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

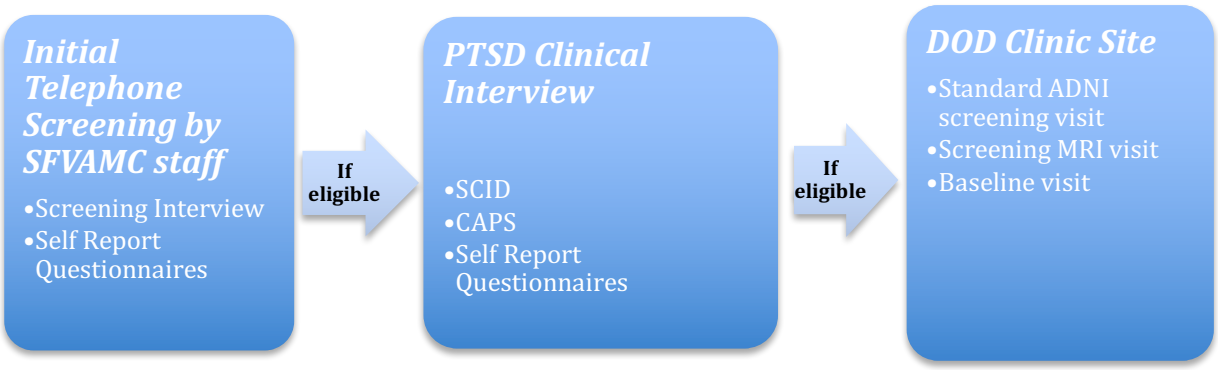
Derogatis, L. and L. Lazarus, SCL-90--R, Brief symptom inventory, and matching clinical rating scales, in The use of psychological testing for treatment planning and outcome assessment, M.E. Maruish, Editor. 1994, Lawrence Erlbaum Associates, Inc.: Hillsdale, NJ. p. 217-248

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

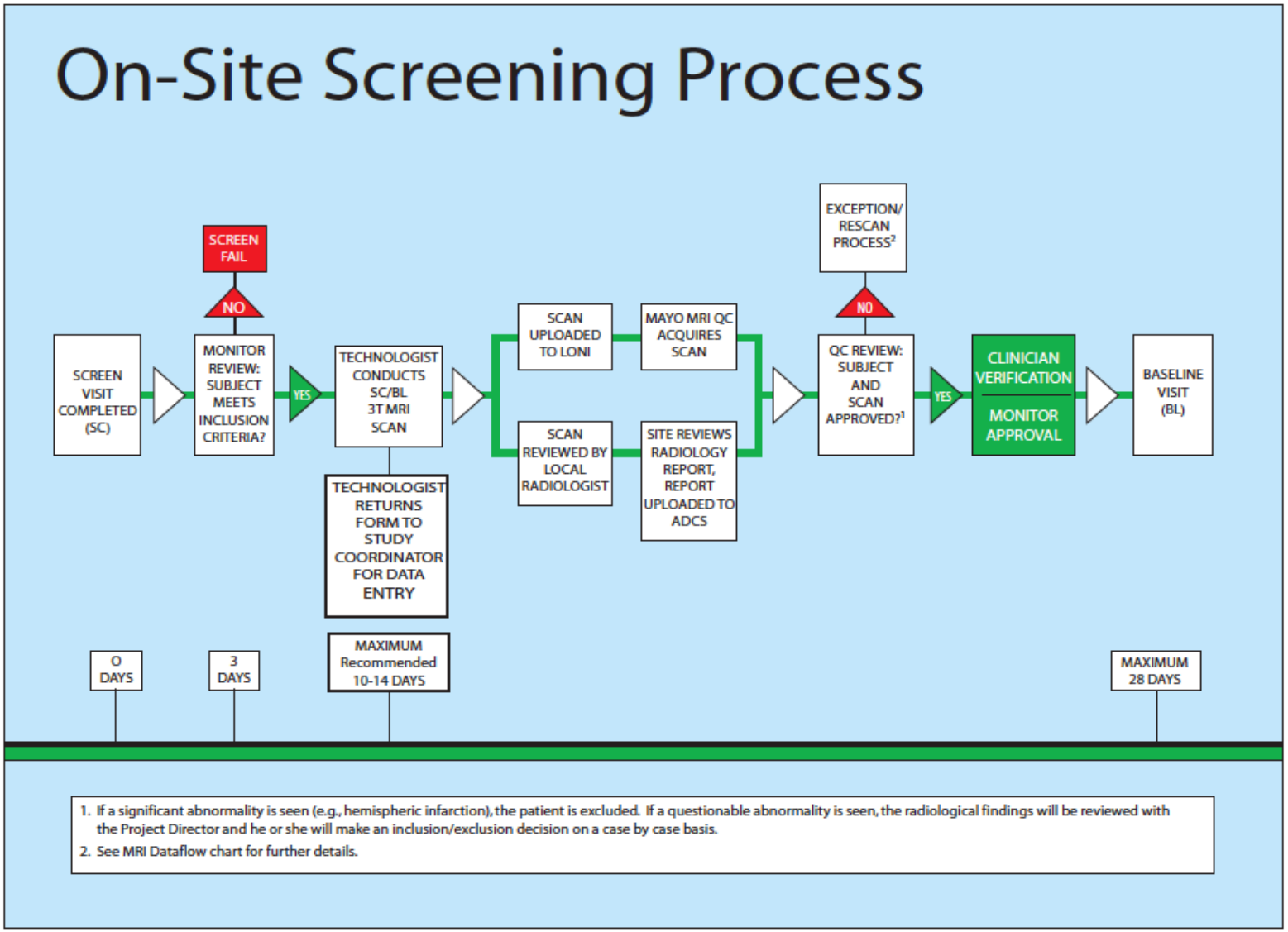
collected by SFVAMC during the pre-screen phase should be addressed at the point of screen to ensure the participant meets eligibility criteria.

