheet located in the visit packet are complete. Include the name of the individual who packaged and shipped the blood specimen, along with their phone number and email. Additionally, list in the comments section of the worksheet any issues that occurred during the blood draw, with packaging or any temperature excursions.

Temperature Requirements:

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

Shipping:

The whole blood samples must be maintained at room temperature and shipped by Federal Express – **Priority Overnight** (Monday – Thursday) at ambient temperature to NCRAD. NCRAD will ***NOT*** be able to accept any shipment on Saturday or Sunday.

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

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Kelley Faber, National Cell Repository for AD
980 W Walnut St R3 C102 Indianapolis, IN 46202
NCRAD Helpdesk: alzstudy@iupui.edu
Tel: (800) 526-2839 Fax: 317-278-1100

For those instances in which a Friday study visit is necessary, the ACD-A (yellow top) tube needs to be stored at room temperature (20-25 degrees Celsius) from Friday until Monday and must be shipped out no later than Monday to NCRAD.

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

Notifying the National Cell Repository for AD (NCRAD):

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

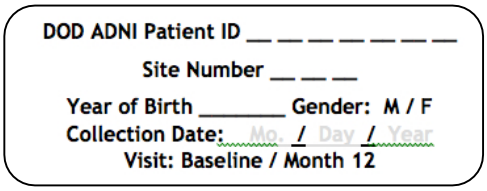
Sample Tracking:

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

RNA SAMPLES

In order to measure gene expression across time, an RNA sample will be collected at Baseline and at the Month 12 Follow Up visit for all study participants. Whole blood will be collected in three 2.5 mL PAXgene Blood RNA tubes.

Begin by confirming the subject consented to RNA testing and sample storage per their informed consent. **Next**, complete the information on the genetic label for each of the PAXgene Blood RNA tubes.



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

Blood Collection:

3 x 2.5 mL PAXgene Blood RNA tubes will be collected at Baseline and Month 12 Follow Up visit for all participants using the RNA sample collection kit provided by the ATRI.

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

1b. If the PAXgene Blood RNA tube is the only tube to be drawn, a small amount of blood should be drawn into a "discard tube" prior to drawing blood into the PAXgene Blood RNA tube. Otherwise, the PAXgene Blood RNA tube should be the LAST tube drawn in the phlebotomy procedure. (Discard tube is included in the RNA collection kit provided by ATRI)

2. Using a BD (Becton, Dickinson and Company) Vacutainer Safety-Lok Blood Collection Set, collect blood into the PAXgene Blood RNA tube using your institution's recommended standard procedure for venipuncture.

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

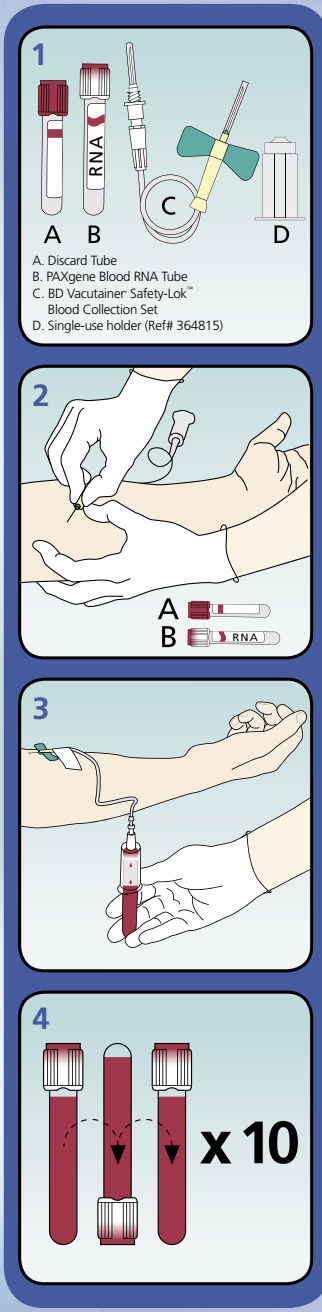
3b. Allow at least 10 seconds for a complete blood draw to take place. Ensure that the blood has stopped flowing into the tube before removing the tube from the holder.

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

4b. Store the PAXgene Blood RNA tube upright at room temperature.

How to Collect Blood Using the PAXgene™ Blood RNA Tube

For Molecular Diagnostic Testing



Required Items:

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

1b. If the PAXgene Blood RNA Tube is the only tube to be drawn, a small amount of blood should be drawn into a "Discard Tube" (A) prior to drawing blood into the PAXgene Blood RNA Tube. Otherwise, the PAXgene Blood RNA Tube should be the last tube drawn in the phlebotomy procedure.

Venipuncture:

2. Using a BD Vacutainer® Safety-Lok™ Blood Collection Set (C), collect blood into the PAXgene Blood RNA Tube using your institution's recommended standard procedure for venipuncture.

Blood Collection:

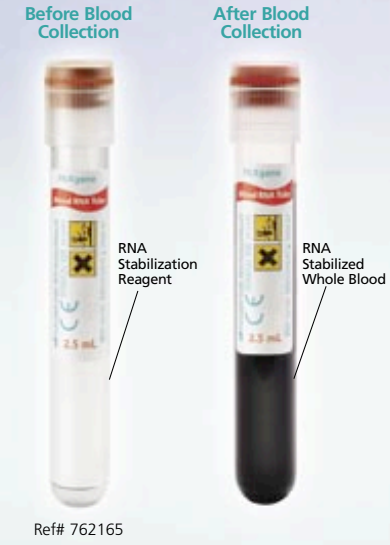
3a. Hold the PAXgene Blood RNA Tube vertically, below the blood donor's arm, during blood collection.

3b. Allow at least 10 seconds for a complete blood draw to take place. Ensure that the blood has stopped flowing into the tube before removing the tube from the holder. (See Figure 1)

After Blood Collection:

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

4b. Store the PAXgene Blood RNA Tube upright at room temperature (18°C-25°C) or at 4°C.*



Ref# 762165

BD Vacutainer® Safety-Lok™ Blood Collection Set

Ref# 367281 North America

Ref# 367286 Other Countries

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

PreAnalytiX
A QIAGEN / BD Company

www.PreAnalytiX.com

CE

*Refer to PAXgene® Blood RNA Tube handbook.

Printed in USA 05/05 VS5933-1

Completion of Sample Collection – Genetic Sample Worksheet:

Ensure all fields on the sample collection worksheet located in the visit packet are complete. Pay particular attention to the questions regarding if the subject consented to RNA testing and sample storage. Ensure the name of the individual who packaged and shipped the blood specimen, along with their phone number and email is listed on the worksheet. Additionally, list in the comments section of the worksheet any issues that occurred during the blood draw, with packaging or any temperature excursions.

Temperature Requirements:

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

Shipping:

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

NCRAD will ***NOT*** be able to accept any shipment on Saturday or Sunday.
Pre-Paid Federal Express Air waybills and Ambient Shippers will be provided by ATRI. If your site needs additional air waybills or ambient shippers complete the Supply Order Form located in the document repository.

NCRAD Shipping Address:
Kelley Faber, National Cell Repository for AD
980 W Walnut St R3 C102 Indianapolis, IN 46202
NCRAD Helpdesk: alzstudy@iupui.edu
Tel: (800) 526-2839 Fax: 317-278-1100

For those instances in which a Friday study visit is necessary, after the sample is obtained the PAXgene Blood RNA tubes **must be held at room temperature for two hours**, and then placed in a -20º or -80º Celsius freezer over the weekend and **shipped frozen (on dry ice)** on Monday. RNA can be shipped with Buffy Coat (since both are to be shipped on dry ice).

