

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN PA 4003

**EVALUATION OF THE ABILITY OF A NOVEL [¹⁸F] AMYLOID LIGAND ([¹⁸F]-AV-45) TO
DISTINGUISH PATIENTS WITH A CLINICAL DIAGNOSIS OF ALZHEIMER'S DISEASE
FROM COGNITIVELY NORMAL ELDERLY INDIVIDUALS**

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***PARTIAL PROTOCOL—CONTACT ACRIN
PROTOCOL DEVELOPMENT AND
REGULATORY COMPLIANCE FOR A
COMPLETE PROTOCOL***

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CONFIDENTIAL

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SCHEMA

ELIGIBILITY/REGISTRATION

People with Alzheimer's disease and normal cognitive control subjects ages 55 to 90 (inclusive) enrolled in the University of Pennsylvania's Alzheimer's Disease Center longitudinal study cohort.

Prior to the experimental portion of the study, potential participants will need to sign an informed consent form (see Appendix I) and undergo specific clinical assessments: medical history; physical examination; functional, behavioral, and mood dynamics; cognitive testing; clinical dementia rating; and baseline safety measures. The participant will also have to undergo an MRI scan. Lumbar puncture is encouraged, but optional.

IMAGING

SAME DAY

Two dynamic PET studies: the first using the [^{11}C]PIB amyloid imaging agent and, the second, using the experimental [^{18}F]-AV-45 amyloid imaging agent—separated by a minimum of 120 minutes from the injection of [^{11}C]PIB to the beginning of the [^{18}F]-AV-45 scan.

Safety assessment for [^{18}F]-AV-45 will comprise pre- and post-imaging assessments of vital signs (blood pressure and pulse).

OR

TWO DAYS

First Day: Dynamic PET study using the [^{11}C]PIB agent

ORDER CAN BE REVERSED

Second Day: Dynamic PET studies using the experimental [^{18}F]-AV-45 agent.

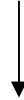
Safety assessment for [^{18}F]-AV-45 will comprise pre- and post-imaging assessments of vital signs (blood pressure and pulse).



FOLLOW-UP: SAME DAY IMAGING

The day following the completion of both of the two PET studies, the participant will be contacted by phone to assess status and any AEs for reporting purposes.

Additional follow-up may be needed to assess for resolution of any AEs.



FOLLOW-UP: TWO DAYS IMAGING

Each day following the completion of each of the two PET studies, the participant will be contacted by phone to assess status and any AEs for reporting purposes; if the participant undergoes the second PET scan on the day immediately after the first-day of imaging, the research staff will assess for AEs in person prior to the second PET scan.

Additional follow-up may be needed to assess for resolution of any AEs.

SPECIFIC HYPOTHESES

1. Individuals with a clinical diagnosis of probable Alzheimer's disease will have increased brain retention of [^{18}F]-AV-45 compared to cognitively normal elderly individuals.
2. There will be no clinically meaningful difference in the amyloid retention performance characteristics of [^{18}F]-AV-45 and [^{11}C]PIB.

SAMPLE SIZE

A total of 30 participants, 15 cognitively normal and 15 with the clinical diagnosis of probable Alzheimer's disease, will be recruited over 2 years.

1.0 ABSTRACT

This protocol for human research study is conducted according to US and international standards of Good Clinical Practice Guidelines (International Conference on Harmonisation [ICH] Guidelines), applicable government regulations (i.e. Code of Federal Regulations), and the American College of Radiology Imaging Network (ACRIN) research policies and procedures.

Alzheimer's disease is the predominant cause of late-life dementia. Neuritic amyloid plaques and neurofibrillary tangles, the hallmark pathologic lesions of Alzheimer's disease, are thought to develop before the symptoms of brain failure are clinically detectable. Imaging methods capable of detecting the presence of neuritic amyloid plaques should improve a clinician's ability to identify Alzheimer's disease during the earliest symptomatic phase. Currently the best studied amyloid imaging ligand is [^{11}C]PIB.¹ However, the 20-minute half-life of this compound limits its use in community-based evaluations. This study will evaluate the performance characteristics of a novel [^{18}F] amyloid detection ligand ([^{18}F]-AV-45) with respect to its ability to distinguish patients with clinically-diagnosed probable Alzheimer's disease from cognitively normal elderly subjects and to independently compare its diagnostic performance characteristics with the ability of [^{11}C]PIB to correctly categorize the same subjects. At the University of Pennsylvania, 15 patients with a clinical diagnosis of probable Alzheimer's disease and 15 cognitively normal elderly control subjects will receive both [^{18}F]-AV-45 and [^{11}C]PIB to compare the diagnostic performance characteristics of each amyloid ligand. In addition to clinical diagnostic category, ligand retention will be evaluated with respect to measures of symptom severity and cerebrospinal fluid levels of amyloid and tau.

2.0 BACKGROUND AND SIGNIFICANCE

Alzheimer's disease is the most common cause of dementia in the elderly, affecting more than 4 million people in the United States. However, diagnosis and treatment of the disease have been hampered by the absence of reliable noninvasive markers for the underlying pathology. Although consensus criteria have been proposed that allow diagnosis based on clinical presentation and history of comorbid conditions,^{2,3} evaluation of these criteria in autopsy-verified cases suggests that there is still room for improvement in diagnostic accuracy.^{4,5} Because of the emphasis on achieving a reliable diagnosis as early as possible in the symptomatic phase of the disease, recent suggested revisions to the clinical diagnostic criteria include the addition of laboratory markers to identify the presence of Alzheimer's disease pathology.⁶ A reliable biomarker might aid diagnosis by documenting the presence of disease-specific pathology, rather than simply excluding alternative pathologies. Additionally, a biomarker could be useful for following disease progression, evaluating the effects of therapy on disease progression, and identifying early (presymptomatic) patients at risk for developing Alzheimer's disease.⁷ The present study is designed as a preliminary evaluation of the potential of a novel [^{18}F]-labeled amyloid ligand, AV-45, that binds with high affinity to the amyloid- β (A β) pathology that constitutes amyloid plaques and, thus, has the potential to be an imaging biomarker for the presence of amyloid plaques in patients with Alzheimer's disease.

Although the etiology of Alzheimer's disease has not been definitively established, converging evidence suggests that the A β peptide may play an important role in the pathogenesis of the disease. Accumulation of A β fibrils in the form of amyloid plaques is one of the hallmarks of the disease and is a key component of the neuropathological criteria for autopsy-based confirmation of diagnosis.^{8,9} While the genetic contribution

to the initiation and rate of progression of Alzheimer's disease pathology remains poorly understood, mutations have been identified in the amyloid precursor protein gene on chromosome 21, presenilin 1 gene on chromosome 14, and presenilin 2 gene of chromosome 1 that produce an autosomal dominant form of the disease. Each results, either directly or indirectly, in an increased production or accumulation of specific forms of A β peptide leading to the formation of pathological aggregation of amyloid.^{10,11} Transgenic mice that express one or more of these mutant human genes also develop amyloid plaques and behavioral/cognitive deficits that are similar in some respects to those seen in Alzheimer's disease.¹²⁻¹⁴ Finally, experimental treatments that reduce A β peptide production or increase the clearance of A β from amyloid plaques have been successful in reversing behavioral deficits in these mice, and some of these treatments are now being tested in patients with Alzheimer's disease.¹³

A variety of biomarkers for amyloid plaque accumulation have been proposed.⁷ In contrast to techniques designed to indirectly estimate levels of brain amyloid plaques from A β levels in cerebrospinal fluid, imaging techniques utilizing radiolabeled positron emission tomography (PET) tracers that bind to the aggregated A β peptides in amyloid plaques have the potential to directly assess relative brain amyloid plaque pathology. To date, the most successful imaging approach has utilized the [¹¹C]-labeled PET tracer 6-OH-BTA-1 (2-(4'-methylaminophenyl)-6-hydroxybenzothiazole) also known as Pittsburgh compound B, or PIB,¹⁵ with about 50 published papers describing the *in-vitro* and *in-vivo* properties of this radioligand. Preliminary studies show that higher levels of radioactivity can be imaged in the cortex of patients with Alzheimer's disease than in the cortex of healthy elderly controls, presumably reflecting the elevated accumulation of A β pathology and consequent binding of PIB in the cortex of patients with Alzheimer's disease.¹⁶

[¹⁸F]-AV-45

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3.0 STUDY OBJECTIVES

3.1 Hypotheses

- 3.1.1** Individuals with a clinical diagnosis of probable Alzheimer's disease will have increased brain retention of [^{18}F]-AV-45 compared to cognitively normal elderly individuals.

- 3.1.2** There will be no clinically meaningful difference in the amyloid retention performance characteristics of [^{18}F]-AV-45 and [^{11}C]PIB in the brains of normal individuals and subjects with the clinical diagnosis of probable Alzheimer's disease.

3.2 Primary Study Goals

To address the feasibility for further development of [^{18}F]-AV-45. Specifically, to conduct a preliminary evaluation of [^{18}F]-AV-45 in 15 cognitively healthy elderly volunteers and 15 patients with the clinical diagnosis of probable Alzheimer's disease in order to:

- 3.2.1** Determine whether differences in the uptake and distribution of AV-45 in the brain can be used to correctly classify subjects; and
- 3.2.2** Estimate the relationship between [^{18}F]-AV-45 and [^{11}C]PIB among all participants.

3.3 Secondary Endpoints

- 3.3.1** To obtain preliminary information regarding the safety of [^{18}F]-AV-45 in cognitively healthy elderly volunteers and patients with probable Alzheimer's disease.
- 3.3.2** To explore the SUV patterns from different regions of the brain between cognitively normal and probable-Alzheimer's disease participants.
- 3.3.3 Post-Study Data Analysis**
To compare the abilities of [^{18}F]3'-F-PIB and [^{18}F]-AV-45 in discriminating probable Alzheimer's disease patients from cognitively normal controls using data from the completed ACRIN PA 4004 study.

4.0 STUDY DRUG INFORMATION

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5.0 STUDY OVERVIEW

This study will use a cross-sectional design to evaluate the classification ability of two amyloid imaging radioligands: [^{18}F]-AV-45 and [^{11}C]-PIB in distinguishing patients with probable Alzheimer's disease from cognitively normal controls and use a paired design to compare the diagnostic performance characteristics between the two amyloid radioligands.

Over a 2 year period, 15 patients with a clinical diagnosis of probable Alzheimer's disease and 15 cognitively normal elderly subjects, evaluated and enrolled through the University of Pennsylvania's Alzheimer's Disease Center, will be scanned using both radioligands. The clinical assessment (see Section 8) will include standardized measures of cognition, behavior, and function included in the National Alzheimer's Coordinating Center Uniform Data Set (see Section 8), measures of CSF total tau, phospho tau 181, A β 1-42, (see Section 8.4.6) and an MRI using the Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol (see Section 10.1).

Each participant will have an [^{18}F]-AV-45 and [^{11}C]-PIB PET scan within a 28-day window (see Section 10). Heart rate and blood pressure data will be collected before and after administration of the [^{18}F]-AV-45 experimental compound.

The primary goals of the study (see Section 3) are:

- 1) To determine whether differences in the uptake and distribution of [^{18}F]-AV-45 and [^{11}C]-PIB in the brain can be used to correctly classify subjects; and
- 2) To estimate the relationship between [^{18}F]-AV-45 and [^{11}C]-PIB among all participants.

6.0 PARTICIPANT SELECTION/ELIGIBILITY CRITERIA

6.1 Inclusion Criteria

6.1.1 All participants

- 6.1.1.1** Current member of the University of Pennsylvania Alzheimer's Disease Center longitudinal study cohort;
- 6.1.1.2** Between 55 and 90 (inclusive) years of age;
- 6.1.1.3** Have a study partner able to provide an independent evaluation of the study subject's functional performance (e.g., activities of daily living);
- 6.1.1.4** Fluent in English;
- 6.1.1.5** Willing and able to undergo all testing procedures including clinical examination, cognitive and functional assessments, MRI, and other procedures, if these testing procedures need to be repeated;
NOTE: The cognitive test and clinical dementia rating assessment will not need to be repeated if the potential participant has undergone these tests within three (3) months prior to enrollment). MRI will not need to be repeated if the scan has been done in the six (6) months prior to enrollment.
- 6.1.1.6** Able to be scheduled for PET amyloid imaging within 28 days after enrollment (see Section 8.0 for details of imaging completed on one day or over two days);
- 6.1.1.7** Women must be postmenopausal as defined by the absence of menses for two (2) years.

6.1.2 Cognitively normal participants

- 6.1.2.1** Mini mental state (MMS) scores between 27–30;
- 6.1.2.2** Clinical dementia rating score of 0;
- 6.1.2.3** Participant has been cleared of symptoms of clinically meaningful depression;
- 6.1.2.4** Cognitive impairment scores have been documented as equal or better than 1 standard deviation below the established age- and education-adjusted means for the ADC-NACC Uniform Cognitive Assessment Battery.