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

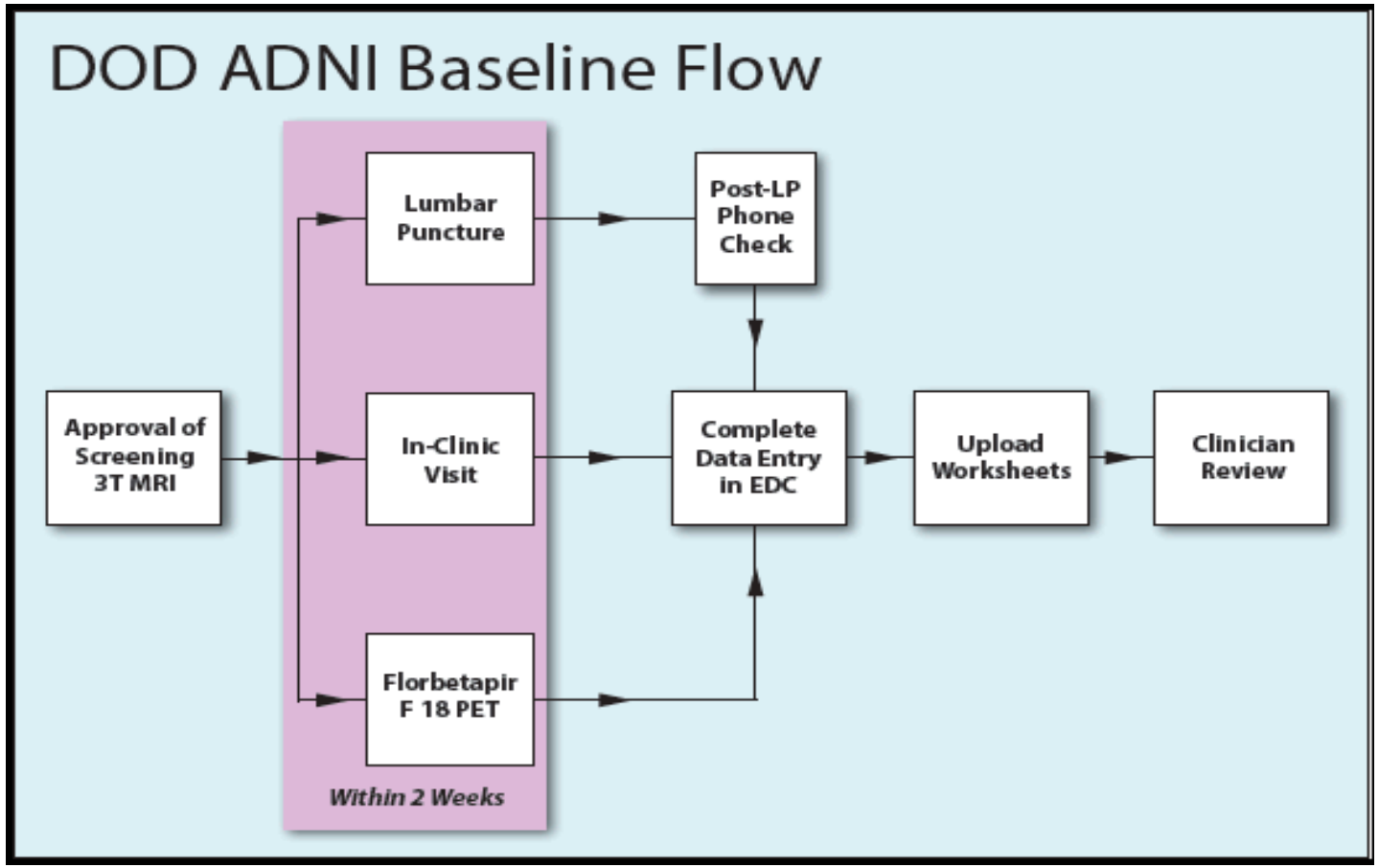
ADNI MRI QC (MRI Inclusion eCRF)