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

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

Notifying the National Cell Repository for AD (NCRAD):

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

Sample Tracking:

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

CHAPTER 14

NEUROPATHOLOGY

DOD ADNI-NPC PURPOSE AND AIMS

The aim of the DOD ADNI Neuropathology Core is to provide a better understanding of the risk factors for the development of AD through validation of clinical diagnoses and imaging surrogates through neuropathological examination of DOD ADNI participants who come to autopsy. Given the importance of the data that can be obtained from the neuropathologic examination of DOD ADNI participants, it is essential that autopsy and brain donation be offered to every DOD ADNI participant. In order to facilitate the autopsy discussion, the DOD ADNI-NPC has developed the following guidelines for obtaining provisional autopsy consent as well as some educational materials to provide to DOD ADNI participants.

Discussing Autopsy and Obtaining Provisional Consent

A DOD ADNI clinician will lead a discussion about autopsy with all participants at the screening visit and annual visits thereafter (study partners and families are welcomed in the discussion). There are 3 objectives of the discussion:

To convey information about the value of brain autopsy and advancing knowledge regarding the prevention of AD;

To initiate consideration of the individual's wishes concerning an autopsy;

To answer questions, misconceptions, or concerns about autopsy.

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

The discussions are repeated at each DOD ADNI clinic visit (unless the participant has provided consent or has clearly refused autopsy), both to ensure the participant's wishes regarding brain donation are carried out and that family members are aware of the participant's wishes. There is no pressure on an individual to decide; they are encouraged to involve family members, clergy, physicians, or other appropriate persons in their decision-making. Participants are assured that

a decision not to have autopsy in no way jeopardizes their research participation or any other patient rights. It is important to note that autopsy will not interfere with funerary arrangements nor will it be a financial burden to the participant's family.

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

After Obtaining Provisional Consent

When voluntary consent is granted, more detailed information should be provided to the participant about procedures to follow at time of death, including telephone numbers to call and other guidelines. The DOD ADNI-NPC has developed autopsy notification materials including wallet cards and autopsy authorization letters.

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

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

At the Time of Expiration

Once your site has been notified of the death of a DOD ADNI participant, please follow the autopsy procedures as outlined in the DOD ADNI-NPC manual or the specific autopsy procedures developed for your site.

Please remember you must notify the DOD ADNI-NPC Coordinator at the time of expiration.

Erin Franklin, MS, CCRP
Department of Pathology and Immunology
Washington University School of Medicine
Tel: 1-314-362-8079
Fax: 1-314-362-4096
Email: efranklin@wustl.edu
Pager: 1-314-841-4738

DOD ADNI-NPC Neuropathology Protocols

Where possible, each center will undertake its own brain assessment and forward a standard set of fixed tissue blocks or sections and frozen tissue to DOD ADNI-NPC. Please refer to the NPC Manual for complete details on the neuropath protocol for removal and shipment of brain tissue.

Autopsy Financial Coverage

The DOD ADNI-Neuropathology Core (DOD ADNI-NPC) will cover brain autopsy costs, with the following limitations. DOD ADNI sites with existing ADRC/ADC neuropathology arrangements in place for handling DOD ADNI Participant brain donations will continue to make their own arrangements for brain autopsies.

DOD ADNI sites with no arrangements in place for handling DOD ADNI Participant brain donations:

1. Local transportation costs may be paid by DOD ADNI-NPC if arrangements are set-up by DOD ADNI-NPC; if not, DOD ADNI-NPC may pay up to a certain amount of the local transportation costs (see NPC Manual for details).

2. Brain removal performed out-of-state or out of local area: DOD ADNI-NPC may pay Transportation costs if arrangements are set-up by DOD ADNI-NPC.

Financial Assistance with Block Sampling, Preservation and Shipping

The DOD ADNI-NPC will also cover the cost in shipping frozen and fixed tissue samples to St. Louis. For details on the reimbursement available for shipping tissue, as well as the preservation of the tissue, refer to the NPC Manual.

NOTE: Any cost requesting to be reimbursed **must be approved** ahead of time. If you have additional questions contact the DOD ADNI – NPC:

Erin Franklin, MS, CCRP
Department of Pathology and Immunology
Washington University School of Medicine
Tel: 1-314-362-8079
Fax: 1-314-362-4096
Email: efranklin@wustl.edu
Pager: 1-314-841-4738

CHAPTER 15

COGNITIVE ASSESSMENTS

GENERAL GUIDELINES

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

Scheduling Testing

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

Creating a Productive Testing Environment

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

Introducing the Testing

The general orientation to the day's activities should include the study partner (if available). Explain the purpose of the testing, what the test(s) will be like, how long testing will take, and what the day's schedule will be, including when the Participant may take breaks. After answering any questions, the study partner (if applicable) should wait outside the test room in the designated waiting area. (Most Participants test better if they are not observed by people they know). If the Participant will comply only with a study partner present, the study partner should be instructed not to provide answers, and to sit in an area of the room where the Participant will not easily turn to him/her for feedback.

Managing Testing Time

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

Keeping Participants Focused

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

Assessing Participant Comprehension

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

Feedback and Prompting

Provide only neutral feedback to the Participant, without indicating if their answers are right or wrong, (e.g., "okay" or "you are doing fine."). Reward all good effort, not just good performance. Often a Participant will give more than one answer. If that should occur, encourage the Participant to choose one of them, without cueing for a specific response. "Which one is it?" or "Choose one" can be useful prompts to get a Participant to choose a single answer.

Scoring and Recording

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

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

REMEMBER THAT THE PARTICIPANT'S NAME OR ANY PERSONAL IDENTIFYING INFORMATION (I.E. DOB, SS #) SHOULD NOT BE WRITTEN ON THE WORKSHEET.

ORDER OF NEUROPSYCHOLOGICAL ASSESSMENTS

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

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

DOD ADNI SITE SCREENING VISIT:

- MMSE
- Logical Memory (LM) I

Conduct other assessments that take AT LEAST 30 AND NO MORE THAN 40 MINUTES before proceeding with LM II assessment (delayed recall). Do not administer the MMSE or CDR during the period of delay; other activities including the GDS and patient demog are permissible.

- Logical Memory (LM) II (30-40-minute delay)

DOD ADNI SITE BASELINE VISIT:

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

DOD ADNI SITE MONTH 12 FOLLOW UP VISIT:

- ADAS-Cog
- MMSE
- Logical Memory IA
- Rey Auditory Verbal Learning Test (Trials 1-6)
- Montreal Cognitive Assessment (MoCA)
- Clock Drawing
- Category Fluency (animals)
- Trails A & B
- Boston Naming Test (30 items)
- Logical Memory IIA
- Rey Auditory Verbal Learning Test (30-minute Delay)
- Everyday Cognition – Participant Self-Report
- Everyday Cognition – Study Partner Report (if applicable)
- Armed Forces Qualification Test (AFQT)

INTRODUCTION TO THE ADAS-COG

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

Administration Instructions

For complete administration and scoring rules for the ADAS-cog refer to the ADAS manual (version 3/20/12) posted to the document repository.

Scoring

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

ADAS-COG: WORD RECALL TASK

Word List 1

Word Recall List 1 and Word Recognition List 1 will be used at Baseline and the Month 12 follow-up visit.

Word Recall List 1

Trial 1	Yes	No
Butter		
Arm		
Shore		
Letter		
Queen		
Cabin		
Pole		
Ticket		
Grass		
Engine		

Trial 2	Yes	No
Pole		
Letter		
Butter		
Queen		
Arm		
Shore		
Grass		
Cabin		
Ticket		
Engine		

Trial 3	Yes	No
Shore		
Letter		
Arm		
Cabin		
Pole		
Ticket		
Engine		
Grass		
Butter		
Queen		

Word Recognition List 1

Word	Yes	No	*R
Nurse			
Magazine			
Wizard			
Van			
Leopard			
Sale			
Sea			
Train			
Coin			
Ship			
Institution			
Map			
Axe			
Board			
Carrot			
Milk			
Volume			
Forest			
Anchor			
Gem			
Cat			
Fund			
Edge			
Cake			

ADAS CERTIFICATION INSTRUCTIONS

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

Certification may only be accomplished by completion of the ADAS Standardization/Certification Questionnaire. ADAS certification renewal is required every 5 years.