6.1.3 Probable Alzheimer's disease participants

- 6.1.3.1** MMS scores between 18–26;
- 6.1.3.2** Clinical dementia rating of ≥ 1.0 ;
- 6.1.3.3** Probable Alzheimer's disease based on NINCDS-ADRDA criteria;

- 6.1.3.3** Absence of clinically meaningful abnormality on MRI (ADNI protocol) other than those consistent with the clinical diagnosis of probable Alzheimer's disease.

6.2 Exclusion Criteria

- 6.2.1 Other significant neurologic disease:** Such as Parkinson's disease, multiple cerebral infarctions, clinical stroke, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic deficits or known structural brain abnormalities.
- 6.2.2 Neuroimaging:** MRI brain scan with evidence of infection, clinically meaningful infarction, or other focal lesions. Subjects with multiple lacunes or a single lacune in a critical memory structure are excluded.
- 6.2.3 MRI exclusions:** Presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments or foreign objects in the eyes, skin or body that would preclude obtaining an MRI as part of the initial study evaluation.
- 6.2.4 Psychiatric disorders or psychotic features:** Major depression (DSM-IV criteria) within the past 1 year, history of schizophrenia (DSM-IV criteria), presence of psychotic features, agitation or behavioral problems within the last 3 months that could lead to difficulty participating in the study protocol.
- 6.2.5 Alcohol abuse:** History of alcohol or substance abuse or dependence within the past 2 years (DSM-IV criteria).
- 6.2.6 Significant medical illness:** Any significant systemic illness or unstable medical condition that could lead to difficulty complying with the protocol.
- 6.2.7 Residence:** Residence in skilled nursing facility.
- 6.2.8 Investigational agents:** Participation in any clinical trial evaluating experimental medication designed to alter amyloid formation or amyloid plaque deposition and/or retention. Participation in any investigational drug study within 1 month prior to enrollment.
- 6.2.9 Previous therapy:** Participants who have received or participated in an experimental trial of any immuno-based therapy within the 2 years prior to enrollment.

6.3 Recruitment and Screening

Flyers, brochures, and other print and Internet methods may be used to promote awareness of the study. All recruitment material will be submitted to the local site Institutional Review Board (IRB) for approval prior to use. Participants will be recruited from individuals who are currently members of the University of Pennsylvania's Alzheimer's Disease Center longitudinal clinical cohort. Normal subjects will be recruited from the cognitively normal cohort followed by the Alzheimer's Disease Center. The investigative team at each site will include a neurologist, geriatric psychiatrist or geriatrician experienced in the diagnosis and care of patients with Alzheimer's disease, nuclear medicine physician, and a radiologist. Subjects who agree to participate will be consented by the study's principal investigator or their designee.

ACRIN will work with the protocol team and site investigators to determine materials that would be helpful for participant recruitment. Site investigators will be responsible for obtaining IRB approval for recruitment materials provided by ACRIN.

Both Alzheimer's disease and control subjects will complete the ACRIN PA 4003 amyloid imaging informed consent process and receive a standardized clinical evaluation.

6.4 Inclusion of Women and Minorities

The ACRIN participating institutions will not exclude potential participants from participating in this or any study solely based on ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible participants into this protocol and therefore address the study objectives in a patient population representative of the entire English speaking Alzheimer's disease population treated by the institution.

Women of all ethnic groups are eligible for this trial.

7.0 SITE SELECTION

7.1 Institution Requirements

The site participating in this study is an ACRIN participating institution that meets qualifications for participating in this study. The site has an ACRIN-qualified PET scanner and an MRI scanner that adheres to the ADNI protocol (see Appendix V).

7.2 IRB Approval and Informed Consent

The participating institution must obtain study-specific IRB approval for the protocol and site-specific informed consent form. The informed consent form is included in this protocol as Appendix I. The investigator and the investigator-designated research staff must follow OHRP-approved consent procedures (Title 45, Part 46 Code of Federal Regulations), as well as those set by their institution's IRB. A copy of the IRB approval letter and the IRB-approved, institutional study-specific informed consent form must be on file at ACRIN Headquarters (fax: 215-717-0936, ATTN: ACRIN Protocol Development and Regulatory Compliance Department) prior to enrolling the first study participant.

7.3 Accrual Goals and Monitoring

The ACRIN Biostatistics and Data Management Center (BDMC) will monitor participant accrual. Total target accrual for this study is 30 participants. During the first year, the accrual goal will be 15 participants. If the target is not reached, a review will be conducted with the intention of discovering and resolving any recruitment barriers.

Accrual and safety information will be presented to the ACRIN PA (Pennsylvania) Data Safety and Monitoring Committee (DSMC) at regularly scheduled meetings thereof; the PA DSMC may, at its

discretion, re-evaluate the study with respect to feasibility or the need for additional participating institutions.

8.0 STUDY PROCEDURES

8.1 Visit 1: Enrollment and Clinical Evaluation Visit

- Informed consent;
- Demographic information/medical history/physical examination;
- Functional, behavior, and mood assessment;
- Overall clinical assessment;
- Cognitive testing—if not done within 3 months prior to enrollment;
- Clinical dementia rating—if not done within 3 months prior to enrollment;
- Safety (vital signs—blood pressure and pulse);
- Lumbar puncture (optional procedure);
- MRI (per ADNI protocol minus the phantom image)—if not done within 6 months prior to enrollment;
- Either the study PI or a trained physician familiar with the protocol must see the participant prior to enrollment.

8.2A Visit 2: Imaging Day (Single Day for Both Agents) – Within 28 Days of Visit 1

Within 28 days of enrollment, the participant must complete the imaging scans. If the participant can complete both PET scans in a single day, then the following protocol will be followed. However, if there are reasons for the participant to need two days to complete the trial, 28 days maximum are allowed between the first imaging day and the second (see Section 8.2B for details). Two-day imaging may be preferable due to participant scheduling or comfort, but the decision should be made in consideration of risks associated with an additional i.v. catheter introduction. Details of the PET imaging protocols can be found below in Section 10.

- Intravenous (i.v.) catheter inserted into the participant's arm vein will be used to inject the two agents into the body by bolus injection;
- [^{11}C]PIB PET (ADNI protocol) to be obtained first if imaging for both experimental ligands is done on the same day;
- A minimum of 120 minutes should separate the injection of [^{11}C]PIB and the beginning of the [^{18}F]-AV-45 scan;
- Vital signs (blood pressure and pulse) will be taken immediately prior to the administration of [^{18}F]-AV-45 and before exiting the PET suite;

- Following administration of [^{18}F]-AV-45, participants will have PET brain imaging as defined in the amyloid ligand-specific PET protocol detailed in Section 10;
- Participants will be observed continuously for signs of AEs or serious adverse events (SAEs) during the PET scans and for approximately 30 minutes after the scanning period;
- Either the study PI or a trained physician familiar with the protocol will see the participant prior to administration of study drug and prior to discharge.

8.2B Visits 2 and 3: Imaging Days (Two Days, [^{11}C]PIB Followed by [^{18}F]-AV-45 or [^{18}F]-AV-45 Followed by [^{11}C]PIB)

If two days of imaging are necessary, they are permissible. Two-day imaging may be preferable due to participant scheduling or comfort, but the decision should be made in consideration of risks associated with an additional i.v. catheter introduction. The order in which the agents are introduced is not mandated. Distinctions in imaging day criteria from the description in Section 8.2A above are detailed below. Details of the PET imaging protocols can be found below in Section 10.

If the [^{11}C]PIB agent is used (first or second imaging day)

- I.V. catheter inserted into the participant's arm vein will be used to inject the agent into the body by bolus injection;
- [^{11}C]PIB PET (ADNI protocol) to be obtained on the first or second day;
- Following administration of [^{11}C]PIB, participants will have PET brain imaging as defined in the amyloid ligand-specific PET protocol detailed in Section 10;
- Either the study PI or a trained physician familiar with the protocol will see the participant prior to administration of study drug and prior to discharge.

If the [^{18}F]-AV-45 agent is used (first or second imaging day)

- Vital signs (blood pressure and pulse) will be taken immediately prior to the administration of [^{18}F]-AV-45 and before exiting the PET suite;
- I.V. catheter inserted into the participant's arm vein will be used to inject the agent into the body by bolus injection;
- Following administration of [^{18}F]-AV-45, participants will have PET brain imaging as defined in the amyloid ligand-specific PET protocol detailed in Section 10;
- Participants will be observed continuously for signs of AEs or serious adverse events (SAEs) during the PET scans and for approximately 30 minutes after the scanning period;
- Either the study PI or a trained physician familiar with the protocol will see the participant prior to administration of study drug and prior to discharge.

8.3 Next Day Following Imaging (Day 1)

Clinical team members (a physician or nurse) make phone contact to assess participant status the day after imaging. If the participant has two days of imaging, then a call will be made following each day of imaging; if the second imaging day immediately follows the first, the research staff will assess for AEs in person prior to the second PET scan.

8.4 Assessment Details

8.4.1 The clinical assessments, including the psychometric evaluation, will be based on the procedures described for implementation of the National Alzheimer's Coordinating Center Uniform Data Set, version 2.0.

8.4.2 **MRI:** An ADNI protocol MRI (excluding the phantom) will be performed prior to either amyloid PET imaging procedure. If an ADNI MRI has been performed within the 6 months prior to enrollment, it need not be repeated.

8.4.3 **Vital Signs:** Vital signs (blood pressure and heart rate) will be taken on the day of the scan, prior to and immediately after administration of the experimental amyloid ligands and at the end of the study prior to the release of the subject.

8.4.4 **Physician or Nurse Visit:** A physician or nurse must see the participant, prior to radiopharmaceutical administration, and at the end of imaging (prior to discharge). At discharge, the physician or nurse should review all safety data and briefly examine/query the subject regarding potential AEs or other treatment issues.

8.4.5 **Lumbar Puncture (optional):** If the participant chooses to undergo lumbar puncture, cerebrospinal fluid (CSF) will be obtained prior to the experimental imaging. The lumbar puncture should be done using an atraumatic needle following standard clinical procedures. Ten milliliters of clear CSF should be placed in a polypropylene plastic tube and kept in wet ice while transported to a -80°C freezer for storage until shipped to the University of Pennsylvania Biomarker laboratory.

8.5 Prior and Concomitant Therapy

All approved anti-dementia therapies are permitted. Use of experimental drugs is prohibited during one (1) month prior to enrollment through one (1) month after the experimental imaging procedure. In addition, participants who have received or participated in an experimental trial of any immuno-based therapy within the two (2) years prior to enrollment are excluded from this study.

8.6 Removal of Participants From Trial

Subjects must be removed from the trial if: (1) informed consent is withdrawn between the time of enrollment and prior to injection with the experiment ligands; or (2) the investigator or the sponsor believes it is in the best interest of the subject to be removed from the trial. Subjects may be withdrawn from the trial if an SAE occurs prior to completion of the experimental imaging procedure. The date and reason for discontinuation should be noted on the case report form (CRF).

8.7 Study Procedures Timetable

PROCEDURES	VISIT 1: CLINICAL EVALUATION VISIT [†]	IMAGING VISIT(S) 2 AND 3: One- or Two-Day Imaging Sequence (Begin Within 28 Days of Enrollment; If Two Days of Scans Are Necessary, Must Be Performed Within 28 Days of Each Other)	FOLLOW-UP: DAY 1 POST IMAGING CONTACT(S)
Informed Consent	X		
Eligibility checklist	X		
UDS demographic & clinical data	X		
UDS cognitive evaluation	X		
LP for CSF*	X		
MRI (1.5T or 3T) – per ADNI protocol	X		
Intravenous catheter placed for bolus injection		X	
Imaging day vital signs taken before injection of [¹⁸ F]- labeled agent and prior to subject release from PET suite		X	
[¹⁸ F]-AV-45 PET		X	
[¹¹ C]-PIB PET		X	
Post-study follow-up phone contact (or personal contact if two scanning days are immediately sequential)			X

UDS, Uniform Data Set; LP, lumbar puncture; MRI, magnetic resonance imaging; ADNI, Alzheimer's Disease Neuroimaging Initiative; PET, positron emission tomography.

* LP is an optional procedure.

† Not all procedures at the Clinical Evaluation Visit may be necessary; see Section 8.1 for details.

9.0 DATA MANAGEMENT / ONLINE REGISTRATION SYSTEM

9.1 General

- 9.1.1 The ACRIN web address is www.acrin.org.
- 9.1.2 Data collection and management will be performed by the Biostatistics and Data Management Center (BDMC) of ACRIN under the direction of Dr. Constantine Gatsonis. The Biostatistics Center (BC) is located at Center for Statistical Sciences at Brown University in Providence, RI, and the Data Management Center (DMC) is located at ACRIN in Philadelphia, PA.
- 9.1.3 Participant enrollment and data collection occurs through a series of programmed screens accessed through the ACRIN web site to register/randomize participants, collect participant data, and maintain calendars of data submissions for each participant. By using the World Wide Web, ACRIN has made participant registration, data entry, and updated calendar information available to clinical sites 24 hours a day, seven days a week. Each successful case registration is confirmed through receipt of an e-mail containing a registration/randomization confirmation and a case specific calendar identifying timelines for data and image submission. If the confirmation e-mail is not received, the enrolling person should contact the DMC before attempting a re-registration. A DMC contact list is located on the ACRIN web site for each protocol.