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

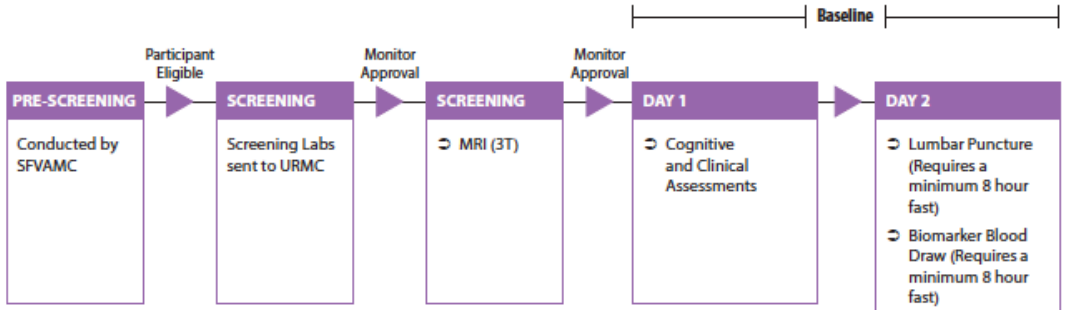
PRE AND POST FLORBETAPIR F 18 INJECTION VITALS WERE REQUIRED UNDER THE ORIGINAL PROTOCOL BUT ARE NO LONGER A REQUIREMENT AS OF AMENDMENT DATED MARCH 2013.

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

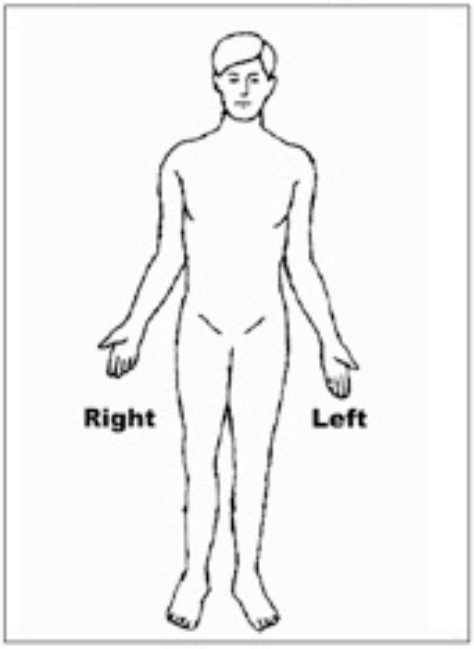
Please Inform MRI Center:

☐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

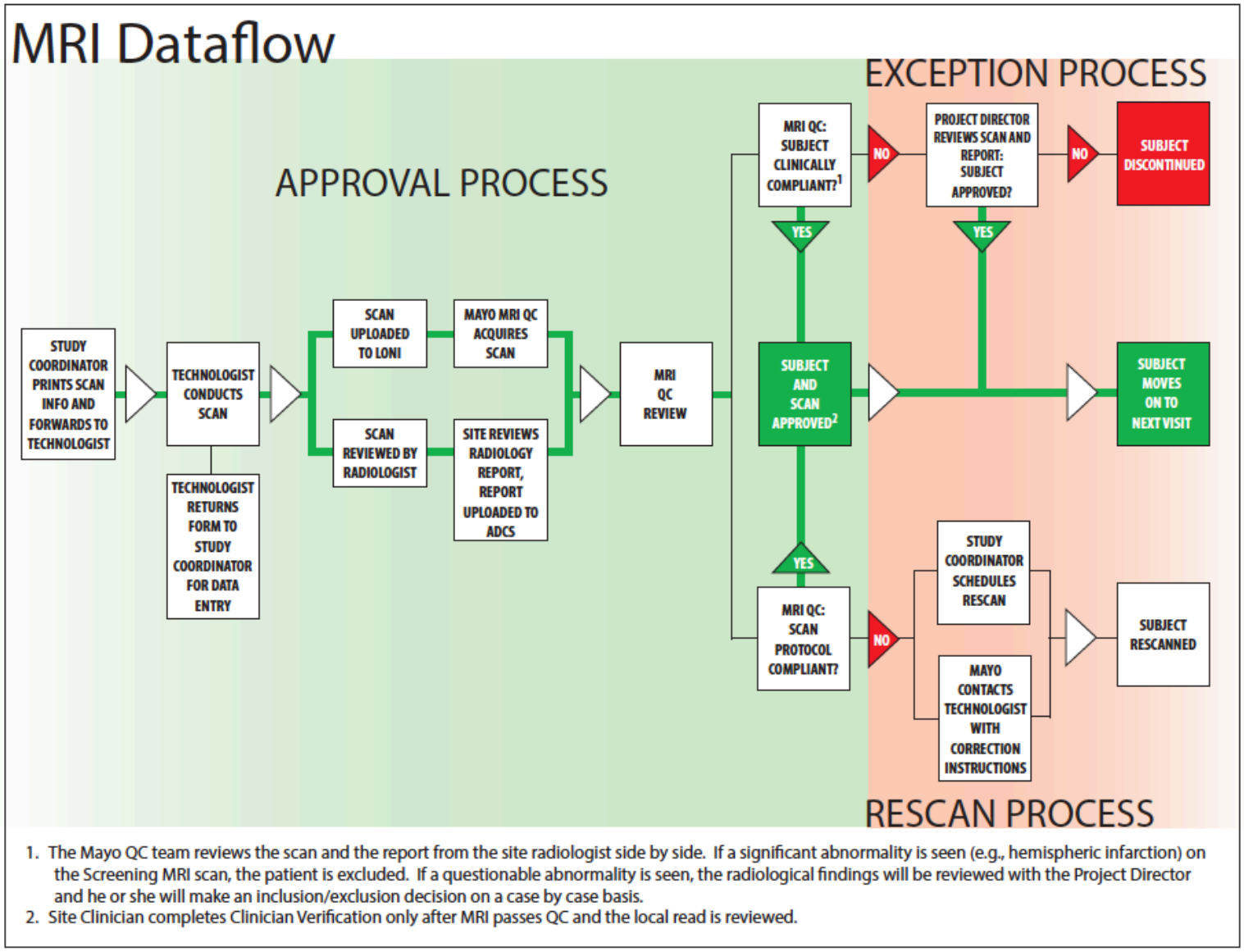
If a significant abnormality is seen (e.g. hemispheric infarction) on the screening MRI scan, the participant is excluded. In the event that a radiological finding that is not normal for age is identified by MRI QC, the site will be informed of this result by email. If a participant must be screen failed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