If you or a member of your team needs to complete the ADAS certification process contact ATRI Operations at atri-clinops@usc.edu.

Completed questionnaires should be emailed to: atri-clinops@usc.edu

ARMED FORCES QUALIFICATION TEST (AFQT)

Description

AFQT is the means of determining mental test acceptability of potential enlistees and inductees. It was developed out of the need to have a uniformed mental screening test among the Services. The test represents a global measure of mental ability, containing essentially those item types that were most common to existing screening tests in all Services (i.e. vocabulary, arithmetic, reasoning and spatial relations).

There are four types of questions in the AFQT: questions about the meaning of words, questions about arithmetic, questions about tools and questions about boxes made by folding pieces of cardboard. There are a total of 100 questions in the AFQT.

Rationale

Preinjury intelligence is a strong predictor of long term decline in many cohorts including those with Traumatic Brain Injury among these variables. Preinjury intelligence can be estimated by the Armed Forces Qualification Test/Army Classification Test which was administered prior to the completion of basic training. As part of the ADNI cognitive battery these exact same tests will be re-administered to the study participant at Baseline and the Month 12 Follow-Up visit. The difference in score of these tests will be used as a major dependent variable in data analysis. The AFQT will be used as 1) measures of cognitive reserve; 2) the change in the score from its original use in Basic Training to the time of the study will be used as an important outcome measure to test hypotheses.

Administration Instructions

About 1 hour and 10 minutes should be allowed for the administration of the AFQT. The actual testing time is 50 minutes. The additional 20 minutes permits time for seating, distributing materials, explaining the test and conducting the practice questions.

The person delegated to act as proctor for the AFQT is not required to remain in the room for the duration of the test. Regular monitoring is sufficient. However, care should be taken to

ensure the participant is completing the AFQT according to instructions, and not referring to a phone or computer to assist.

The administration of the AFQT must follow exactly as presented in the AFQT Manual posted in the document repository without deviation. **No omissions or changes in the wording of the instructions to the examinee are permitted**.

Scoring

The AFQT will not be scored or entered by the DOD Clinic, rather upload the answer sheet to the study portal via the Study Document Upload eCRF. The SFVAMC staff is responsible to enter the data online and score.

AMERICAN NATIONAL ADULT READING TEST (ANART)

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

Administration Instructions

Present the Participant with the word list and say, "I'm going to ask you to read a list of words aloud. Some of the words may be unfamiliar and difficult to pronounce, but do the best you can to pronounce them."

The Participant may self-correct; however, do not prompt them to repeat a word unless it was difficult to hear what was said and necessary to determine whether the pronunciation was correct or incorrect.

If the Participant reads a word with two different pronunciations, one correct and the other incorrect, ask which one they think is best.

Administer all words, even when the Participant begins having difficulty pronouncing them.

Scoring

Total score = total # of **errors** made.

Manually enter the total number of errors made on the online case report form.

NOTE: Some words have multiple correct pronunciations. Be familiar with these, so as to score accurately!

BOSTON NAMING TEST

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

Description

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

Administration Instructions

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

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

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

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

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

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

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

Scoring

There are 6 scores:

1. Total correct without a cue

2. Total semantic cues given

3. Total correct with a semantic cue

4. Total phonemic cues given

5. Total correct with phonemic cues

6. Total correct = sum of 1 + 3 above

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

Calculate and enter the total score on the online form. After submitting the form, an error will be generated if the total score entered doesn't equal the summation of items 1 and 3.

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

Mispronunciations are treated as incorrect unless they clearly reflect a regional or dialect specific pronunciation (e.g. someone from the Boston area may omit the 'r' sound in 'dart').

If a mispronunciation does not reflect such a regionalism (e.g. 'esculator'), the answer is incorrect and cueing proceeds as appropriate.

If the Participant gives a more general or circumlocutory response (e.g. 'boat' or 'it floats on water' for the word 'canoe'), say "Can you think of a more specific name for it?"

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

If the Participant gives the correct name, but says it is not that object (e.g. "Well it's not a canoe"), the response is considered incorrect and cueing proceeds if appropriate.

CATEGORY FLUENCY TEST

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

Description

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

Administration Instructions

Read the initial instruction:

"I am going to give you a category and I want you to name, as fast as you can, all of the things that belong in that category. For example, if I say 'articles of clothing,' you could say 'shirt,' 'tie,' or 'hat.' Can you think of other articles of clothing?"

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

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

Next, read the instructions for the Animal category:

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

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

Scoring

Defer scoring until after test administration is finished.

The total score on the Worksheet for Category Fluency–Animals is the number of correct **unique** animal names produced within the one-minute time limit.

Intrusions are defined as any non-categorical word (i.e. a word that is not considered an animal name) said by the study participant.

If a subject **repeats** either an intrusion or correct animal name, this is considered a **perseveration**. The first time a subject states the animal name it is counted as correct. If later, in the same trial, the same animal name is said again, the second time it is a perseveration. With non-categorical words, it is considered an intrusion the first time the subject states the non-animal name and if the same word is stated again (in the same trial), it is counted as a perseveration.

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

> **CREDIT:** breeds (e.g., terriers); male, female, and infant names of a species (e.g., bull, cow, calf); both superordinate and subordinate examples of a species (e.g., both dog and terrier are credited); birds; fish; reptiles, insects.
>
> **DO NOT CREDIT:** Repetitions, mythical animals.

CLOCK DRAWING TEST

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

Description

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

Clock Drawing Administration Instructions

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

> To begin, present the Participant with a felt-tipped pen (or a pencil without an eraser) and an 8 1/2" x 11" blank sheet of white paper and say, "Draw the face of a clock showing the numbers and two hands set to ten after eleven."

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

> If the Participant tries to erase or scratch out an error, immediately intervene and gently instruct them to try again by saying, "Don't' take the time to make corrections." While pointing to a clean area of the paper, say, "You may start over here and draw the clock again. Remember you are to draw the face of a clock showing the numbers and two hands set to ten after eleven."

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

Clock Copying Administration Instructions

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

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

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

Scoring

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

1. Approximately circular face. The clock face may be slightly oval, especially if the Participant hastily begins to draw. The examiner may always determine that the Participant 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 Participant for tremor. In some cases, Participants will draw an "old fashioned" mantle clock or grandfather clock (i.e., with a square clock face). If this occurs, ask the Participant 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).

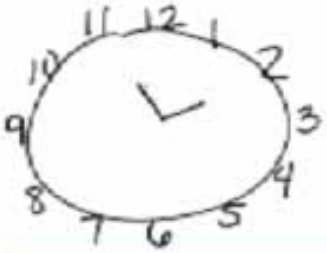
Indicate correct or incorrect for each of the 5 items above on the online case report form for both clock drawing and clock copying. Each 'correct' item for clock drawing and clock copying is equal to 1 point, calculate and enter the total score for each task. After submitting the form, an error will be generated if the total score for clock drawing or clock copying entered doesn't equal the summation of items marked as 'correct'.

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

Clock Drawing Test (Cont'd)

5 points

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



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

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

0 points

LOGICAL MEMORY (STORY "A" - ANNA THOMPSON STORY)

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

Description

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

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

Use of the alternate story (Greg Fortune) is permitted if a Participant had been tested on the Anna Thompson story within 3 months of the clinic screening visit or any subsequent visit where the Logical Memory task is administered under DOD ADNI. ***Prior approval from the clinical monitor or protocol PI is required in any instance where the alternative story will be administered.***

Administration Instructions

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

Say:	**"I am going to read to you a little story of just a few lines. Listen carefully and try to remember it just the way I say it, as close to the same words as you can remember. When I am through I want you to tell me everything I read to you. You should tell me all you can remember even if you are not sure. Are you ready?"**
When the examiner has finished reading the story, say to the participant:	**"Now what did I read to you? Tell me everything and begin at the beginning."**

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

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

Recording

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

Scoring

The phrases and words separated by diagonal lines in the passages are treated as items (or units), and each item correctly repeated is worth one point, for a total of 25 points.