9.2 Clinical Data Submission

- 9.2.1 Upon successful participant registration, a confirmation e-mail containing the registration and case specific calendar is sent to the research staff enrolling the participant via the web. In addition, the investigator-designated research staff may download the participant specific data submission calendar, which lists all forms and designated reports required by protocol, along with the form due dates at the DMC. These calendars will be updated as the study proceeds to reflect data that have been received, reply deadlines for queries about unclear data, deadlines for follow-up reports of adverse events, or changes in the protocol that change the data being collected or the timeframe. Updated calendars for each participant can be obtained 24 hours a day from the ACRIN web site. The research associate may use the calendar as a case management tool for data submission and follow-up scheduling.
- 9.2.2 The investigative site is required to submit data according to protocol as detailed on each participant's calendar, as long as the case status is designated as open/alive or until the study is terminated. The case is closed when all data have been received, reviewed, and no outstanding data query exists for the case.
- 9.2.3 To submit data via the ACRIN web site, the appropriate investigator-designated research staff will log onto the ACRIN web site and supply the pre-assigned user name and password. Case report forms will be available on the web site through a series of links. Each web form is separated into modules; each module must be completed sequentially in order for the internal programming to be accurate. The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the web form application, various logic checks will be performed. These logic checks look for data that are missing, data that are out of range, and data that are in the wrong format (e.g. character data in a field requiring numeric

responses). Such errors will be detected as soon as the user attempts to either submit the form or move to the next data element. They must be corrected before the form is transmitted to the DMC. The user will not be able to finalize form transmission to the DMC until all data entered pass these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The form will remain available on the web until the “Complete Form Submission” button is depressed.

9.2.4 Once data entry of a form is complete, and the summary form is reviewed for completeness and accuracy, the investigator or the research staff presses the “Complete Form Submission” button on the form summary screen and the data is transferred into the clinical database. No further direct revision of the submitted data is allowed after this point. E-mail confirmation of web data entry is automatically generated and sent to the site investigator or research associate listing all of the data generated and just submitted. Should a problem occur during transmission and the e-mail confirmation of data submission is not received, the investigator or research associate should contact the DMC for resolution of the submission.

9.2.5 If a temporary problem prevents access to the Internet, all sites are notified of the event and estimated down time through an ACRIN broadcast message. The investigative site should wait until access is restored to submit data. The site RA or investigator should notify the DMC of the problem and the DMC will give an estimated time when access will be restored. If access will be unavailable for an extended period, sites must seek another Internet Service Provider (ISP). On a short-term basis, the ACR can serve as an ISP.

NOTE: Data will be transferred electronically from the University of Pennsylvania’s Alzheimer’s Disease Center (the National Alzheimer’s Coordinating Center database) to ACRIN.

9.3 Data Security

The registration and data collection system has a built-in security feature that encrypts all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of identification codes and passwords.

9.4 Electronic Data Management

9.4.1 Data received from the web-based forms are electronically stamped with the date and time of receipt by the ACRIN server. The data are then entered into the database. A protocol-specific validation program is used to perform more extensive data checks for accuracy and completeness. Complementary validation programs are initiated at the Brown BC and the DMC. The logic checks performed on the data at this point are more comprehensive than those built into the web-based data entry screens. They include checking that answers are logical, based on data entered earlier in the current form and the more thorough checks. Data elements that fail validation are followed up by the DMC research associate. The validation program generated by BC produces a log of errors, which is sent to the DMC Data Manager (DM) for resolution. The program is frequently updated to incorporate exceptions to rules so that subsequent validity checks minimize the time the DM at the DMC needs to spend resolving problems. Additional data review will take place once the data is transferred to the BC. The BC will run thorough cross-form validations, frequency distributions to look for unexpected

patterns in data, and other summaries needed for study monitoring. Any errors found at the BC will be reported to the DM for resolution. All BDMC communication with the participating sites is normally done through the DMC.

- 9.4.2** If checks at DMC or BC detect missing or problematic data, the Protocol DM sends a Request for Information (Z1 query letter) to the site RA or investigator specifying the problem and requesting clarification. The DM updates the participant's data submission calendar with the due date for the site RA or investigator's response.

9.5 Missing and Delinquent Data Submission

In addition to providing the investigator a data collection calendar for each case, the DMC periodically prompts institutions for timely submission of data through the use of a Forms Due Report. Distributed at intervals via the electronic mail system directly to both the RA and the investigator at each site, this report lists data items (e.g. forms, reports, and images) that are delinquent and those that will be due before the next report date. In addition to prompting clinicians to submit overdue data, the Forms Due Report helps to reconcile the DMC's case file with that of the RA and/or investigator. Future Due Forms Report may be sent on an as needed basis in addition to past due reports. The site investigator or RA may use the Forms Due and Future Due Reports as a case management tool.

9.6 Data Quality Assurance

- 9.6.1** The BC at Brown University will maintain a study database at its site for monitoring data quality and for performing analyses. These data are drawn directly from the permanent database of the DMC. The transfer of data between the DMC and the BC has been validated through a series of checks consisting of roundtrip data verification in which data are sent back and forth to verify that the sent data are equivalent to the received data. These checks are repeated at random intervals during the course of a given study. Any discrepancies and other data quality issues will be referred to DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.
- 9.6.2** A goal of the monitoring of data is to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. If patterns are discovered in the data that appear to arise from causes specific to an institution, the BDMC will apprise the ACRIN Headquarters and the site of the problem, and work with the site, along with ACRIN Protocol Development and Regulatory Compliance (PDRC) Department, until the problem has been resolved. If the BDMC, along with the PDRC, cannot find a resolution to the problem, it will be brought to the ACRIN Quality Assurance (QA) Committee for further discussion and resolution.
- 9.6.3** In addition, the QA Monitor will review case report forms and source documents at several different time points: after first few participants enrolled and during the conduct of the trial, including staff changes at the participating sites. In addition, the QA Monitor will review the initial and annual regulatory documents and any revised regulatory documents. This monitoring process ensures protocol and regulatory compliance, participant's welfare and safety, and provides resources to sites for clarification to the protocol and guidance in completion of the case report forms.

10.0 IMAGING PROTOCOL

10.1 MRI Protocol

The 1.5T or 3T MRI scans will be collected according to a standardized protocol (see Appendix V) and transmitted to ACRIN for archival storage. Scan time will be about 45 minutes per subject per session.

10.2 PET Scan Subject Preparation

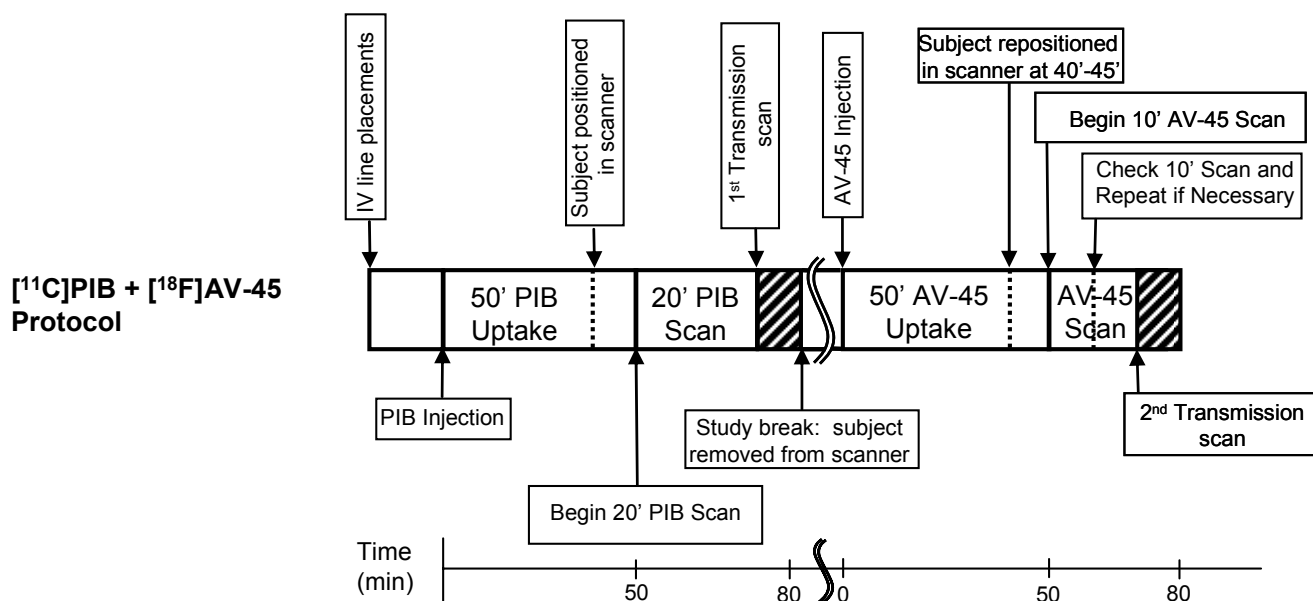
Subjects will have a single intravenous access catheter placed in one arm for administration of the experimental ligand.

10.3 [^{11}C]PIB PET Imaging Protocol

Approximately 40 minutes following the bolus intravenous injection (administered over 10-20 seconds) of 15+1.5 mCi of [^{11}C]PIB, subjects will be placed in the PET scanner, positioned so that the entire brain is in the field of view. The PIB PET scans will be acquired in dynamic, 3-D imaging mode for 20 minutes (4 x 5 minute frames) beginning 50 minutes after injection of [^{11}C]PIB. No vital sign assessment will be performed for the PIB PET study. Subjects will receive 5–10 minute transmission scans following each PET scan.

The subject will be removed from the PET scanner, and allowed to rest prior to the injection of the second experimental ligand. A minimum of 120 minutes must elapse between the injection of [^{11}C]PIB and the start of the second ligand image acquisition (i.e., 6 half-lives of [^{11}C]PIB). A schematic indicating the PET scanning sequences is shown below (Figure 11) and is intended to be flexible enough to be sensitive to subject comfort but allow for complete data acquisition from subjects who wish to complete the full protocol on the same day.

Figure 11. PET imaging protocol for [^{11}C]PIB and [^{18}F]-AV-45



10.4 [^{18}F]-AV-45 PET Imaging Protocol

Prior to the administration of [^{18}F]-AV-45 PET vital signs (blood pressure and pulse) will be obtained for safety studies as described in Section 8.0.

[^{18}F]-AV-45 will be administered by intravenous bolus injection. Approximately 50 minutes following the injection, the subject will be placed on the scanning table with their head in a comfortable head holder and moved into the scanner. Brain images will be acquired continuously for a period of 10 minutes. The images will be immediately assessed for technical validity. If considered inadequate, the subject will have an additional 10 minutes of continuous imaging. All images will be obtained within 90 minutes of initiating the infusion.

Vital signs will be taken a second time after the [^{18}F]-AV-45 PET scan, prior to discharge from the PET suite.

It may not be possible to perform both the [^{11}C]PIB and the second amyloid ligand PET study on the same day for technical or subject-related reasons. If this is the case, the paired studies may be performed on different days within a maximum time period of 28 days of each other. Follow-up phone calls will be made after each day of imaging, except in the case when the second day of imaging is the day after the first imaging day. In these cases, the research staff can assess for AEs in person prior to the [^{18}F]-AV-45 PET scan.

10.5 PET Image Acquisition Technical Details

PET scans will be obtained on either the Allegro or G-PET scanners that are currently operational at the University of Pennsylvania. Emission and transmission data will be reconstructed with an iterative reconstruction algorithm, the expectation maximization algorithm with ordered subsets. This algorithm models camera performance and avoids the image artifacts associated with filtered back projection such as negative pixel counts and inconsistencies between adjacent pixels. The resulting images are more uniform, without loss of spatial resolution, and with preservation of the quantitative accuracy.

10.6 Quantitative Image Analysis

Quantitative analysis of the PET scan with each agent will be performed by a third-party contract research organization (CRO) using methods well established in previous assessments of the AV-45 agent. A blinded clinical read of each study PET scan will be made to confirm baseline diagnosis based on MRI assessment of probable Alzheimer's disease or cognitively normal control. Clinical reads will be blinded to the radioligand used in the imaging. There is also interest in using a common analysis method across image data from both the University of Pittsburgh and the University of Pennsylvania as the sites are conducting complementary protocols.

That analysis could compare the SUVR for [^{18}F]3'-F-PIB, [^{11}C]PIB, and [^{18}F]-AV-45 in discriminating probable Alzheimer's-disease patients from cognitively normal controls, using [^{11}C]PIB as the reference.