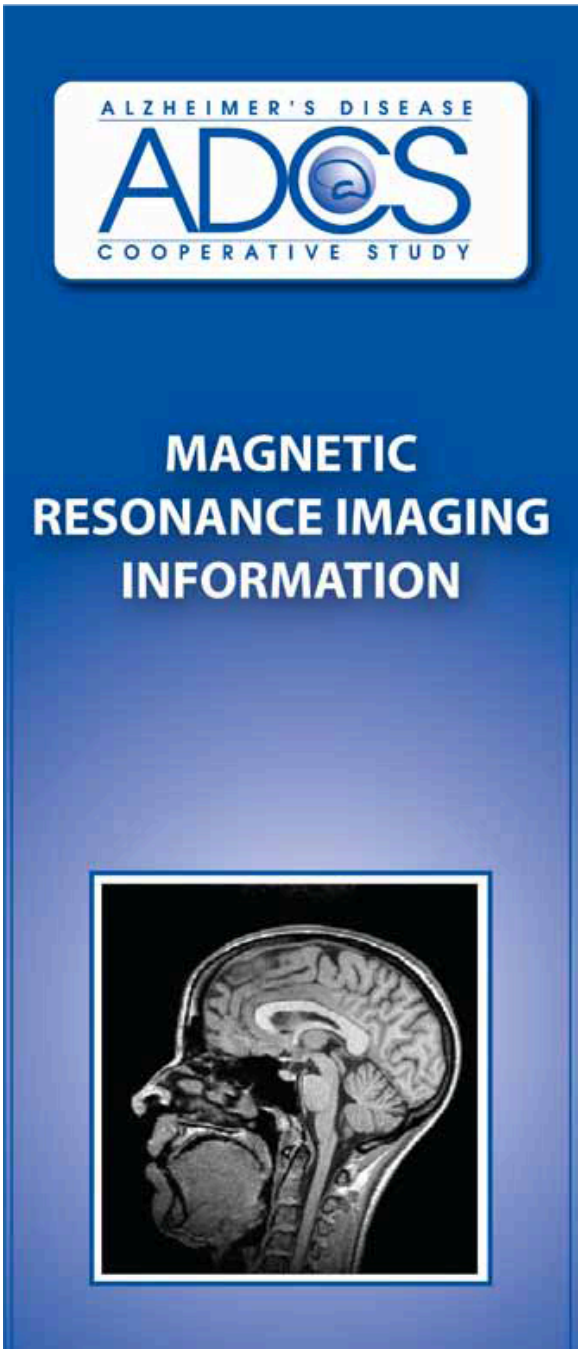
ARCHIVE PROCEDURES

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.