Non-verbatim responses for the Anna Thompson story that are acceptable and receive full credit are listed in the Wechsler Memory Scale-Revised manual, as follows:

TEXT FOR STORY A	GENERAL RULE	EXAMPLES OF ALTERNATIVE 1-POINT RESPONSES	EXAMPLES OF 0-POINT RESPONSES
Anna	"Anna" or variant of the name	Ann; Annie; Annette	Angela; Allison
Thompson	"Thompson" is required	NONE	Thompkins; Thomas
of South	"South" (in any context)	from South; who lived in South; who came from the South	NONE
Boston,	"Boston" (in any context)	who worked in Boston; on a trip to Boston	NONE
employed[1]	An indication that she held a job	worked; had a job as; who was; who earned a living as	who wanted to be; employed a cook
as a cook[1]	"Cook" or some form of the word is required	who cooked	as a waitress; in the kitchen
in a school	"School" is required	at a high school; by a school	in a hospital; at a company
cafeteria,	"Cafeteria" is required	NONE	lunchroom; dining hall; diner; restaurant; kitchen
reported	Indication that a formal statement was made to someone in authority (in any context)	filed a complaint; said to the police; made a statement; notified the police; called the police; told the police	said; told how
at the City Hall	"City Hall" (in any context)	went to City Hall; called City Hall	NONE
Station	"Station" in any context, or a word or phrase denoting a police station	police station; train station; stationhouse; police headquarters; precinct house; police department	office; building
that she had been held up	An indication that she had been held up (i.e., gun point or knife)	that someone held her up; that she was in a stick-up	that she was beaten; she was attacked; that she was robbed; she got mugged
on State Street	"State Street" (in any context)	she lived on State Street; on her way to State Street	on some street; State Avenue
the night before	Indication that the hold-up occurred the previous night	last night; the previous night	at night; one night; yesterday; the day before
and robbed	Indication that a robbery took place	was robbed; her money was stolen; they took her money; someone took her purse	lost her money somebody took her things

Story A Scoring (Cont'd)

TEXT FOR STORY A	GENERAL RULE	EXAMPLES OF ALTERNATIVE 1-POINT RESPONSES	EXAMPLES OF 0-POINT RESPONSES
of fifty-six dollars	Indication that an amount of money greater than $49 but less than $60 was taken from her	fifty-some dollars; fifty-five dollars; about fifty dollars	sixty-five dollars; a lot of money; the police collected fifty-six dollars for her
She had four	"Four" is required together with an indication that the children were hers	she was the mother of four	she had two; she had some; there were some
small children,	"Children" or a synonym is required	little children; kids; small kids; young children	babies; girls; sons; small boys
the rent was due,	A phrase indicating that the rent was due	she had not paid the rent; she owed for the rent; the landlord had to be paid; she needed money for the rent	she owed money; she needed money; there was no money
and they had not eaten	Indication that her children, or the family, were without food	they had gone without food; they were hungry; there was no food; her kids had nothing to eat; she couldn't feed her family	there wasn't much food; they had only a little food; she had not eaten; didn't have money to buy food
for two days.	"Two days" is required, or a phrase meaning about two days	for a couple of days; for one or two days; for two or three days	for days; for several days; for a day; for three days
The police,	A word or phrase signifying one or more members of the police department (in any context)	the cops; the policeman; the detectives; the police officer; they (where police is clearly meant)	they (unspecified); some people; her neighbors; somebody
touched by the woman's story,	An indication that her story evoked sympathy	were touched; felt sorry for the woman; wanted to help her; were sympathetic; were impressed by her story (implying emotional reaction)	listened to her story; helped her; believed her
took up a collection	A phrase indicating that money was collected	chipped in; collected money; donated; collected some food	gave her some money; found some money
for her.	An indication that the money collected was for her or her children	and gave it to her; for her children; for her family; for them; to help her out	as a gift; to make things better; for food

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

Alternative Paragraph Scoring

Alternate Paragraph for Logical Memory (Scoring Criteria)

For Use With "Greg Fortune" Paragraph

Text for Story A	General Rule	Examples of Alternative 1-Point Responses	Examples of 0-Point Responses
Greg	"Greg" or variant of the name	Gregory	Frank
Fortune	"Fortune" is required	—	Foreman
captain	"Captain" is required	—	coach
and quarterback	"Quarterback" is required	—	fullback
for the Atlanta	"Atlanta" in any context	from the Atlanta team	Georgia
Panthers	"Panthers" in any context	who played for the Panthers	—
football team	"Football team" in any context	who played football	played ball; baseball
was injured	"Injured" or variant is required	hurt; wounded	—
on a fishing trip	"Fishing trip" or variant is required	went fishing; on a fishing trip; while fishing; on a fishing boat	went on a trip;
last week	"last week" is required	—	earlier; last month
After bringing a large	"Bringing a large" or variant required	catching a large (big); reeling in a large; bagged a big; landed; caught; after landing a sizable	catching; got

81

Alternative Paragraph Scoring Cont'd

Alternate Paragraph for Logical Memory (Scoring Criteria)

For Use With "Greg Fortune" Paragraph

Text for Story A	General Rule	Examples of Alternative 1-Point Responses	Examples of 0-Point Responses
bluefish	"Bluefish" is required	—	fish; bluegill
aboard his cabin cruiser	An expression indicating aboard his [cabin] cruiser	aboard his cruiser; onto his cabin cruiser; yacht	aboard his sailboat; onto his fishing boat; onto his boat
it jumped up	An expression indicating the fish jumped	it leaped; sprang; bounded; bolted	it moved
and bit	"Bit" or variant is required	bit into	grabbed onto
his left	"Left" is required	—	right
ring	"Ring" is required	—	third, fourth, little
finger	"Finger" is required	—	hand
Even though it took 17	"17" in any context is required	they put 17; he needed 17	—
stiches	"Stiches" is required	sutures; he was sewn up	a bandage
to close	"to close" or variant is required	to fix; to doctor it up; to treat; to repair it	—
the wound	"Wound" or variant is required	the open wound; the cut; the injury	use of the word "it" in place of "the wound" (e.g., close it up)

82

Alternative Paragraph Scoring Cont'd

Alternate Paragraph for Logical Memory (Scoring Criteria)

For Use With "Greg Fortune" Paragraph

Text for Story A	General Rule	Examples of Alternative 1-Point Responses	Examples of 0-Point Responses
he was still able to play	An expression indicating that he was able to play	he was well enough to play; it healed enough for him to play	he couldn't play; he watched the game; he wanted to play
in Sunday's game	"Sunday's game" or variant is required	the game on Sunday; the football game on Sunday	the Monday night game
against the Thrashers	An expression indicating the game was against the Thrashers	when his team played the Thrashers	An expression indicating he played on the Thrashers team; Trashers

83

LOGICAL MEMORY TEST II – DELAYED RECALL (STORY "A" ANNA THOMPSON)

Administration Instructions

Administer this test at least 30 minutes and no more than 40 minutes after Logical Memory I - Immediate Recall. It is preferred to not administer the MMSE or CDR during the delay, instead use 'non word list' assessments to fill 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 (delayed recall). Once the Logical Memory II has been fully completed, resume the interrupted test.

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

Say,	**"Do you remember the little story I read to you a few minutes ago? Now I want you to tell me the story again. Tell me everything; begin at the beginning."**

If the Participant does not recall the Anna Thompson story, it is permissible to offer the following reminder which is also printed on the testing worksheets.

Say,	**"The story was about a woman who was robbed."**

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

If the alternative story was used (Greg Fortune) and the Participant does not recall the story, it is permissible to offer the following reminder which is also printed on the testing worksheets.

Say,	"The story was about a man who went fishing"

Recording

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

Scoring

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

Note if the reminder was given, do not then give a point for that item (i.e., "robbed") when scoring.