The SUVR will be assessed in 8 regions of the brain to include: anterior and posterior cingulate, precuneus, frontal cortex, parietal cortex, lateral temporal cortex, and pons with cerebellum grey matter as reference tissue. Both hand-drawn regions of interest and semi-automated template methodologies will be reviewed to determine a common analysis methodology.

Additional post-study analysis may include looking for evidence that atrophy and vascular changes detected by MRI contributes to the interaction between amyloid ligand retention and measures of brain impairment, and exploring the patterns of SUVR among regions of the brain for both novel amyloid ligands under investigation.

10.7 Image Quality Review

An ongoing review will be performed by the ACRIN Imaging Specialist to ensure protocol images meet the study specific parameters.

10.8 Image Submission

Imaging examinations should be submitted to the ACRIN-Image Management Center (IMC) after each timepoint/visit. After quality assessment of the images at ACRIN IMC, the images will be transferred to the third-party CRO for assessment.

A completed, signed Image Transmittal Worksheet (ITW) MUST accompany all imaging exams submitted to ACRIN IMC for each time-point. For exams submitted via the internet, complete this worksheet and fax to (215) 923-1737 (see Appendix IV for ITW). For exams submitted via media, complete this worksheet and include with the media shipment. Please affix a label to the jacket of the media to include: study name, site name, NCI inst., code, case no., date of exam(s), timepoint, and type of imaging. ***Reminder for PET imaging: All PET exams should contain three trans-axial series, attenuated and non-attenuated corrected PET and CT or transmission series (*PET only units*).**

For further information or questions, email imagearchive@phila.acr.org.

ACRIN can provide software (TRIAD, see www.triad.acr.org) for installation on a PC at your site that collects and submits image sets from your MRI computer or from your PACS. The images are “DICOM pushed” either from the MRI computer or from the PACS to the PC on which the software is installed. This software anonymizes, encrypts and non-destructively compresses the images as they are transferred by FTP to the ACRIN database in Philadelphia.

Image Submission software PC requirements:

1. Network capability to transmit data from a MR and PET scanner to a linked workstation or PC?
2. Do you have a PC available to transmit data (patient data, MR and PET image data) to ACRIN?
 - a. Operating System Windows XP Pro
 - b. Access to the Internet: Internet Explorer
 - c. Minimum of 50 GB available hard drive
 - d. At least 1 GB RAM
 - e. Ability to view PDF documents
3. Software utilities required to run image transmission software:
 - a. Windows Installer 3.1
 - b. Microsoft .NET framework 2.0
 - c. MDAC Type 2.8
 - d. MS SQL 2005 Express

Please contact ACRIN to arrange the installation of the TRIAD software prior to first accrual. Contact the TRIAD help desk (Triad-Support@phila.acr.org) or 215-940-8820.

For Imaging Core lab image submission questions contact the lead technologist for this trial at: (imagearchive@phila.acr.org) or 215-940-8880

Images on CD, DVD, or MOD should be addressed and sent to:

ACRIN Image Archive
ACRIN Protocol PA 4003 Images
American College of Radiology
1818 Market Street, Suite 1600
Philadelphia, PA 19103
Attn: Core lab ACRIN PA 4003

11.0 TISSUE SPECIMENS/BIOMARKERS

11.1 CSF Collection

Polypropylene tubes should be used for collection and storage, since A β is known to stick to glass and polystyrene containing plastic.

CSF should be obtained using a small caliber atraumatic needle (e.g., 24 or 25 gauge Sprotte needle). Syringes (generally using multiple 5 cc syringes) to withdraw CSF from subjects should only be used with a side port needle. The lumbar puncture may be performed with the subject in a lateral decubitus or sitting position, according to the preference of the physician doing the procedure. To clear any blood from minor trauma associated with needle insertion, the first 1-2 mL of CSF (or more if needed) should be discarded to eliminate blood, and then 15 mL of CSF should be collected from each patient for research use. The CSF should be processed in the following manner:

1. The first 3 mL will be used for standard tests such as cell counts, glucose, and total protein with determinations done at local laboratories;
2. The remaining 12 mL of CSF will be stored in polypropylene tubes at -80°C until shipped to the University of Pennsylvania.

11.1 Shipment of CSF to the University of Pennsylvania Biomarker Fluid Bank Laboratory

Appropriately labeled polypropylene tubes containing frozen CSF should be placed in a biological hazards shipping container containing an adequate amount of dry ice and sent by express mail with overnight delivery to the University of Pennsylvania Biomarker Fluid Bank Laboratory. When samples are received in the Laboratory, they will be thawed and aliquots transferred to plastic vials, bar code labeled, and placed in designated locations in -80°C freezers. All samples will be inventoried and tracked using commercially available software. A database will be created and used for the inventory of stored samples, in conjunction with a bar code reading system. Bar code labels affixed to each sample vial will contain the following information: sample ID# (to preserve confidentiality), date of collection and processing, total volume received by the biomarker lab, sample type (i.e., CSF), volume, aliquot number, freezer, shelf, rack, box, location in the box. A bar code label will be used on the sample tracking form that is used by the technologist when processing and storing samples. When the data are entered into the database the bar code label is scanned in and the sample aliquots entered. Removals of samples will also be tracked on the database, including the date removed and the recipient center.

12.0 ADVERSE EVENTS REPORTING

12.1 Definition of Adverse Event

An **Adverse Event (AE)** is any untoward medical occurrence in a participant that does not necessarily have a causal relationship with the study procedure.

A **pre-existing condition** is one that is present at the start of the study. A pre-existing medical condition is defined as an AE if the frequency, intensity, or character of the medical condition worsens during the study period. At screening visit, any clinically significant findings/abnormalities should be recorded as a pre-existing condition. At the end of study, any new clinically significant findings/abnormalities that meet the definition of an AE must be documented as AEs.

12.2 Definition of Serious Adverse Event

A **Serious Adverse Event (SAE)** is defined as any untoward medical occurrence that:

- results in death;
- is life-threatening (at the time of the event);
- requires inpatient hospitalization or prolongation of an existing hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly/birth defect;
- is considered a medically-important event.

Medically-important events are those based upon appropriate medical judgment that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject and may require intervention to prevent one of the other serious outcomes noted above.

12.3 Adverse Event Grading

Grade is used to denote the severity of the AE (refer to the CTCAE version 3.0):

- 1 – Mild
- 2 – Moderate
- 3 – Severe
- 4 – Life-threatening or disabling
- 5 – Fatal

12.4 Adverse Event Attribution

Attribution is used to determine whether an AE is related to a study treatment or procedure.

Attribution categories are:

Definite – AE *is clearly related* to the study treatment or procedure.

Probable – AE *is likely related* to the study treatment or procedure.

Possible – AE *may be related* to the study treatment or procedure.

Unlikely – AE *is doubtfully related* to the study treatment or procedure.

Unrelated – AE *is clearly NOT related* to the study treatment or procedure.

12.5 Expected Adverse Events

12.5.1 Expected Adverse Events Associated With I.V. Catheter—the Injection Site:

- Pain;
- Bruising;
- Infection.

12.5.2 [¹⁸F]-AV-45 Investigational Agent—Known Potential Risks:

This section has been intentionally left blank.

12.5.3 [¹¹C]PIB Investigational Agent—Known Potential Risks:

This section has been intentionally left blank.

12.5.4 Expected Adverse Events Associated With PET Scan:

- Discomfort, including shoulder pain;

- Anxiety/claustrophobia.

12.5.5 Expected Adverse Events Associated With Lumbar Puncture:

- Pain, usually temporary and confined to the lower back;
- Paresthesia and/or discomfort;
- Headaches occurring in fewer than 5% of elderly subjects;
- Tinnitus;
- Allergic reaction;
- Less likely, a persistent low-pressure headache may develop (an atraumatic [Sprotte] 25-gauge needle has been noted to reduce post-lumbar puncture headache risk, and will be used in this trial);
- More serious, very rare risks (< 1% risk of complication) include vomiting, infection, damage to radicular nerves, temporary weakness of the eye muscle, bleeding into the lumbar CSF space, and death.

For more information about safety precautions instituted for the lumbar puncture procedure, see Appendix VI.

12.6 Recording of Adverse Events

At each contact (site visit and/or telephone) with the study participant, the investigator or investigator-designee must seek information on AEs through discussion and, as appropriate, by examination. Information on all expected and unexpected AEs with the severity level of grades 1, 2, 3, 4, 5 should be recorded immediately into the source document, e.g. AE Log and/or progress notes of the study participant's chart, and retained at the site. Please note that source documentation (ACRIN AE Log, ACRIN AE CRF, printed AE web confirmation, or the participant's chart) must have the investigator's signature. These AEs must also be recorded in the AE CRF and reviewed by the site PI in real time to determine grade and attribution of the event.

12.7 Reporting of Adverse Events

Prompt reporting of AEs is the responsibility of each investigator, clinical research associate, and/or nurse engaged in clinical research. Anyone uncertain about how an AE should be reported should contact the ACRIN headquarters for assistance and ask for the ACRIN AE Coordinator at (215) 574-3150.

Routine reporting is defined as documentation of AEs on the source documents and AE CRF, and submission to ACRIN for preparation of a report for DSMC review and preparation of the final study report. ACRIN will collect and report all AEs that occur during study participation and up to 30 days after the last study procedure. Local IRBs may stipulate additional AE reporting based upon their review of the protocol.

Expedited reporting is defined as the immediate notification of Avid, ACRIN, and the University of Pittsburgh (when the AE is [¹¹C]PIB related) per Section 12.9. Routine reporting requirements will also apply. All serious AEs (SAEs) will be documented in the study

participant's chart and AE CRFs, in addition to meeting all study-specific reporting requirements of ACRIN, Avid, the FDA, and the local IRB (per local IRB policy).

All unresolved AEs should be followed by the investigator until the events are resolved (up to 30 days after the participant's final study procedure), the subject is lost to follow up, or the AEs are otherwise explained. Any death or AE occurring at any time after a participant has discontinued or terminated study participation that may be reasonably related to the study imaging effect should be reported.

Assignment of grades (severity level) and attribution for each AE is to be completed at the site by the site PI.

12.8 Routine AE Reporting Process

All AEs occurring during study participation require telephone reporting to the ACRIN AE Coordinator at (215) 717-2763; the coordinator will add the AE form to the calendar for web entry. Sites must also fax an investigator-signed confirmation of web entry or completed paper version of AE form (in the event that the ACRIN web site is down).

- ACRIN Fax Number: (215) 940-8819
- ACRIN contacts to confirm receipt of report:
Cornelia Tsikos (215) 574-3236
Patty Blair (215) 717-0833

NOTE: The AE must also be documented in the participant's chart with the investigator's signature. Significant new information and/or follow-up information (e.g., test results . . .) on any ongoing AEs should be promptly reported to ACRIN.

12.9 Expedited AE Reporting Process

An SAE requires the notification of Avid and ACRIN by telephone within 24-hours of first knowledge of the event. In the event that the SAE is [¹¹C]PIB related, the site will need to report to the University of Pittsburgh SAE line in addition to Avid and ACRIN within 24 hours of first knowledge of the event. In the case of a [¹¹C]PIB-related emergency event (e.g., life threatening) where Avid would be well advised to hold dosing pending further investigation, ACRIN and the University of Pittsburgh will notify Avid immediately.

ACRIN will be responsible for helping the site as necessary to collect information, which will include details of participant's concomitant medications. Avid will review all SAEs. If the SAE meets expedited criteria, Avid will work with the site to prepare a Council for International Organizations of Medical Sciences (CIOMS) form. Avid will send a written report to the FDA (within the 7 or 15 days as required), the investigator (who will send the written report to the IRB), and ACRIN. If the event does not meet the expedited criteria, Avid will still prepare a CIOMS form, as specified above, but the form will only be sent to the investigator and ACRIN. The CIOMS form will not be sent to the FDA.

12.9.1 24-Hour Telephone Expedited Reporting for SAEs

All SAEs occurring during study participation and up to 30 days after the last study procedure require telephone reporting within 24 hours of first knowledge of the event to the:

1. Avid safety line at (609) 356-9955
2. ACRIN SAE line at (215) 717-2763
3. In the event that the SAE is determined to be possibly related to [¹¹C]PIB, contact the University of Pittsburgh Hotline at (412) 692-2700

NOTE: In addition to the 24-Hour Telephone Expedited Reporting Process, SAE reports must be completed and submitted as specified in Sections 12.9.2–12.9.4.