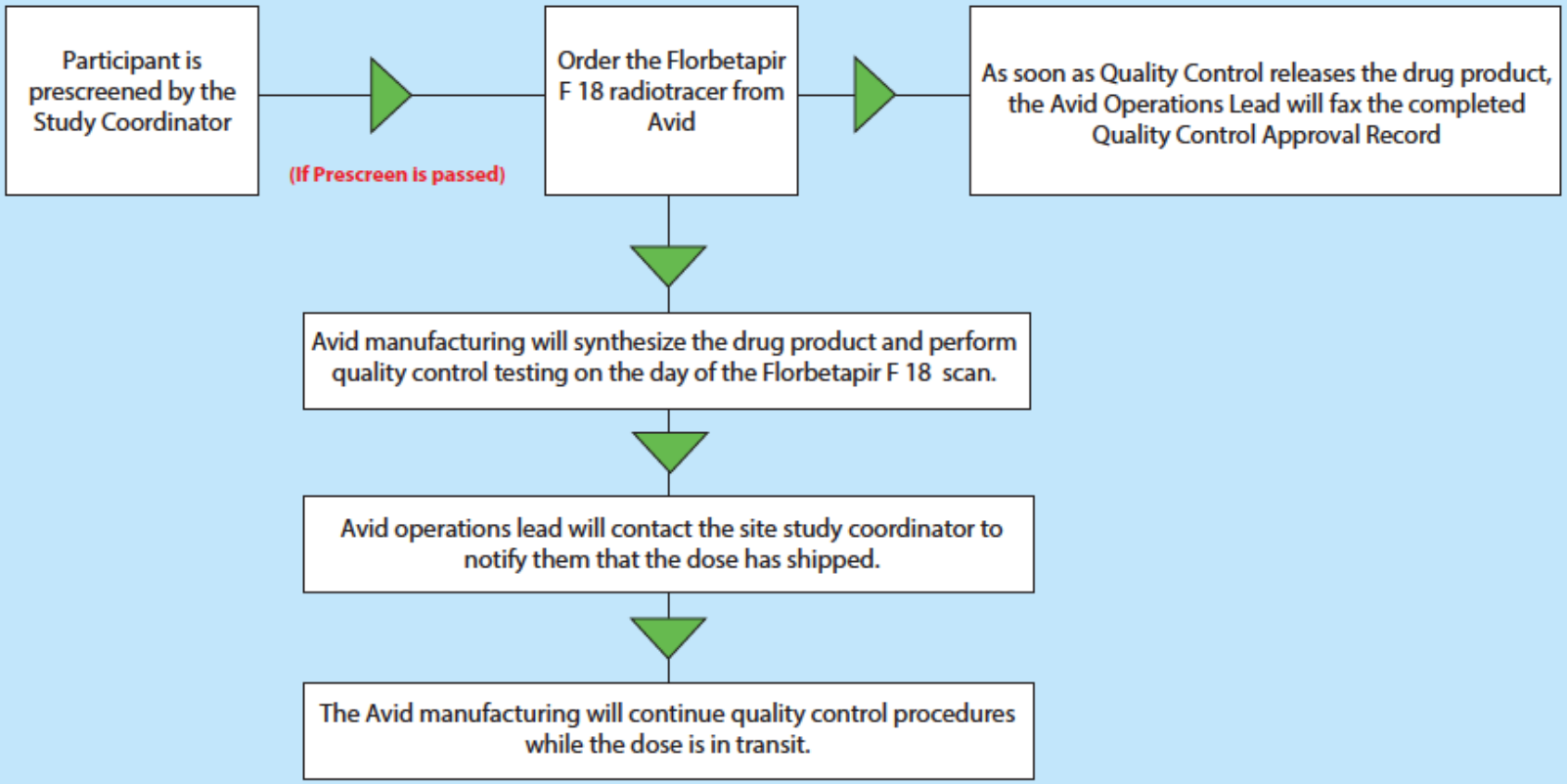
Changes to the scheduling or deviations from the Avid Clinical Supplies Guidance Document may be possible (e.g. scheduling a participant with only 3 days' notice), but if they are required, the site should contact Avid as soon as possible to work with the manufacturing team on the logistics.

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.