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

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

MINI MENTAL STATE EXAM

Description

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

It is strongly recommended that the same person administer the MMSE at all appropriate visits.

If the Participant is unable to perform any item, the item should be scored as "incorrect."

MMSE total score will automatically be calculated on the electronic case report form based on the item level data entered

Administration Instructions

Following a polite and friendly introduction to the Participant, begin the MMSE by asking, **"Do you have any trouble with memory?"** Regardless of his or her answer, say, **"May I ask you some questions about your memory?"** These two questions are not scored; however, they serve to orient the Participant to the nature of the examination. This conversation also can assess the person's hearing, alertness, attention, and responsiveness.

Prior to administration, ensure that eyeglasses (if needed) are being worn and hearing aids (if needed) are adjusted appropriately.

If the Participant is anxious, it may be helpful to periodically say, "you're doing fine."

Orientation Instructions

Items 1 – 10: Each scoreable item should be queried separately as indicated on the online CRF.

For each item, record the Participant's response in the space provided on the worksheet. Indicate on the worksheet if each response was correct or incorrect.

If a Participant gives the date when prompted for day, he/she should be given credit for date if the response is correct. If a Participant gives a partial response for year (e.g. "11", prompt with, "what is the full year?") **Give credit only if the full year is given.**

Orientation Scoring

Each item is worth one point. No partial credits are given.

For hospital, any correct name is acceptable except for generic names such as "medical center" or "hospital".

For county, only the county in which they are currently in, is considered correct. The participant's home county (if different from their current location) is considered incorrect.

If it is near the transition between 2 seasons, that is one week before and two weeks after the onset of a new season, either season is acceptable and considered correct.

All other items require **EXACT** answers to be considered correct.

Year: 2012	Winter = 12/22/11 – 3/19/12
	Spring = 3/20/12 – 6/19/12
	Summer = 6/20/12 – 9/21/12
	Fall = 9/22/12 – 12/20/12
Year: 2013	Winter = 12/21/12 – 3/19/13
	Spring = 3/20/13 – 6/20/13
	Summer = 6/21/13 – 9/22/13
	Fall = 9/23/13 – 12/20/13
Year: 2014	Winter = 12/21/13 – 3/19/14
	Spring = 3/20/14 – 6/20/14
	Summer = 6/21/14 – 9/22/14
	Fall = 9/23/14 – 12/20/14
Year: 2015	Winter = 12/21/14 – 3/19/15
	Spring = 3/20/15 – 6/20/15
	Summer = 6/21/15 – 9/22/15
	Fall = 9/23/15 – 12/20/15

Immediate Recall Instructions
Say, **"Listen carefully. I am going to say three words. You say them back after I stop. Ready? Here they are…."**

Pause 1 second after each of the three words.

"Now repeat those words back to me."

Immediate Recall Scoring
Score one point for each correct response in the FIRST trial (the order of the answers does not matter). Continue to repeat the three words until he/she is able to say all three words back to you, with a maximum of five additional trials to repeat all three words. If the Participant does not repeat all three words correctly by the sixth trial, stop the task and enter "6" for 13a.

Attention Instructions
In the attention task, begin by having the Participant spell the word, "WORLD," first forward (correct any misspellings), then backwards. Only the backwards spelling is scored.

Attention Scoring
For DOD ADNI, scoring was adapted from the CERAD scoring rules. Record the actual letters of the Participant's final response in the order they were said out loud on the provided worksheet.

Delayed Recall Instructions
After a 3 minute delay from Immediate Recall, ask the Participant, **"Now what were those three words I asked you to remember?"** Do not prompt the Participant or provide any cues or hints.

Delayed Recall Scoring
One point for each correct response for a total of three points. The order of answers does not matter.

IF THE ATTENTION TASK IS COMPLETED IN LESS THAN 3 MINUTES, PERFORM REMAINING NON-VERBAL PARTS OF THE MMSE UNTIL 3 MINUTES HAVE ELAPSED. GO DIRECTLY TO QUESTIONS 25, 26, 27 AND 30. ONCE 3 MINUTES HAVE ELAPSED, RETURN TO THE DELAYED RECALL TASK.

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

Language Naming Scoring
Score one point for each correct response.

Repetition Instructions	Repetition Scoring
Say, **"Now I am going to ask you to repeat what I say. Ready? 'No ifs, ands, or buts.' Now you say that."** "Make sure to articulate clearly so that all the 's' endings are audible."	One point for precise repetition of sentence.
Command Instructions	**Command Scoring**
Present a piece of paper at the mid-line of the Participant. Say, **"Take the paper in your right hand, fold it in half and put it on the floor."** One repetition is permitted at the Participant's request, but the entire command must be repeated. The Participant is allowed to fold the paper using both hands.	**One point for each of the three segments:** 1. **Take in right hand** 2. **Fold in half** 3. **Place on floor** A total of three points
Reading Instructions	**Reading Scoring**
Present card with command. Say, **"Please read this and do what it says."** Then show the Participant the words CLOSE YOUR EYES that appear on the one side of the stimulus card. It is acceptable if the Participant reads the command aloud, but only give credit if he/she closes their eyes (without prompting).	Instruction must be followed completely to give one point.
Writing Instructions	**Writing Scoring**
The next task tests the Participant's ability to write a sentence. Give the Participant a blank piece of paper and a pen or pencil and say, **"Please write a sentence."** If he or she does not response, say, "Write about the weather."	One point for any complete sentence even if not about weather. Grammar, spelling and punctuation are not scored, but the Participant must write a sentence which contains a subject and a verb and is sensible. If it is illegible, ask the Participant to read it aloud for scoring. A sentence with an implied subject (e.g., "close the door") is acceptable.
Construction Instructions	**Construction Scoring**
The drawing task assesses the Participant's visuospatial ability. Turn over the paper on which the individual previously wrote a sentence, and place it in front of him or her so that the blank side is up. Then place the stimulus card showing the interlocking pentagons design next to the blank paper, and say, **"Please copy this design."**	The design should be two intersecting pentagons (i.e., five-sided designs). The intersection should result in a four-sided figure. All ten angles must be present and two must intersect.
Do not allow erasures. If the Participant appears dissatisfied with his/her drawing or requests a second attempt, allow the Participant to redraw the figure. Clearly label the first and second attempt. The best drawing should be scored.	

REMINDER: MMSE TOTAL SCORE WILL AUTOMATICALLY BE CALCULATED ON THE ELECTRONIC CASE REPORT FORM BASE D ON THE ITEM LEVEL DATA ENTERED

MONTREAL COGNITIVE ASSESSMENT (MOCA)

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

Description

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

Use a check mark on the worksheet to indicate correct items. The EDC will ask for each item to be entered as correct or incorrect.

Record verbatim responses so that scoring can be confirmed by the clinical monitor.

IMPORTANT

Use the ADNI-adapted worksheet and ADNI administration and scoring procedures provided here rather than instructions provided by the instrument author. ADNI scoring and test administration differs slightly from the published instrument. Rather than calculating a total score, please enter the item level data as specified on the worksheet and ECRF.

1. Alternating Trail Making Administration:
Instruct the Participant: "Please draw a line, going from a number to a letter in ascending order. Begin here [point to (1)] and draw a line from 1 then to A then to 2 and so on. End here [point to (E)]."

Alternating Trail Making Scoring:

Mark as correct if the Participant successfully draws the following pattern**:**

1 - A - 2 - B -3 - C - 4 - D - 5 - E, without drawing any lines that cross.

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

2. Visuoconstructional Skills (Cube) Administration:
For Cube and Clock, the Participant may be allowed to use an area other than those provided on the MoCA test sheet to reproduce the items (e.g., an additional blank page, with Participant ID and visit date). The first drawing is the one to use and score. If the participant, however, spontaneously insists on doing it again (i.e. self corrects), then the 'self-corrected' version should be used for scoring. **Participants should never be told to try a second time to see if they can do better**.