12.9.2 Completion of SAE Reports

All SAEs occurring during study participation and up to 30 days after the last study procedure require the submission of an SAE report within three (3) calendar days of first knowledge of the event is required. The SAE report must be sent to the following:

- Avid Fax Number: (413) 826-0416
Avid representatives will then submit the CIOMS report to the FDA within the seven (7) calendar days (if the event is fatal) or within 15 calendar days (if the event is life-threatening).
 - Avid contact to confirm receipt of SAE report:
Sylvia Lewis (267) 966-6141
Mark Lowry (267) 499-2042
- ACRIN SAE Fax Number: (215) 940-8819
 - ACRIN contact to confirm receipt of SAE report:
Cornelia Tsikos (215) 574-3236
Patty Blair (215) 717-0833
- Local Institutional Review Board (IRB).

NOTE: In addition to documentation listed above, the AE must also be documented in the participant's chart and an AE CRF in order to satisfy routine reporting requirements. Concomitant medication details will be collected in the event of an SAE. Significant new information and/or follow-up information (e.g., test results, autopsy, discharge summary) on any on-going SAEs should be promptly reported to ACRIN.

12.9.3 Completion of SAE Reports Related Specifically to [¹¹C]PIB

All SAEs occurring during study participation and up to 30 days after the last study procedure that the investigator considers **possibly, probably, or definitely related to [¹¹C]PIB** require the submission of an SAE report within three (3) calendar days of first knowledge of the event. The SAE report must be sent to the following:

- University of Pittsburgh Fax Number: (412) 692-2700

University of Pittsburgh representatives will then submit the CIOMS report to the FDA within seven (7) calendar days (if the event is fatal) or within 15 calendar days (if the event is life-threatening).

- ACRIN SAE Fax Number: (215) 940-8819
 - ACRIN contact to confirm receipt of SAE report:
Cornelia Tsikos (215) 574-3236
Patty Blair (215) 717-0833
- Avid Fax Number: (413) 826-0416
 - Avid contact to confirm receipt of SAE report: Sylvia Lewis (267) 966-6141
Mark Lowry (267) 499-2042
- Local Institutional Review Board (IRB).

NOTE: In addition to documentation listed above, the AE must also be documented in the participant's chart and an AE CRF in order to satisfy routine reporting requirements. Concomitant medication details will be collected in the event of an SAE. Significant new information and/or follow-up information (e.g., test results, autopsy, discharge summary) on any on-going SAEs should be promptly reported to ACRIN.

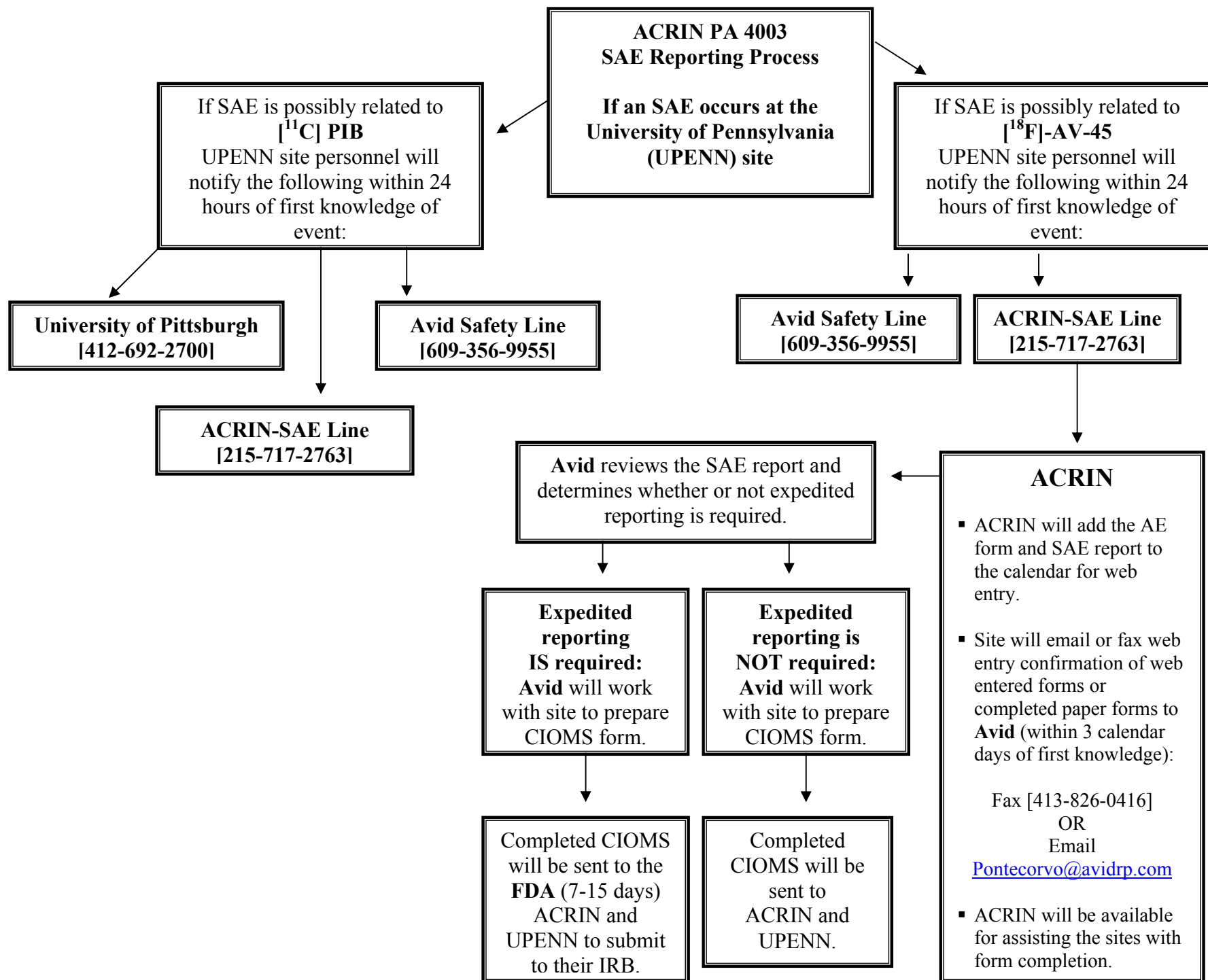
12.10 Local IRB Reporting

12.10.1 Adverse Event Reporting and Local IRB

All expedited AE reports should be sent to your local IRB. AEs not requiring expedited reporting are normally reported to the local IRB in an annual report and/or continuing review report. **Please refer to your local IRB's policies regarding AEs/SAEs and safety reports.**

12.10.2 Expedited Serious Adverse Event Reporting and Local IRB

All expedited SAE reports should be sent to your local IRB per your local IRB policies and procedures.



13.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (International Conference of Harmonisation [ICH] guidelines), applicable government regulations, and ACRIN research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or IRB for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator, and a copy of this decision will be provided to ACRIN before implementation of the study. The investigator will provide ACRIN with the institution's federal wide assurance (FWA) number, along with the IRB approval letter and copy of the IRB approved informed consent form. The investigator will provide a copy(s) of IRB approval letter(s) for any amendment(s), and copy(s) of annual renewal(s).

All study participants in this study will receive an IRB-approved, site-specific informed consent form describing the study and providing sufficient information for participants to make informed decisions about their participation in this study (see Appendix I for a copy of the sample informed consent form). This informed consent form will be submitted along with the protocol for review and approval by the EC/IRB. The study participant MUST be consented with the EC/IRB approved informed consent form before the participant is subjected to any study procedures. The approved consent form MUST be signed and dated by the study participant or legally acceptable representative and the investigator-designated research staff obtaining the consent.

14.0 CONFLICT OF INTEREST

Any investigator and/or research staff member who has a conflict of interest with this study (such as patent ownership, royalties, or financial gain greater than the minimum allowable by their institution) must fully disclose the nature of the conflict of interest in accordance with ACRIN policies and applicable federal, state, and local laws and regulations.

15.0 PUBLICATION POLICY

Neither complete nor any part of the results of the study obtained under this protocol, nor any information provided to the investigator for the purposes of performing the study, will be published or passed on to any third party without the consent of ACRIN and the Study Chair. Any investigator involved in this study is obligated to provide ACRIN with complete test results and all clinical data obtained from the participants in this protocol. Investigators will follow ACRIN Publication Policy (available on the web at www.acrin.org/PublicationsPolicy.aspx).

16.0 INSTITUTIONAL MONITORING AND AUDITS

The investigator will permit study-related monitoring, auditing and inspections of all study-related documents by the EC/IRB, government regulatory agencies, the Avid Monitor, and the ACRIN QA Monitor. The investigator will ensure the capability for inspection of the participating site's study-related facilities (e.g. imaging center, satellite sites). The investigator will allocate adequate time for these activities, allow access to all study-related documents and facilities, and provide adequate space to conduct audit visits.

Monitoring ensures protocol and regulatory compliance and an opportunity to provide any clarification to the protocol and guidance to the completion of the CRFs. Institutional monitoring will be implemented according to the Avid Site Monitoring Plan. Instructions for preparation for the monitoring will be sent to the site prior to the implementation of monitoring. The instructions will specify regulatory documents and participant case records to be monitored. CRFs and source documents of selected study participants enrolled at each site will be reviewed. In addition, the initial regulatory documents and any revised regulatory documents will also be monitored.

Initial on-site audits will be completed within 18 months after first participant enrollment of each site's enrollment of its first ACRIN participant. Subsequent audits will be scheduled per the outcome of the initial audit. The audits will be conducted per procedures established by the Cancer Imaging Program (CIP) of the NCI. Instructions for preparation for the audit visit will be sent to the site prior to the scheduled audit visit. These instructions will specify which participant case records will be reviewed during the audit. On-site records will be verified against the submitted form, and the findings will be recorded on specially prepared audit reports. Major discrepancies will be forwarded to the appropriate oversight body within ACRIN. IRB procedures, approvals, and consent forms will also be reviewed at the time of the audit visit. The ACRIN Audit Manual is available online at www.acrin.org.

To help sites prepare for monitoring and audits and assure that the investigator and the research staff maintain records appropriately, the ACRIN Headquarter staff will offer training to the site. This training will cover all aspects of data collection, including special instructions to obtain and file the various source documents needed to verify the accuracy of submitted data for this trial.

16.1 Source Documents

Source data are found in all information, original records of findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents represent the first recording of any observations made or data generated about a study participant while he or she is enrolled in a clinical trial. Source documents for each study participant substantiate the data that are submitted to ACRIN. Source documents must verify the eligibility criteria and data submitted on all CRFs.

Research records for each case should contain copies of the source documents for the data collected and reported to ACRIN. If data is abstracted from medical charts that are not filed at the investigative sites (e.g. hospital charts), copies of these records should be filed in the research chart. Every attempt must be made to obtain all records/charts that were used to abstract any study data for this protocol. This will prevent any discrepancies and the inability to verify the document and the data reported.

16.2 Case Report Forms

CRFs, both web-based and paper forms, are the primary data collection instruments for the study. All data requested on the CRFs must be recorded, and any missing data must be explained. If a space is left blank on paper CRFs because the procedure was not done or the question was not asked, "N/D" must be noted. If the item is not applicable to the individual case "N/A" must be noted. All entries on paper CRFs must be printed legibly in black ink on the paper CRFs. In the event of any entry errors, corrections must be made by drawing a **single straight line** through the incorrect entry, writing **the initials of the person making the correction, recording the date** when the correction is being made, and entering the correct data above the strike through. Do not use white out or an eraser. Please refer to ICH Good Clinical Practice Guidelines.

Data elements that are extracted from the medical record (such as participant history or official clinical interpretations of images, pathology, or surgery results) and recorded on the CRFs will be reviewed against the appropriate component of the medical record. Data elements gathered from signed participant questionnaires must be available for review. Required study image interpretation data that are more detailed in information than the image and not typically documented in the standard radiology report may be documented on the CRF and are considered acceptable source documentation **if signed by the Investigator**. At the time of audit, the auditor will verify the occurrence of the imaging examination, the reader, and the date of the exam(s) from the medical record(s). Any use of approved CRFs as source documentation require a signature and date on the CRF with a reference to the information source (participant questionnaire, CT, MR, etc.). Any use of CRFs as source documentation when the protocol has designated the medical record documentation as source data will be considered a deficiency.

17.0 STATISTICAL CONSIDERATIONS

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Appendix I

Informed Consent Form Template

University of Pennsylvania Informed Consent and HIPAA Authorization Form

Protocol Title: AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN PA 4003

**EVALUATION OF THE ABILITY OF A NOVEL [¹⁸F] AMYLOID
LIGAND ([¹⁸F]-AV-45) TO DISTINGUISH PATIENTS WITH A
CLINICAL DIAGNOSIS OF ALZHEIMER'S DISEASE FROM
COGNITIVELY NORMAL ELDERLY INDIVIDUALS**

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[Note: ACRIN complies with the privacy measures put forth by the Health Insurance Portability and Accountability Act (HIPAA). However, ACRIN does not monitor compliance with HIPAA; that is the responsibility of the local institutions and their Institutional Review Boards (IRBs).]

Why am I being asked to volunteer?