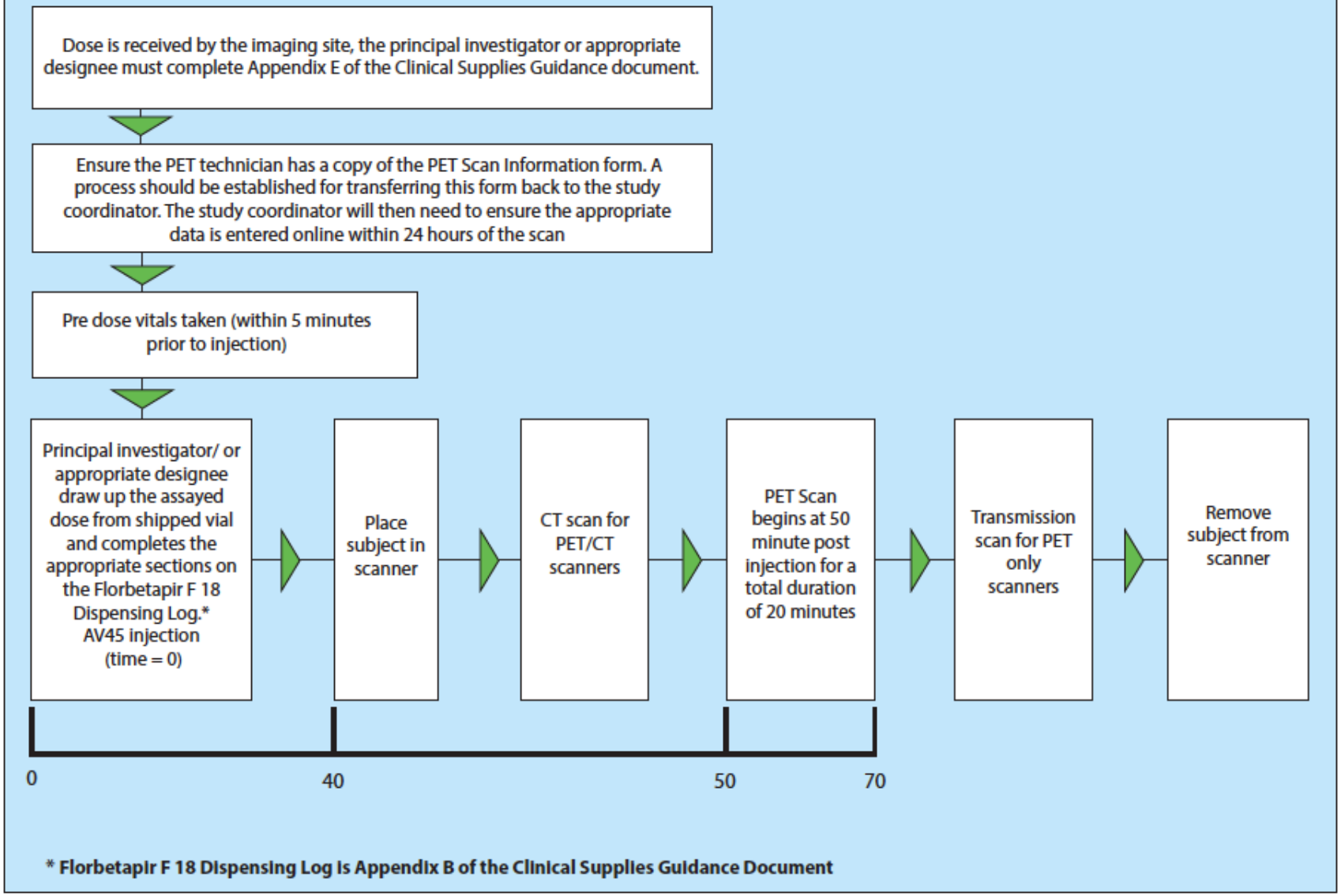
ON THE DAY OF EACH APPOINTMENT THE STUDY COORDINATOR SHOULD PHONE THE RADIOLOGY CENTER, CONFIRM THE APPOINTMENT, AND REMIND THE RADIOLOGIST TO UPLOAD THE PET SCAN TO LONI WITHIN 24 HOURS OF THE SCAN.