Pointing to the cube, say: "Copy this drawing as accurately as you can, in the space below."

Visuoconstructional Skills (Cube) Scoring:

A correctly executed drawing must meet each criteria:

Drawing must be three-dimensional

All lines are drawn

No line is added

Lines are relatively parallel and their length is similar (rectangular prisms are accepted) Place a checkmark on the worksheet next to the cube drawing task if all criteria are met.

3. Visuoconstructional Skills (Clock) Administration:
A separate blank piece of paper may be used for the MoCA Clock drawing. **Indicate the right third of the space and give the following instructions: "Draw a clock. Put in all the numbers and set the time to 10 after 11.**"

Please note that Clock Draw and Copy is repeated again separately in the DOD ADNI battery on a separate piece of paper.

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

Visuoconstructional Skills (Clock) Scoring:

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

Contour: The clock face must be a circle with only minor distortion acceptable (*e.g.,* slight imperfection on closing the circle).

Numbers: All clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour.

Hands: There must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centered within the clock face with their junction close to the clock center.

The first clock drawing is the one to use and score. If the participant, however, spontaneously insists on doing it again (i.e. self corrects), then the 'self-corrected' version should be used for scoring. **Participants should never be told to try a second time to see if they can do better.**

4. Naming Task Administration:
Beginning on the left, point to each figure and say: "Tell me the name of this animal".

Naming Task Scoring:

Indicate each item is correct with a checkmark:

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

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

> Mark a check in the allocated space for each word the Participant ***CORRECTLY*** produces on this first trial.

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

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

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

Memory Task Scoring:

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

6. Attention Task Administration:
Digit Span Forward

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

Scoring: Place a checkmark on the worksheet for each sequence correctly repeated

Digit Span Backward

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

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

Vigilance - Letters and Tapping:

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

Circle any incorrect responses on the worksheet.

Scoring: Record the **NUMBER OF ERRORS** made (*i.e.*, either a tap on a wrong letter, or failure to tap on an A).

Vigilance - Serial 7s

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

Give this instruction twice if necessary.

Scoring: Record Participant's verbatim response. If a Participant makes an error on the first subtraction, but then correctly subtracts 7 from that number, the second subtraction would be considered a correct response. Place a checkmark next to each correct subtraction.

7. Sentence Repetition Administration:

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

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

Sentence Repetition Scoring:

A checkmark is given for each sentence correctly repeated. **REPETITION MUST BE EXACT**.

Be alert for errors that are omissions (*e.g.*, omitting "only", "always") and substitutions/ additions (*e.g.*, "John is the one who helped today;" substituting "hides" for "hid", altering plurals, are all **not** correct).

8. Verbal Fluency Administration:

Use the separate page provided in the worksheet packet to record the *ver*batim responses for this test.

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

Any duplication of words (perseverations) should not be counted as correct words.

If a Participant begins to say proper nouns or numbers you should quickly inform the Participant that proper nouns or numbers cannot be used during the task.

Verbal Fluency Scoring:

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

9. Abstraction Administration:
Ask the Participant to explain what each pair of words has in common, starting with the example: **"Tell me how an orange and a banana are alike".**

If the Participant answers in a concrete manner, then say only one additional time: **"Tell me another way in which those items are alike".**

If the Participant does not give the appropriate response (fruit), say, **"Yes, and they are also both fruit."** Do not give any additional instructions or clarification.

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

Do not give any additional instructions or prompts. **Record the Participant's verbatim response.**

Abstraction Scoring:

<u>The following responses are considered correct:</u>

Train-bicycle = means of transportation, means of travelling, you take trips in both.

Ruler-watch = measuring instruments, used to measure.

<u>Examples of incorrect responses</u>:

Train-bicycle = they have wheels.

Ruler-watch = they have number

10. Delayed Recall Administration:
Give the following instruction: **"I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember."**

Give a checkmark for each of the words correctly recalled spontaneously without any cues.

For any word not free recalled, prompt the subject with the semantic category cue provided below.

If the Participant does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, **"Which of the following words do you think it was, NOSE, FACE, or HAND?"**

Make a check mark (√) in the allocated space if the Participant remembered the word with the help of a category or multiple-choice cue.

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

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

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

11. Orientation Task Administration:
Give the following instructions: ***"Tell me the date today."***

If the Participant does not give a complete answer, then prompt accordingly by saying: **"Tell me the [year, month, exact date, and day of the week]."**

Then say: "Now, tell me the name of this place, and which city it is in."

Orientation Task Scoring:

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

THE MOCA TOTAL SCORE IS NOT CALCULATED FOR DOD ADNI.

REY AUDITORY VERBAL LEARNING TEST (AVLT)

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

Description

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

Trial II – V Administration

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

List B Administration

Immediately after the fifth learning trial, the examiner says, **"Now I'm going to read a second list of words. Listen carefully, for when I stop you are to repeat back as many words as you can remember. It doesn't matter in what order you repeat them, just try to remember as many as you can."** Immediately after the words are read on each trial, the Participant recalls as many as possible and these are recorded by the examiner.

Trial VI Administration

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

30 Minute Delay Administration

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

Scoring

For each trial, record verbatim responses. Correct responses are defined as stimulus words recalled correctly by the study participant.

PLEASE NOTE: PLURALIZATION OF AN ACTUAL STIMULUS WORD IS COUNTED AS CORRECT. SINGULARIZATION OF AN ACTUAL STIMULUS WORD IS ALSO COUNTED AS CORRECT.

Intrusions are defined as any non-stimulus word (i.e. a word that is not on the list) recalled by the study participant. If a subject repeats either an intrusion or correct stimulus word, this is considered a perseveration. The first time a subject recalls a stimulus word it is counted as correct. If later, in the same trial, the same stimulus word is recalled, the second recall is a perseveration. With non-stimulus words, it is considered an intrusion the first time the subject recalls the word and if the same non-stimulus word is recalled again (in the same trial), it is counted as a perseveration.

Total correct and total intrusions are captured on the worksheet and on the eCRF. Total perseverations are not captured.

Recognition Administration

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

TRAIL MAKING 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 neuropsychologi- cal tests. New York: Oxford University Press; 1998.

Description

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

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

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

Administration Instructions:

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

> ***"There are numbers in circles on this page. Please take the pencil and draw a line from one number to the next, in order. Start at 1*** (point to the number)***,then go to two*** (point to the number)***,then go to three*** (point to the number) ***and so on. Please try not to lift the pencil as you move from one number to the next. Work as quickly as you can."***

If the Participant makes an error, mark through the line and go back to the point at which the error was made and say, for example:

> ***"You were at number two. What is the next number?"***

Wait for the Participant's response and say:

> ***"Please start here and continue."***

If the Participant completes the sample correctly, go to Test A. Repeat the instructions given for the sample. Start timing as soon as the instruction is given to begin. Stop timing when Trail is completed, or stop Participant when maximum time is reached. Allow a maximum of 150 seconds for the test.

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

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

If the Participant makes an error, mark through the line and go back to the point at which the error was made and say, for example:

> ***"You were at number two. What is the next letter?"***

Wait for the Participant's response and say:

> ***"Please start here and continue."***

If the Participant completes the sample correctly, go to Test B. Repeat the instructions given for the sample. Start timing as soon as the instruction is given to begin. Stop timing when trail is completed or stop Participant when maximum time is reached. Allow a maximum of 300 seconds for the test.

Scoring:

Record the total number of seconds to complete Part A, up to a maximum of 150 seconds. If the Participant is not finished by 150 seconds, the score is 150.

Record the total number of seconds to complete Part B, up to a maximum of 300 seconds. If the Participant is not finished by 300 seconds, the score is 300.

For both Part A and Part B, record errors of commission and omission as described below:

‘**Errors of commission’** are defined as errors occurring when the Participant connects two circles in the incorrect sequence. Each time this occurs, one error of commission is scored.