You are being invited to participate in a research study. Your participation is voluntary which means you can choose whether or not you want to participate. If you choose not to participate, there will be no loss of benefits to which you are otherwise entitled. Before you can make your decision, you will need to know what the study is about, the possible risks and benefits of being in this study, and what you will have to do in this study. The research team is going to talk to you about the research study, and they will give you this consent form to read. You may also decide to discuss it with your family, friends, and/or family doctor. You may find some of the medical language difficult to understand. Please ask the study doctor and/or the research team if you have any questions about this study and what is expected of you if you participate in this study. If you decide to participate, you will be asked to sign this form.

The American College of Radiology Imaging Network (ACRIN) and the University of Pennsylvania are conducting a research study known as a clinical trial. Your study doctor will explain to you what is involved in the clinical trial. Clinical trials include only people who choose to take part. Your participation in the study is voluntary. Please take your time in deciding whether you want to be involved in the clinical trial. This is an imaging clinical trial, meaning that the procedures in the study will be looking at what is going on inside of your body.

This document, the consent, is designed to help you understand the study as you talk with your doctor. It should help you understand what will happen in the study, why the study is being done, and the risks or benefits to you if you decide to be in the study. Your participation in the study is voluntary. If you decide to participate, you must sign this informed consent form before any study procedures are performed and before you are registered into the clinical trial.

You are encouraged to discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions after reading this informed consent form, you should ask your study doctor for more explanation.

You are being asked to be in this study because either: 1) you have Alzheimer's disease and are registered with the University of Pennsylvania's Alzheimer's Disease Center; or 2) you do not have Alzheimer's disease but are registered with the Alzheimer's Disease Center as a 'cognitively normal' person. In this study, the brain scans of a person with normal cognitive skills will be compared with the brain scans of a person that has Alzheimer's disease to better understand how Alzheimer's disease develops in the brain.

What is the purpose of this research study?

The overall purpose of this study is to determine whether an investigational radioactive agent, a 'radiotracer' called [^{18}F]-AV-45, will help doctors diagnose Alzheimer's disease and identify when Alzheimer's disease gets worse. The radiotracer will help doctors see the brain through images created using a positron emission tomography (PET) scanner.

Currently for patients with Alzheimer's disease, a radioactive agent, [^{11}C]PIB is commonly used in PET scans. For this research study, you will have one PET scan with the [^{11}C]PIB and one PET scan with the investigational radioactive agent, [^{18}F]-AV-45.

This study intends to find out if this new investigational radioactive agent for PET scans will help view Alzheimer's disease in the brain. It may help doctors and radiologists better view and understand how Alzheimer's disease develops in the brain using PET scans and [¹⁸F]-AV-45.

How many people will be in the study?

About 30 people will take part in this study, 15 'cognitively normal' people called control subjects and 15 people with Alzheimer's disease. Participants in this study can be either male or female, ages 55 to 90. If you are female, you must be postmenopausal (not had menses for at least two [2] years). Since not all participants who enroll in the study will complete the full study, we will enroll a total of 35 individuals at this medical center so that at least 30 subjects can complete the full study.

How long will I be in the study?

You will be participating in the study for less than three (3) months. After your initial baseline/screening visit and enrollment into the study, you will be scheduled for two (2) PET scans. These two (2) PET scans must be done within 56 days of your enrollment (the first scan within 28 days of enrollment and then the second scan within the following 28 days).

What am I being asked to do?

To participate in this study, first you will be asked to read and sign this consent form (for yourself or as the legal representative of a potential participant with Alzheimer's disease). If you agree to participate in the study and are eligible to be in the study, you will have two (2) research PET scans.

First, we will determine if you are eligible to take part in the study through a group of examinations called "screening procedures." For this study, the screening procedures include:

1. A review of your prior medical history, medical records, and a magnetic resonance imaging (MRI) scan.

If you have not had an MRI scan of your brain within the 6 months before enrollment in the trial, then you will have one done to make sure you meet the requirements for participation in the trial. The MRI scan will be performed at the MR Research Center on the 8th floor of UPMC at Presbyterian University Hospital.

About MRI Scans

You may be given an MRI scan for your doctors to use as a reference of your body structure for the PET studies. MRI is widely used in routine clinical practice. An MRI uses powerful magnets and radio waves linked to a computer to create cross-sectional images of the brain. Because of the powerful magnet used for creating MR images, you will be instructed to remove all jewelry and other metal-containing objects before entering the scan room. (For more information about risks from MRI, see below.) If you may have metal in your body, your doctor may ask you to undergo an x-ray first to ensure you are not at risk from the metal while in the MRI magnet.

The MRI scan will require laying on a narrow table that slides into a small tunnel for imaging. The MRI scan will require approximately 40 minutes of your time. You will be asked to lie very still during the scan. During the MRI scan, loud noises will be heard.

2. Your study doctor or research staff will obtain your current medical history and conduct a physical examination, including checking your heart rate and blood pressure.
3. You will be asked to take tests of memory, thinking skills, daily functioning and behavior. If you have had these tests within 3 months prior to enrollment, you will not need to repeat them.

Lumbar puncture—this is an optional procedure: The research team would also like to study the fluid that surrounds your brain and spinal cord. This fluid is called spinal fluid and is obtained through a procedure called a lumbar puncture or spinal tap. This portion of the study is optional so you may choose to be in the study but not to have the spinal tap. If you choose to have the lumbar puncture, you will be asked to sign another consent form.

After reviewing the results of your prior screening tests, exams, and MRI scan, the study doctor and research staff will determine if you are eligible to be enrolled in the study. If you are eligible, and you choose to take part, you will be registered as a participant. You will be scheduled to have two (2) PET scans within 56 days after you have been registered for this study.

About PET Scans

Positron emission tomography, or PET, is a nuclear medicine imaging technique that produces a 3-D image of functional processes in the body. In other words, PET scans take pictures of the cells and how they function in the body—in this case, in the brain.

- Two (2) PET scans:
 - 1) The first with an agent called [^{11}C]PIB, which is commonly used in patients with Alzheimer's disease; and
 - 2) The second with the study agent, [^{18}F]-AV-45.

The two (2) PET scans in the study can be done on the same day, with a minimum of two (2) hours between scans. This in-between time (minimum of two [2] hours) are needed to let one radiotracer leave your body before you receive the other radiotracer.

If you cannot have both PET scans in the same day for your safety and comfort, then two (2) appointments will be scheduled. You and your doctor can discuss whether a one-day or two-day schedule is best for you, including additional risks. Your first PET scan will be scheduled within 28 days of your enrollment and the second PET scan will be scheduled within 28 days of the first PET scan.

If you choose to have the two PET scans done on the same day, the following will take place:

1. Before you have the PET scans, your study nurse will place a plastic tube (called an intravenous [i.v.] catheter) in a vein in one of your arms. This i.v. catheter will allow your research staff to inject the radiotracers [^{11}C]PIB and [^{18}F]-AV-45.
2. When you have your PET scans, you will be asked to lie on your back and remain very still on a table.

You will have the following PET scans:

- a. First, you will have a PET scan using [^{11}C]PIB. The [^{11}C]PIB radiotracer will be injected into the i.v. catheter in your arm. Fifty (50) minutes after the [^{11}C]PIB injection, you should already be placed in the PET scanner. The PET scan will take about 30 minutes to complete.
- b. Then, you will have a transmission scan. The transmission scan will take about 10 to 15 minutes to make sure the equipment is set properly.
- c. Next, you will have the investigational [^{18}F]-AV-45 PET scan. The investigational [^{18}F]-AV-45 radiotracer will be injected in the i.v. catheter about two (2) hours after the [^{11}C]PIB injection. Ninety (90) minutes (1.5 hours) after the [^{18}F]-AV-45 is injected, you should already be placed in the PET scanner. The PET scan will last about 30 minutes.

Lastly, you will have a second transmission scan. This will take 10 to 15 minutes to adjust the scanner.

If you choose to have two (2) days of imaging: If you and your study doctor choose to have the imaging scans completed in two (2) days, it will not matter which PET scan is completed first. The [^{18}F]-AV-45 PET scan (or [^{11}C]PIB PET scan) can be done at a second visit as long as it is within 28 days of your first PET scan.

Day of the imaging procedures: On the day of the PET scan(s), you will be told not to eat or drink for four (4) hours before the PET scan. There is a cafeteria in the hospital where you will have your pet scan, and you will be able to have something to eat immediately following your scan(s).

When you arrive to have the PET scan, an i.v. catheter (a needle attached to a small tube) will be placed in one of the veins in your arm to inject the radioactive agent. Before each PET scan, a small amount of the radioactive agent, either the [^{11}C]PIB or [^{18}F]-AV-45, will be injected into your vein through the i.v. catheter.

Monitoring/follow-up procedures: Procedures performed to evaluate the safety and effectiveness of the investigational procedures are called “monitoring” or “follow-up” procedures. Your vital signs (including your heart rate and blood pressure) will be monitored before and after you are given the investigative radioactive agent, the [^{18}F]-AV-45. You will be monitored throughout the PET scans and for about 30 minutes after the second scan to help ensure your safety.

The day after the PET scans are completed, your study doctor or a nurse on the research team will call you to ask you how you are feeling and to see if you are having any side effects. If you have the PET scans on two different days, you can choose to receive either the [^{11}C]PIB radioactive agent or the [^{18}F]AV-45 radioactive agent on the first day, and the other radioactive agent the other day. The day after each of the PET scans are completed, your study doctor or a nurse on the research team will call you to ask you how you are feeling. If they see you in person the following day because you are having the second scan the next day, they will ask you in person about how you are feeling prior to the next scan instead of calling you. If you do experience any side effects, you should report them to your study doctor right away.

Chart of Visits

Visit 1: At the Baseline/ Screening Visit	• Sign the informed consent form; • Have a physical examination, including tests for behavior, mood, and function; • Have a test for cognitive skill level (meaning testing of your ability to think, reason, and remember) and presence of dementia. These tests may not be needed if you have had cognition testing and dementia rating assessment within three (3) months prior to enrollment; • Have a lumbar puncture to remove some spinal fluid. This procedure is optional. You may not be asked to have a lumbar puncture if one has been performed within six (6) months prior to enrollment; and • Have an MRI scan of the brain—may not be needed if an MRI has been performed within six (6) months prior to enrollment.
Visit 2: Imaging Day for Only One (1) Day of Imaging (Within 28 Days of Enrollment)	Within 28 days of enrollment, you will need to go for your PET scan. (The two experimental scans can be done either on one [1] day, per the scenario below, or for two [2] days. Your doctor can help you decide whether one [1] day or two [2] days of imaging will work better for you, as well as the risks associated with these options.) If both PET scans are scheduled for the same day: • Have your vital signs taken as safety measures; • Have an i.v. catheter placed in a vein in your arm; • [¹¹C]PIB will be injected into the i.v. catheter; • Have a PET scan fifty (50) minutes after the injection (after you have been positioned in the PET scanner). The scan itself will take about 30 minutes; • Have [¹⁸F]AV-45 injected into the i.v. catheter at least two (2) hours after the first PET scan; • At least two (2) hours after the [¹¹C]PIB injection, the second PET scan will be done using [¹⁸F]-AV-45 as the radiotracer agent; • Your vital signs (blood pressure and heart rate) will be taken as a safety measure before and after you receive the [¹⁸F]-AV-45. The scan itself will take about 30 minutes. You will be monitored throughout the PET scans and for at least 30 minutes afterwards. Your study doctor or nurse will check-in on you prior to being released from the PET center.
Visit 3: (Optional) Second Imaging Day, Two (2) Days of Imaging (Second Imaging Day Must Occur	If you cannot or choose not to have both PET scans in the same day, a second visit will be scheduled to complete the study (the order of the PET scans does not matter if it will take two [2] days). The second scan

Within 28 Days of First Imaging Day)	must be completed within 28 days of the first scan: • Have the second PET scan using an agent that was not used in the first PET scan, either [¹¹C]PIB or [¹⁸F]-AV-45 as the radiotracer agent (see details above); You will be monitored throughout the PET scans and then for at least 30 minutes afterwards. Your study doctor or nurse will check in on you prior to being released from the center.
Follow-Up at Day 1: The Day After the Second PET Scan	The day after the PET scan imaging day (or after each PET scan imaging day), your study doctor or a nurse will call to ask you how you are doing. If a second PET scan imaging day is immediately after the first scan, the research staff will ask you how you are doing in person prior to having your second PET scan.

What are the possible risks or discomforts?

You may or may not have side effects while on the study. Possible risks and side effects during this study are related to mood and behavior tests, the placement of an i.v. catheter, the lumbar puncture (if you choose to have this procedure done), the MRI, the radiation exposure from the scans and the [¹¹C]PIB and [¹⁸F]-AV-45, the PET scans, and/or having to lie still during the imaging scans. (If you have two days of imaging, note that you will have additional risk from a second i.v. catheter that you will need on that second day.) Trained research staff members are involved in this trial to minimize any risks. As with any investigational study, some side effects of [¹⁸F]-AV-45 may be unknown, and it is possible that certain unknown risks could be serious.