Prior to Florbetapir F 18 Scan



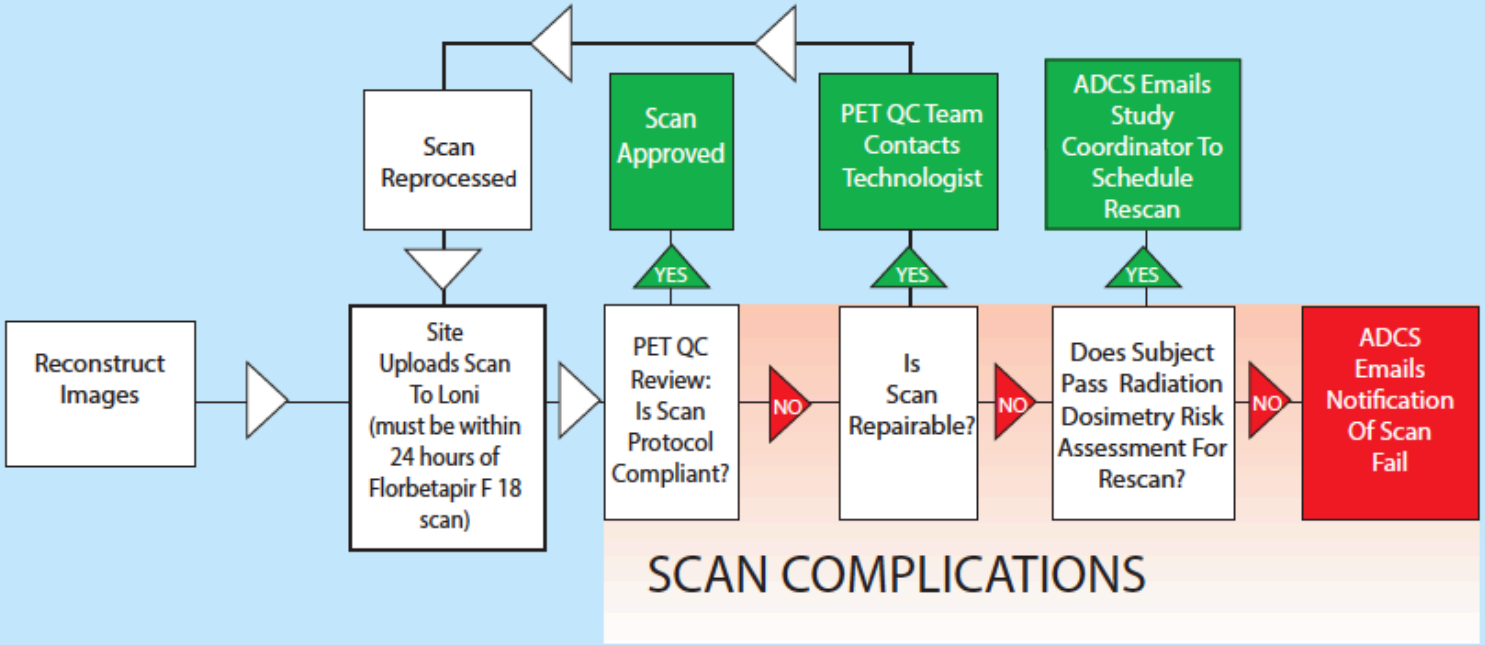
NOTE: Complete Appendix A (Avid Dose Request Form) of the Clinical Supplies Guidance Document located in the document repository when ordering the Florbetapir F 18 radiotracer.

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

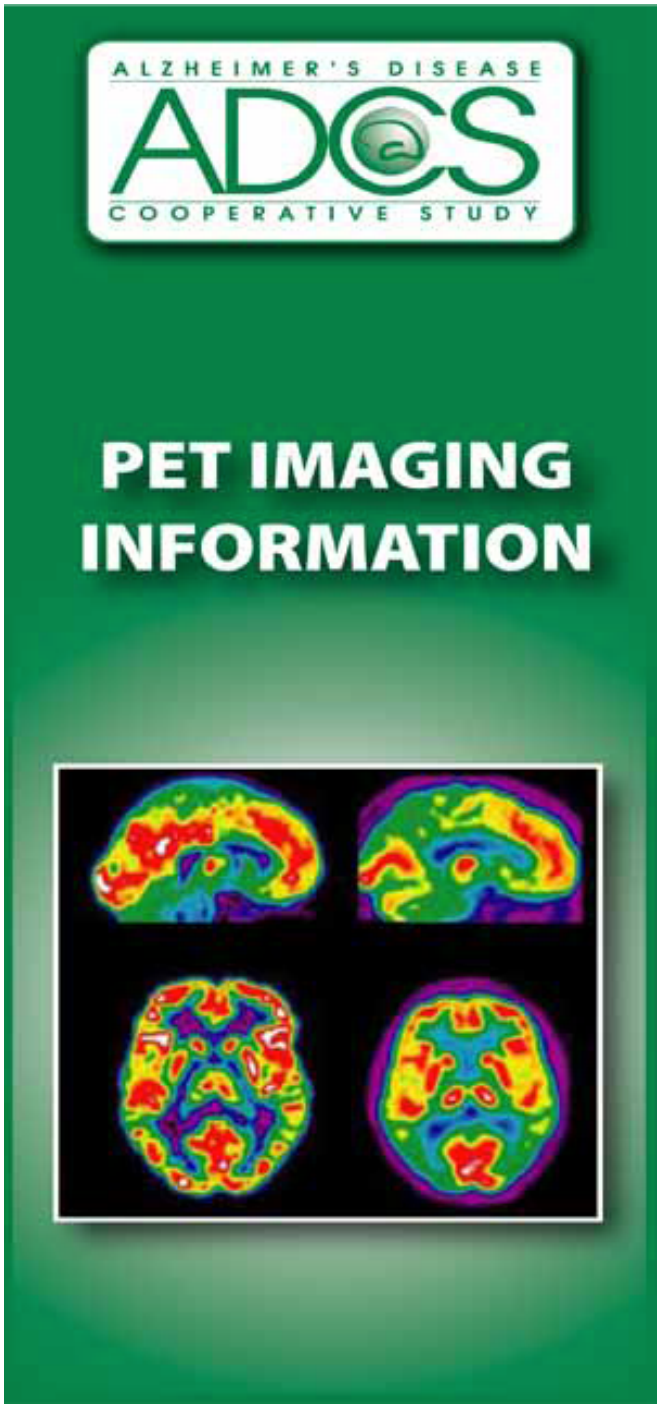
The PET pamphlet should be distributed to any participant undergoing a PET scan for the DOD ADNI study.