‘Errors of omission’ are defined as errors occurring because the Participant failed to draw a connecting line to a given circle in the correct sequence. This only occurs when the Participant is very slow and does not complete the task in the time allotted.

One incorrectly sequenced number/letter may, in rare instances, be counted as both an error of commission and an error of omission (e.g., if the Participant incorrectly draws a line to the letter ‘K’, but then never makes it back to that letter in the correct sequence).

If it is clear that the Participant intended to touch a circle but barely missed it, do not count it as an omission. However, caution the Participant to touch circles when you first observe this.

If the Participant passes through another circle while clearly on the way to the next circle in the sequence, caution to avoid touching circles other than the ones intended, and make a note of what occurred on the raw data form, but do not count as an error of commission.

The Participant may be unable to complete this test due to physical problems (e.g., tremor, dystonia). In that event, indicate the reason for incomplete data (i.e., physical problem, other problem, cognitive/behavioral problem, refusal) by completing an additional comment form online, referencing the test not administered and reason.

CHAPTER 16

GLOBAL, FUNCTIONAL, AND BEHAVIORAL ASSESSMENTS

CLINICAL DEMENTIA RATING (CDR) VERSIONS

CDR Version 1- Full interview with informant and participant

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

CDR Version 2- Full interview with only informant

Used in cases where the interview is being conducted over the phone in replace of the in person clinic visit, as CDR version 1 should NOT be used for telephone interviews.

Or in cases when a standard in clinic study visit is being conducted but the participant is unable to participate in the interview.

CDR Version 3- Abbreviated interview with only informant

Limited interview that should only be used if the informant refuses the full interview.

This version is a very brief questionnaire.

CDR Version 4- Full interview with only participant

If the study participant doesn't have a study partner / informant this version should be used when conducting the CDR interview.

All four versions of the CDR interview are able to determine a global CDR score.

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

CLINICAL DEMENTIA RATING (CDR)

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

The scores acquired from the CDR are key Inclusion Criteria and are critical for ruling out the presence of cognitive impairment at enrollment. The CDR is conducted at Screening and the Month 12 Follow Up visit.

CDR Rater

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

Anyone administering the CDR must be certified. Certification is required every five years and can be done online through the Washington University website:

http://alzheimer.wustl.edu/cdr/Application/Step1.htm

A certificate is sent to the rater upon completion. Please ensure to email a copy of the certificate to **adcs-clinops@ucsd.edu** or fax to **(858) 246-1415**.

THE PERSON ADMINISTERING THE CDR SHOULD NOT ALSO ADMINISTER THE ADAS-COG DURING A SINGLE CLINIC VISIT.

Instructions

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

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

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

Use all information and make the best judgment. Score each category (M, O, JPS, CA, HH, PC) as independently as possible.

Mark in only one box, rating impairment as decline from the person's usual level due to cognitive loss alone, not impairment due to other factors, such as physical handicap, depression, or personality change.

Occasionally the evidence is ambiguous and the clinician's best judgment is that a category could be rated in either one of the two adjacent boxes, such as mild (1) or moderate (2) impairment. In that situation, the standardized procedure is to check the box of greater impairment.

Global CDR Score

The eCRF will automatically calculate the global CDR score based on the assigned box scores, upon submission of the eCRF.

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

participant is rated according to the general dementia. Supply evidence of non-language cognitive function.

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

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

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

CDR = Global Box Score

M = Memory Box Score

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

When M = 0.5, CDR = 1 if at least three of the other categories are scored 1 or greater.

If M = 0.5, CDR cannot be 0; it can only be 0.5 or 1.

If M = 0, CDR = 0 unless there is impairment (0.5 or greater) in two or more secondary categories, in which case CDR = 0.5.

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

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

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

FOR MORE INFORMATION ON THE SCORING RULES, PLEASE ACCESS THE WASHINGTON UNIVERSITY CDR WEB PAGE: HTTP://WWW.BIOSTAT.WUSTL.EDU/ADRC/

Sum of Boxes CDR Score

The eCRF will automatically calculate the CDR Sum of Boxes (SOB) score based on the assigned box scores, upon submission of the eCRF.

EVERYDAY COGNITION (ECOG)

Farias ST et. al. The measurement of everyday cognition (ECog): scale development and psychometric properties. Neuropsychology. 2008 Jul;22(4):531-44.

The ECog is a brief questionnaire assessing the participant's capability to perform normal everyday tasks, in comparison to activity levels 10 years prior, on a 5-point scale. Three domains are assessed: Memory, Language and Executive Functioning. The ECog is conducted at Baseline and the Month 12 Follow Up visit by both the participant and study partner (if applicable).

Participants and their study partners will independently complete a separate questionnaire.

If no study partner is available, conduct the Everyday Cognition – Participant interview only.

Check all ECog forms before the end of the visit to ensure they are completed fully and, if necessary, direct the participant or study partner to complete the form.

If the reading level of either the participant or the study partner is low, you may read the items out loud and record their ratings.

Instructions

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

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

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

ECOG Score

You do not need to calculate total score, as the eCRF will not capture total score for this assessment.

GERIATRIC DEPRESSION SCALE (GDS)

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

The Geriatric Depression Scale is a brief questionnaire that consists of 15 questions and is designed to identify symptoms of depression in the elderly. The GDS is conducted at screening, but is not used as an inclusion criteria for the DOD ADNI study. Site staff should administer the GDS as a direct interview with the participant only, *NOT* the study partner.

Instructions

Say, **"In the next part of this interview, I will ask you questions about your feelings. Some of the questions I will ask you may not apply, and some may make you feel uncomfortable. For each question, answer 'yes' or 'no', depending on how you have been feeling in the past week, including today."**

Answers in **BOLD CAPS** suggest depression. Although differing sensitivities and specificities have been obtained across studies, for clinical purposes a score >5 points is suggestive of depression and should warrant a follow-up interview. Scores >10 are almost always depression.

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

If the Participant does not comprehend the first 5 questions adequately enough to give answers, then check the box that states, "Participant is unable to complete the GDS based on the clinician's best judgment."

Choose the best answer for how you have felt over the past week:

yes or **NO**	**1.** Are you basically satisfied with your life?
YES or no	**2.** Have you dropped many of your activities and interests?
YES or no	**3**. Do you feel that your life is empty?
YES or no	**4.** Do you often get bored?
yes or **NO**	**5.** Are you in good spirits most of the time?
YES or no	**6.** Are you afraid that something bad is going to happen to you?
yes or **NO**	**7.** Do you feel happy most of the time?
YES or no	**8.** Do you often feel helpless?
YES or no	**9.** Do you prefer to stay at home, rather than going out and doing new things?
YES or no	**10.** Do you feel you have more problems with memory than most?
yes or **NO**	**11.** Do you think it is wonderful to be alive now?
YES or no	**12.** Do you feel pretty worthless the way you are now?
yes or **NO**	**13.** Do you feel full of energy?
YES or no	**14.** Do you feel that your situation is hopeless?
YES or no	**15.** Do you think that most people are better off than you are?

IF THE PARTICIPANT SAYS HE/SHE CANNOT CHOOSE AN ANSWER, ASK HIM/HER TO SELECT THE BEST RESPONSE.

GDS Score

Individual responses are only captured on the eCRF. You do not need to calculate total score for the GDS. The total score is calculated automatically in the data system and will not be displayed on the eCRF.

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.

Based on an interview with a study companion or qualified partner, the FAQ measures the participant's ability to carry out ten complex activities of daily living. The interview is conducted at Baseline and the Month 12 Follow Up visit.

Instructions

The study partner (if applicable) should be queried based on the participant's level of difficulty on each item in the past four weeks. **If there is no study partner available, the interview should not be conducted and the first question on the eCRF and worksheet 'was this assessment completed by the study partner' should be documented as 'not applicable - no study partner'.**

FAQ Score

Individual responses are only captured on the eCRF. You do not need to calculate total score for the FAQ. The total score is calculated automatically in the data system and will not be displayed on the eCRF.