Everyone taking part in the study will be watched carefully for any side effects. However, study doctors don't know all the side effects that may happen. Your study health care team may give you medication to help lessen side effects. Medication may also be given to lessen the seriousness or discomfort of side effects.

You should talk with your study doctor about any side effects that you have while taking part in the study.

Risks of the Clinical Tests:

- Frustration;
- Fatigue;
- Boredom.

Risks Associated with MRI Scans:

- Anxiety/stress;
- Claustrophobia;
- Discomfort.

The known risks associated with this procedure are minimal. The greatest risk is a metallic object flying through the air toward the magnet and hitting you. To reduce this risk we require that all people involved with the study remove all metal from their clothing and all metal objects from their pockets. No metal objects are allowed to be brought into the magnet room at any time. In addition, once you are in the magnet, the door to the room will be closed so that no one inadvertently walks into the magnet.

While there are no significant risks from MRI, you may be uncomfortable due to the loud noise and/or feelings of claustrophobia during the MRI. If you experience a sensation of claustrophobia while in the magnet, the MRI will be immediately stopped.

You will be excluded from the study if you have a pacemaker, aneurysm clips, ear (cochlear) implants, or metal fragments in your eyes because of the possibility that the strong magnetic field generated by the MRI will move these foreign objects and cause considerable injury. If you are unsure whether you contain metal in your body, your study doctor may recommend that you have an x-ray to check for metal and help protect you. No serious biologic effects have been reported from the magnetic fields used in clinical MRI.

Risks Associated with PET Scans:

- Discomfort, including shoulder pain;
- Anxiety/claustrophobia.

Risks Associated with I.V. Catheter Placement:

Likely:

- Minor discomfort;
- Bruising;
- Pain in the injection site.

Rare:

- Fainting;
- Bleeding;
- Infection.

Risks Associated with the Imaging Agent [¹¹C]PIB:

- Allergic reaction.

You will receive a low dose of the radioactive agent [¹¹C]PIB. Although no serious adverse events have been linked to the use of this radioactive agent in the past, investigators are still learning about it. Especially if you take medications for other medical conditions or take vitamins or other supplements, let your study doctor and the research staff know about all of them. You may need to adjust the timing of your PET scan(s) to avoid possible interactions between your medications and the radioactive agent.

Risks Associated with the Investigational Imaging Agent [¹⁸F]-AV-45:

- Nausea;
- Allergic reaction.

This research study involves exposure to radiation from the [^{18}F]-AV-45 PET scans and therefore you will receive a radiation dose. This radiation dose is not necessary for your medical care and will occur only as a result of your participation in the study. At doses much higher than you will receive, radiation is known to increase the risk of developing cancer after many years. At the doses you will receive, it is very likely that you will see no effects at all.

Radiation Exposure:

You will receive one injection of [^{11}C]PIB (15 mCi), one [^{18}F]-AV-45 injection (10 mCi), and two PET scans. The radiation exposure from these procedures falls well below (about 16% or one-sixth) federal guidelines that set limits permissible for radiation workers. That means that you would need to have all of these procedures completed about 15 more times to go above the federal exposure guidelines in a year.

Although the radiation exposure from this study is considered to be low, any radiation exposure can put a person at risk for cancer or genetic defects (abnormal cells). You will be asked to drink fluids and to urinate frequently after the [^{11}C]PIB and [^{18}F]-AV-45 scans to further reduce your radiation exposure.

Reproductive Risk:

The risk of these radioactive agents to unborn children is unknown. Therefore, only postmenopausal women (meaning women who have not had menses [their period] for at least two [2] years) will be included in the study.

For more information about risks and side effects, ask your study doctor.

What if new information becomes available about the study?

During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

What are the possible benefits of the study?

You will not receive any direct benefit from participation in this research study. The information from this study will help study doctors learn whether the radioactive agent [^{18}F]-AV-45 will identify abnormal brain tissue (lesions) that are associated with Alzheimer's disease. This knowledge could help doctors better understand Alzheimer's disease, how it worsens, and how well future treatments work. The results from this study could benefit people with Alzheimer's disease in the future. No treatment decisions will be made based on the outcome of this study.

We hope that the information from this research will benefit the community by increasing the ability for doctors to view amyloid (abnormal brain tissue) in the brain and be of future use in the care of patients with Alzheimer's disease.

What other choices do I have if I do not participate?

You may choose not to take part in this study. If you choose not to participate, there will be no penalty or loss of benefits to which you are otherwise entitled. Your treating doctor can tell you the different available imaging scans for your Alzheimer's disease.

Will I be paid for being in this study?

You will be paid for your time and travel. You will receive \$25 for each completed PET scan study visit. If you need to have an MRI at the baseline visit, you will receive \$25 for the completion of the baseline visit. If you choose to participate in the lumbar puncture/spinal tap, you will receive an additional \$100.

If you do not complete the study visits, you will receive partial payment for the portion(s) of the study visits you have completed. Payments will be given for any part of the study which you attempt in good faith but that cannot be completed due to circumstances out of your control (including claustrophobia in the scanner). A check will be mailed to you four to six (4–6) weeks after you complete the study.

Will I have to pay for anything?

There will be no charge to you or your health insurance for participating in any part of this study.

What happens if I am injured or hurt during the study?

It is important that you tell your study doctor if you feel that you have been injured because of taking part in this study. If you believe that you are injured as a result of the research procedures being performed, please immediately contact your study doctor, Dr. Steven Arnold, or a research staff member listed on the first page of this form.

In the event of any physical injury resulting from research procedures, medical treatment will be provided without cost to you, but financial compensation is not otherwise offered from the University of Pennsylvania. There is no plan for monetary compensation if you are injured. You do not, however, waive any legal rights by signing this form.

If you have an illness or injury during this research trial that is not directly related to your participation in this study, you and/or your insurance will be responsible for the cost of the medical care of that illness or injury. You and/or your health insurance may be billed for the costs of medical care during this study if these expenses would have happened even if you were not in the study, or if your insurance agrees in advance to pay.

If you have a medical emergency during the study you should go to the nearest emergency room. You may contact the Principal Investigator or Emergency contact listed on page one of this form. You may also contact your own doctor, or seek treatment outside of the University of Pennsylvania. Be sure to tell the doctor or his staff that you are in a research study being conducted at the University of Pennsylvania. Ask them to call the telephone numbers on the first page of this consent form for further instructions or information about your care.

When is the study over? Can I leave the study before it ends?

This study is expected take place over a two (2) year period and is expected to end after all participants have completed all visits and all information has been collected. This study may also be stopped at any time by your study doctor (the Principal Investigator), the study Sponsor, or the Food and Drug Administration (FDA) without your consent because:

- Your study doctor feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed if such a decision is made and the reason for this decision.
- You have not followed the study instructions.
- The Sponsor, the study doctors, and/or the FDA has decided to stop the study.

If you decide to participate, you are free to leave the study at any time. Withdrawing from this study will not interfere with your future care.

Who can see or use my information? How will my personal information be protected?

We will do our best to make sure that the personal information in your medical record will be kept private according to the law. Your personal information may be given out if required by law.

However, we cannot guarantee total privacy. Although it is highly unlikely, there is still the possibility that information on your identity could be linked back to your research information. For this reason, additional protections will be taken with the information linking the case numbers with your identity. For example, information linking case numbers to your identity will be kept in locked or password-protected files separate from the research records.

Records of your participation on this study, your progress, and images submitted (such as MRI or PET scans) while you are on the study will be kept private at this institution and in a de-identified computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN) in Philadelphia, PA. Your research records and images will be kept permanently on file at ACRIN. Your spinal fluid specimen labeled with an identification number will be stored at the University of Pennsylvania.

If information from this study is published or presented at scientific meetings, your name and other personal information will not be used. If this study is being overseen by the FDA, they may review your research records.

What personal health information is collected and used in this study that might also be disclosed?

The following personal health information will be collected, used for research, and may be disclosed during your involvement with this research study:

- Name, address, telephone number, date of birth
- Personal and family medical history
- Current and past medications or therapies
- Information from a physical examination that generally includes blood pressure reading, heart rate, breathing rate, and temperature
- Results of tests and procedures you will undergo during this research study as described in the informed consent form

Why is your personal contact and health information being used?

Your personal contact information is important for the research team to contact you during the study. Your personal health information and results of tests and procedures are being collected as part of this research study. The information will be collected during the research study will not specifically help you. But, it might help people who have Alzheimer's disease and other conditions in the future.

Which of our personnel may use or disclose your personal health information?

The following individuals may use or disclose your personal health information for this research study at University of Pennsylvania:

- The study doctors and the study team
- Authorized members of the workforce of the University of Pennsylvania Hospital System (UPHS) and the School of Medicine, and University of Pennsylvania support offices, who may need to access your information in the performance of their duties (for example: for research oversight and monitoring, to provide treatment, to manage accounting or billing matters, etc.).

Who, outside of UPHS and the School of Medicine, might receive your personal health information?

As part of the study, the study doctors, the study team and others listed above, may disclose your personal health information, including the results of the research study tests and procedures.

Individuals or organizations responsible for administering the study: Records of your participation on this study, your progress, spinal fluid specimens, and images submitted (such as MRI or PET scans) while you are on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of ACRIN in Philadelphia, PA.

All data sent to ACRIN over the internet will be coded so that other people cannot read it. All personal identifiers are removed and replaced with a unique identifying number. Your research records and images will be kept permanently on file at ACRIN.

The research information of your study participation including the spinal tap specimens may be used for future research. The research that may be done with the information will not specifically help you. But, it might help people who have Alzheimer's disease and other conditions in the future. If any publication or presentations result from this study, you will not be identified by name. Results will be reported in a summarized manner such that you cannot be identified.

Regulatory and safety oversight organizations: Authorized representatives of ACRIN, the Center for Statistical Sciences at Brown University, the FDA, the Institutional Review Board (IRB) of the University of Pennsylvania, and other groups or organizations such as AVID that have a role in this study will have access to and may inspect and/or copy both your medical and research records due to your participation in this study. This access is necessary to ensure the accuracy of the findings and your safety and welfare.

Once your personal health information is disclosed to others outside of UPHS or the School of Medicine, it may no longer be covered by federal privacy protection regulations.

Your study doctor or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may UPHS and the School of Medicine be able to use or disclose your personal health information?

Your authorization for use of your personal health information for this specific study does not expire. Your information may be held in a research repository (database). However, UPHS and the School of Medicine may not re-use or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization to do so
- The University of Pennsylvania's IRB grants permission after ensuring that appropriate privacy safeguards are in place
- As permitted by law

Will you be able to access your records?

During your participation in this study, you might not be able to access some or all of your medical records that pertain to the study information. You will not have access to information generated by this research, which is part of your research record only and not part of your medical record. For example, access to portions of your medical records may be denied where your knowledge of study results could affect the reliability of the study. Your study doctor is not required to release research information to you that is not part of your medical record. You and your informant will be notified of any results found in the MRI or PET scans that will immediately affect your health.

Is your participation in this study voluntary?

Your participation in this study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. However, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed, in general, to participate in the study.

Whether or not you provide your consent for participation in this study will have no effect on your current or future relationship with and medical care at the University of Pennsylvania, Hospital of University of Pennsylvania, and/or affiliated health care provider or your current or future relationship with a health care insurance provider.

Your study doctor may be involved as an investigator in this study. As both your study doctor and a research investigator, s/he is interested both in your medical care and the conduct of this study. Before agreeing to participate in this study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this study. You are not under any obligation to participate in any study offered by your study doctor.

Can you change your mind?

At any time, you may withdraw your consent to allow the use and disclosure of your personal health information as described above and withdraw from participating in the study. You must do so in writing to your study doctor and/or study team at the address on the first page. Even if you withdraw your permission, your personal health information that was collected before we received your written request may still be used and disclosed, as necessary for the study and by law. If you withdraw your permission to use your personal health information, you will also be withdrawn from the research study.

You will be given a copy of this Research Subject HIPAA Authorization describing your confidentiality and privacy rights for this study. You will also be given the UPHS and School of Medicine's Notice of Privacy Practices that contains more information about the privacy of your personal health information.

By signing this document you are permitting the UPHS and the School of Medicine to use and disclose personal health information collected about you for research purposes as described above.

If you agree to participate in this study, can you be removed from the study without your consent?

It is possible that you may be removed from the study by the study doctors if, for example, you are claustrophobic or cannot undergo the MRI or PET scans for any reason.

This study may also be stopped at any time by your study doctor, the study Sponsor, and/or the FDA without your consent because:

- Your study doctor feels it is necessary for your health or safety. Such an action would not require your consent, but you will be informed of the decision and the reason for this decision.
- You have not followed study instructions.
- The Sponsor, the study doctor, and/or the FDA has decided to stop the study.