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

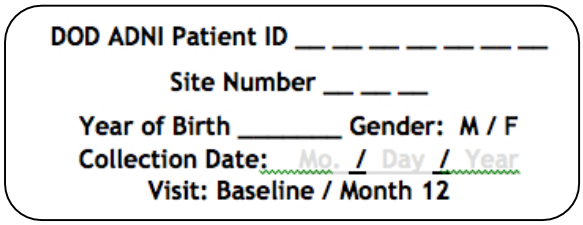
Please see URMC lab manual for sample amounts obtained with clinical labs at screening.

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.

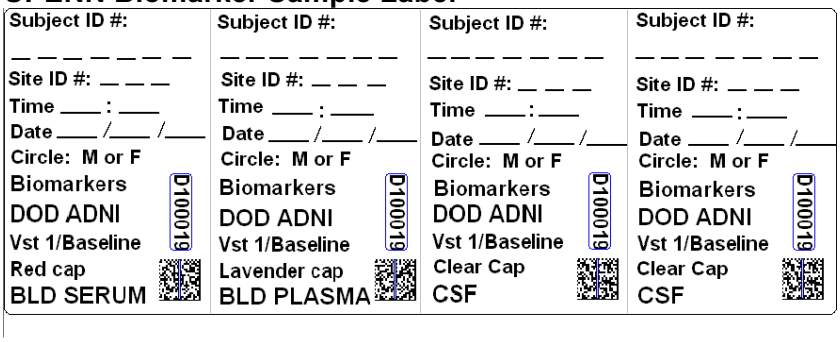
All genetic samples (ApoE, GWAS, RNA, Cell Immortalization, and Buffy Coat) must be identified using the NCRAD Sample Identification label provided by the ATRI.

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:

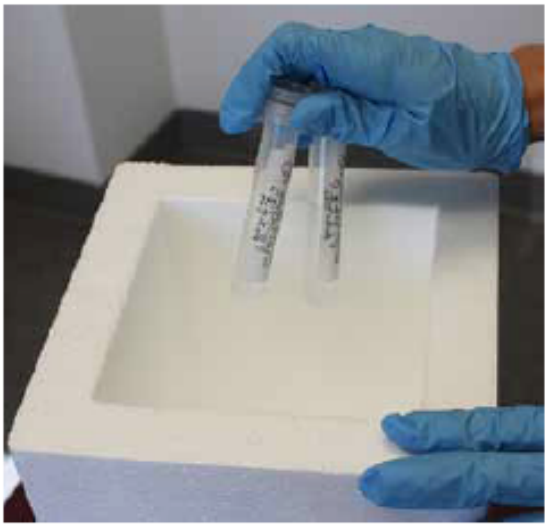
1. 13-mL polypropylene transfer tubes with colored screw caps (red screw-capped for transfer of serum; lavender screw-capped for transfer of plasma)
2. 10-mL, lavender top plastic Vacutainer blood tubes (for collection of blood for plasma samples)
3. 10-mL, plain red top plastic Vacutainer blood tubes (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.

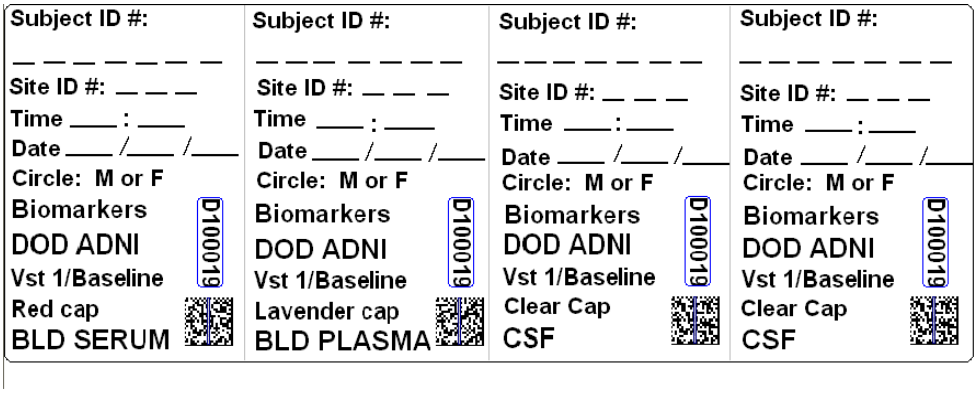
FASTING OVERNIGHT (MINIMUM 8 HOURS) IS REQUIRED FOR PLASMA, SERUM, AND CSF SAMPLE COLLECTION.

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.