MODIFIED HACHINSKI

Rosen, Modification of Hachinski Ischemic Score (Ann Neurol 7: 486-488, 1980)

Instructions

Complete the Modified Hachinski using information obtained from the medical history, physical and neurological exams and/or medical records. Indicate if a characteristic is present by checking 'present' or 'absent'.

Clarification of Test Items

1. **Abrupt Onset of Cognitive Impairment:** Reported rapid onset with acknowledgement that gradual changes may have also occurred.
2. **Stepwise Deterioration of Dementia:** Cognitive decline, aside from onset, noted to occur over days and followed by plateaus.
3. **Somatic Complaints:** *e.g.*, headache; tinnitus; chest pain; malaise.

4. **Emotional Incontinence:** Occasional displays of intense emotional expression such as crying, beyond that which would be considered appropriate to a given situation.
5. **History of Hypertension:** History of blood pressure of >150/95 for 6 months.
6. **History of Strokes:** Hemiparesis, aphasia.
7. **Focal Neurologic Symptoms:** Transient dizziness; diplopia lasting hours; seizures.
8. **Focal Neurologic Signs:** Unequal deep tendon reflexes, extensor plantar response, nystagmus.

Modified Hachinski Total Score

The eCRF will automatically calculate the modified hachinski total score as data is entered. The participant must have a total score of 4 or less at the screening visit to be included in the study.

If "history of stroke" is checked, participant is excluded from the study unless an exception is granted by the Project Director

NEUROPSYCHIATRIC INVENTORY (NPI)

The purpose of the Neuropsychiatric Inventory (NPI) is to obtain information on the presence of psychopathology in participants with brain disorders. The NPI was developed for application to participants with Alzheimer's disease and other dementias, but it may be useful in the assessment of behavioral changes in other conditions. The NPI is to be administered by a site clinician. Certification is not required.

Twelve behavioral areas are included in the NPI:

Delusions
Hallucinations
Agitation / Aggression
Depression
Anxiety
Elation / Euphoria
Apathy / Indifferent
Disinhibition
Irritability
Aberrant motor behavior
Sleep / Night-time behavior
Appetite and eating changes

The NPI is based on responses from a study partner, preferably one living with the participant. The interview is best conducted with the study partner in the absence of the participant to facilitate an open discussion of behaviors that may be difficult to describe with the participant present. The interview is conducted at Baseline and the Month 12 Follow Up visit.

If there is no study partner available, the interview should not be conducted and the first question on the eCRF and worksheet 'was this assessment completed by the study partner' should be documented as 'not applicable - no study partner'.

Several points should be made when you introduce the NPI interview to the study partner:

Purpose of the interview

Ratings – frequency, severity, distress (described below)

Answers apply to behaviors that are new since the onset of the disease and have been present for the past four weeks or other defined period

Questions usually can be answered with "yes" or "no" and responses should be brief

Questions should be asked exactly as written.

Clarification should be provided if the study partner does not understand the question.

Acceptable clarifications are restatements of the questions in alternate terms.

The questions pertain to changes in the participant's behavior that have appeared since the onset of the illness (i.e. PTSD or TBI):

Behaviors that have been present throughout the participant's life and have not changed in the course of the illness (i.e. PTSD or TBI) are not scored even if they are abnormal (e.g., anxiety, depression).

Behaviors that have been present throughout life but have changed since the illness are scored (e.g., the participant has always been apathetic but there has been a notable increase in apathy during the period of inquiry).

FOR ALL VISITS, ASK THE STUDY PARTNER TO INDICATE WHETHER THE PARTICIPANT BEHAVIORS OCCURRED DURING THE PREVIOUS 4 WEEKS. IF SO, USE THE FOLLOWING SCALES TO RATE THE FREQUENCY, SEVERITY, AND AMOUNT OF DISTRESS THE BEHAVIORS CAUSED THE CAREGIVER.

The SCREENING QUESTION is asked to determine if the behavioral change is **present or absent.** If the answer to the screening question is negative, mark NO and proceed to the next screening question without asking the subquestions.

If the answer to the screening question is positive or if there are any uncertainties in the study partner's response or inconsistencies between the response and other information known by the clinician (e.g., the study partner responds negatively to the euphoria screening question but the participant appears euphoric to the clinician), the category is marked YES and is explored in more depth with the subquestions.

If the subquestions confirm the screening question, the severity and frequency of the behavior are determined according to the criteria provided with each behavior. When

determining frequency and severity, use the behaviors identified by the subquestions as most aberrant.

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

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

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

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

If they provided information relevant to the behavioral domain but in different terms, the behavior should be scored for severity and frequency as usual.

If the original affirmative response was erroneous, leading to a failure to endorse any subquestions, then the behavior is changed to "NO" on the screen.

Some sections, such as the questions pertaining to appetite, are framed so as to capture whether there is an increase or decrease in the behavior (increased or decreased appetite or weight).

If the study partner answered "yes" to the first member of the paired question (such as has the participant's weight decreased?), do not ask the second question (has the participant's weight increased?) since the answer to the second question is contained in the answer to the first.

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

When determining **FREQUENCY**, say to the study partner:	"Now I want to find out how often these things [define using the description of the behaviors they noted as most problematic on the subquestions] occur." "Would you say that they occur less than once per week, about once per week, several times per week but not every day, or every day?"

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

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

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

> In each case, be sure that the study partner provides you with a definite answer as to the frequency and severity of the behaviors.
>
> Do not guess what you think the study partner would say based on your discussion.

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

Frequency Descriptions:
Less than once per week
About once per week
Several times per week
Daily or continuous

Severity Descriptions:
Mild
Moderate
Marked

This also saves the examiner from reiterating the alternatives with each question.

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

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

If the clinician or study partner believes that the questions are inappropriate, then the section should be marked NA (upper right corner of each section), and no further data are recorded for that section. Likewise, if the clinician feels that the responses are invalid (e.g., the study partner did not seem to understand the particular set of questions asked), NA should also be marked.

When each domain is completed and the study partner has completed the frequency and severity rating, you may want to ask the associated **CAREGIVER DISTRESS** question if your protocol includes the distress assessment.

To do this, ask the study partner how much, if any, “emotional or psychological” distress the behavior he or she just discussed causes him or her (the study partner / caregiver).

The study partners must rate their own distress on a five point scale:

0	Not at all
1	minimally
2	mildly
3	moderately
4	severely
5	very severely or extremely

The distress scale of this instrument was developed by Daniel Kaufer, M.D.

NPI Score

Total score does not need to be calculated by the site for the DOD ADNI study. It will automatically be calculated based on the item level responses entered. Total score is not visible on the eCRF.

FREQUENCY is rated as:

1.	Occasionally	less than once per week
2.	Often	about once per week
3.	Frequently	several times per week but less than every day
4.	Very frequently	daily or essentially continuously present

SEVERITY is rated as:

1.	Mild	produces little distress in the participant
2.	Moderate	more disturbing to the participant and are distressing and disruptive, but can be redirected by the study partner
3.	Severe	very disruptive and are a major source of behavioral disruption

DISTRESS is scored as:

0.	not at all
1.	minimally

2.	mildly
3.	moderately
4.	severely
5.	very severely or extremely

THUS, FOR EACH BEHAVIORAL DOMAIN THERE ARE FOUR SCORES:

1.	Frequency
2.	Severity
3.	Total (frequency x severity)
4.	Caregiver distress

The score for each domain is:
DOMAIN SCORE = FREQUENCY x SEVERITY

A **NPI TOTAL SCORE** can be calculated by adding all domain scores together.
The distress score is not included in the total NPI score.
Individual and total distress scores can be generated from the NPI.

Instructional Videotape

An instructional videotape demonstrating the use of the NPI is available through:

UCLA Alzheimer's Disease Center
Neuropsychiatric Institute
710 Westwood Plaza
Los Angeles, California 90095-1769

The cost of the videotape is $25 (subject to change).

NPI References

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994; 44: 2308-2314.

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