Any identifiable research or medical information recorded for, or resulting from, your participation in this study prior to the date that you were withdrawn from participation may continue to be used and disclosed by the investigators for the purposes described.

Who can I call with questions, complaints, or if I'm concerned about my rights as a research subject?

If you have questions, concerns, or complaints regarding your participation in this research study, or if you have any questions about your rights as a research subject, you should speak with your study doctor, the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any questions, concerns, or complaints at the University of Pennsylvania by calling (215) 898-2614.

When you sign this form, you are agreeing to take part in this research study. This means that you have read the consent form, your questions have been answered, and you have decided to volunteer. Your signature also means that you are permitting the University of Pennsylvania to use your personal health information collected about you for research purposes within our institution. You are also allowing the University of Pennsylvania to disclose that personal health information to outside organizations or people involved with the operations of this study.

A copy of this consent form will be given to you.

Name of Subject (Please Print)

Signature of Subject

Date

Name of Person Obtaining
Consent (Please Print)

Signature

Date

For subjects unable to give authorization, the authorization is given by the following authorized subject representative:

Authorized Subject
Representative (Please Print)

Authorized Subject
Representative Signature

Date

Provide a brief description of above person authority to serve as the subject's authorized representative.

University of Pennsylvania

**Informed Consent and
HIPAA Authorization Form**

Protocol Title: **AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK**
ACRIN PA 4003

**EVALUATION OF THE ABILITY OF A NOVEL [¹⁸F] AMYLOID
LIGAND ([¹⁸F]-AV-45) TO DISTINGUISH PATIENTS WITH A
CLINICAL DIAGNOSIS OF ALZHEIMER'S DISEASE FROM
COGNITIVELY NORMAL ELDERLY INDIVIDUALS**

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**Research
Coordinator:** **Deb Rooney, RN**
(215) 662-7057

Emergency Contact: Geriatric Psychiatry Attending On-Call
(800) 789-PENN (800-789-7366)

*[Note: ACRIN complies with the privacy measures put forth by
the Health Insurance Portability and Accountability Act (HIPAA). However,
ACRIN does not monitor compliance with HIPAA; that is the responsibility
of the local institutions and their Institutional Review Boards (IRBs).]*

Consent for Lumbar Puncture **(Optional)**

You are being asked to participate in an optional part of the study that involves having a lumbar puncture, sometimes called a “spinal tap.” This procedure is optional for this study, so you may choose to be in the study but not to have the spinal tap. A lumbar puncture is a procedure in which a small amount of the spinal fluid that surrounds the brain and spinal cord is removed by inserting a needle in the lower back.

If you agree to have the spinal tap, your spinal fluid will be stored at the University of Pennsylvania Biomarker Laboratory for future use in research. All your personal information will be removed from the sample before it is stored. Your spinal fluid sample will be labeled with an identification number, but your name will not be provided.

What is the purpose of the lumbar puncture?

The purpose of the lumbar puncture is to collect and analyze the spinal fluid the surrounds the brain and spinal cord, known as cerebrospinal fluid (CSF). CSF contains proteins and other important chemical particles, known as “biomarkers,” that may indicate the existence of Alzheimer’s disease in an individual.

What am I being asked to do?

On the day of the spinal tap, we will ask you to restrict your caffeine intake and not to smoke on the study day.

For this procedure, you will be positioned lying on your side and curled up in a ball, or sitting in a chair next to a bed with your arms and head resting on the bed, whichever is easier for you. The lower part of your back will be cleaned with antiseptic. Your study doctor will inject local anesthetic (lidocaine, 2%) into the skin and muscle of your lower back. When the area is numb, a very thin, long needle will be inserted into the spinal canal in the lower back, well below the level where the spinal cord ends. About 22 milliliters (1½ tablespoons) of spinal fluid will be removed for analysis and storage. Your body replaces this spinal fluid within one to two (1–2) hours.

Most lumbar punctures are successfully completed after the first attempt; however, there are some cases that are more difficult because of arthritis in the lower back, a curve in the spine, or other reasons. If it cannot be completed after the first try we may ask permission to complete the lumbar puncture using a procedure called “fluoroscopy.” This involves using a machine to x-ray the area on your back where the lumbar puncture is done in order to find the best place to insert the needle.

After the lumbar puncture is completed, you will remain in the General Clinical Research Center for about 30 minutes. You will be given something to eat and drink before you leave. You should not do any strenuous physical activity for the next 24 hours. This includes lifting, bending, doing housework and gardening, or doing exercise such as jogging or bicycle riding.

During this study, members of the research team will be monitoring your condition.

Can I be excluded from the lumbar puncture?

Even if you agree to the lumbar puncture, your study doctor may not allow you to have the lumbar puncture procedure. You may or may not be able to undergo the lumbar puncture if you are taking blood thinners, if you have had lower back surgery, if you have severe arthritis in your lower back, or if you have other issues associated with your back or spine. You and your study doctor will discuss these issues before the lumbar puncture is scheduled.

How will my personal information be protected?

All personal identifiers are removed from the CSF and replaced with a unique identifying number. It is then sent out to the lab for analysis. A portion of the spinal fluid will be stored so that it may be available for use in future research studies.

The privacy details as described in the main consent form also apply to the lumbar puncture.

What are the possible risks or discomforts?

Risks of the lumbar puncture/spinal tap (optional procedure):

If you agree to have the optional lumbar puncture/spinal tap, approximately 22 milliliters (1½ tablespoons) of spinal fluid may be taken for this study. Your body will make up for the fluid that was taken. Risks include the following:

Likely

- Temporary pain;
- Tingling sensation;
- Discomfort.

Unlikely

- Headache may occur in people who have had a lumbar puncture. Headache occurs in less than 1 in 100 people who have had this procedure. It is likely caused by a leaking of spinal fluid. If this headache doesn't go away, it may require additional treatment, such as a blood patch. A blood patch is an injection of some of your blood into the lumbar puncture site to patch the spinal fluid leak. This helps the headache immediately.
- Ringing in the ear;
- Dizziness;
- Allergic reaction to the local anesthetic (lidocaine, 2%, which causes numbness) used prior to the lumbar puncture. Less than 1 out of 100 people will have an allergic reaction. The symptoms of an allergic reaction after the injection include:
 - Excessive pain, redness or swelling near the injection site;

- Body rash;
- Wheezing and difficulty breathing.

Please tell your study doctor and/or research staff if you have ever had an allergic reaction to local anesthetic before (such as when you were visiting the dentist).

Rare

- Vomiting;
- Infection;
- Temporary weakness of the eye muscle causing double vision;
- Damage to nerves in your back;
- Bleeding into the spinal fluid space;
- Death.

Less than 1 out of 100 people have had any of these rare risks. To minimize these risks, the lumbar puncture procedure will be done by a neurologist who is trained and experienced in the procedure.

If you have a lumbar puncture done under fluoroscopy, there may be a risk of exposure to radiation. This radiation dose is not necessary for your medical care and will occur only as a result of your participation in this part of the study. With the dose of fluoroscopy that you receive, it is very likely that you will see no side effects at all.

Will I be paid for the lumbar puncture?

As mentioned in the main consent form, you will be paid \$100 for your time and travel to have the lumbar puncture procedure. A check will be mailed to you four to six (4–6) weeks after the lumbar puncture visit has been completed.

Can I stop or refuse the lumbar puncture?

You are free to refuse the lumbar puncture at any time, even if you have agreed to it in this consent form. You may also stop the lumbar puncture at any time during the procedure. Stopping or refusing the lumbar puncture will not interfere with your future care or with your participation in the remainder of the clinical trial.

I agree to participate in the optional **Lumbar Puncture** portion of this study.

☐ YES ☐ NO Subject Initials: _____ Date: _____

Appendix II

ACRIN PA 4003 Eligibility Checklist

The ACRIN PA 4003 Eligibility Checklist is available on the ACRIN web site at ACRIN PA 4003 web page (www.acrin.org/4003_protocol.aspx). For more detailed information, contact the ACRIN PA 4003 Data Manager at ACRIN. The contact information can also be found on the above-mentioned web page.

Appendix III

ACRIN PA 4003 Protocol-Specific Application Information

Application Process

All participating institutions must be ACRIN-approved institutions prior to study participation and accrual. The approval process for ACRIN PA 4003 includes submitting an ACRIN Protocol Specific Application (PSA) and having the PET scanner credentialed for study imaging. Detailed information is available on the ACRIN website (www.acrin.org) under list of current protocols (ACRIN PA 4003). The complete Protocol-Specific Application is on the ACRIN web site at www.acrin.org/4003_protocol.aspx.

Appendix IV

ACRIN PA 4003 Qualification Procedures for PET Imaging and the Image Transmittal Worksheet

Facilities participating in ACRIN clinical research that involves PET or PET/CT must complete a qualifying application for each scanner to be used during the study. Instructions and the qualification application are available online in the Core Labs section of ACRIN's Web site at: www.acrin.org/PETCoreLab.aspx.

Additionally, the Image Transmittal Worksheet needed for submission of imaging materials after each time point/visit is available on the ACRIN web site at www.acrin.org/4003_protocol.aspx under the Imaging Materials section.

Appendix V

ADNI MRI Methods for Non-ADNI Studies

Use of ADNI MRI Methods for Non-ADNI Studies

Version 1: 6-26-2006

ADNI has received a number of inquiries about making ADNI methods available for non-ADNI studies. For MRI, this topic can be divided into three areas, which are addressed individually below. These are the imaging protocol, image corrections, and the ADNI phantom and analysis software.

IMAGING PROTOCOL

The ADNI Exam consists of the following sequences:

Subject Scan

1. Localizer/Scout Scan (20 secs)
2. Straight Sagittal 3D MPRAGE (7-10 mins)
3. Straight Sagittal 3D MPRAGE - REPEAT - (7-10 mins)
4. B1 Calibration Scan Phase Array Coil (*if applicable*) (30 secs)
5. B1 Calibration Scan Body Coil (*if applicable*) (30 secs)
6. Axial Dual Echo T2 FSE (5-7 mins)

Total Scan Time with Phantom 40-45 minutes

The ADNI MRI core has worked closely with contacts at General Electric Healthcare, Siemens Medical Solution and Philips Medical Systems to create protocols which, for a given field strength, produce very similar spatial resolution, contrast, and SNR proper-ties, across vendors and across various systems within each vendor product line. System-specific ADNI protocols can be found listed by MR vendor at the following link: <http://www.loni.ucla.edu/ADNI/Research/Cores/>. Also, a Message/Billboard has been created allowing users to post questions, comments: www.loni.ucla.edu/ADNI then select billboard.

The localizer, and axial dual echo fast spin echo (or turbo spin echo) sequences used in the ADNI protocol are product sequences for all systems; and therefore do not require installation of any special (non-product, also called works-in-progress, WIPS or research) software on the MRI system. The 3D T1-weighted sequence used for morphometric analysis in ADNI is the MPRAGE. Because the MRI portion of ADNI is primarily focused on brain morphology, the MPRAGE sequence constitutes the heart of the ADNI MRI protocol. This sequence is repeated in the protocol in order to increase the probability of obtaining at least one high quality morphometric scan in each exam, and thereby minimize the probability that the subject will need to be rescanned because of scan quality problems (e.g. motion artifact, etc). Variations among the MR manufacturers and within manufacturer product lines exist with respect to the need for image corrections. Also the availability of an MPRAGE pulse sequence that produces images acceptable for ADNI, or an MPRAGE-like equivalent imaging sequence varies across and within manufacturer product lines.

The ADNI MPRAGE sequence is equivalent to product for Siemens systems running software release

VB13 and later, and for Philips systems. It is similar to product for Siemens systems before release VB13. (Also for the Siemens systems a WIPS pulse sequence was required for the B1-calibration prior to release VB13). The ADNI MPRAGE differs from the analogous product on GE systems (IR-FSPGR). Consequently, for the ADNI study, an electronic protocol (but no WIPS pulse sequence) was distributed to ADNI Philips sites. The pulse sequence(s) and electronic protocol software were distributed as a Works-In-Progress (WIP) disc for installation on Siemens and GE scanners. Therefore if you wish to incorporate the ADNI MRI methods into your study we suggest the following:

Philips Systems – use the system specific parameters outlined at: <http://www.loni.ucla.edu/ADNI/Research/Cores/>. Using this PDF documentation, you can enter in the appropriate pulse sequence parameters into your system to replicate the acquisition method used for ADNI. The appropriate Philips contact for information about ADNI is Gregory Metzger, PhD (gmetzger@cmrr.umn.edu).

Siemens Systems – the pulse sequence parameters at <http://www.loni.ucla.edu/ADNI/Research/Cores/> will result in similar image properties when used with the product MPRAGE on pre-VB13 systems. (Note that for VB11 and VB12 systems, protocols that use the “prescan normalization” feature rather than the ADNI B1-calibration are—scheduled to be posted for non-ADNI studies in late summer 2006. This removes the need to obtain any WIPS pulse sequences.) Final crossover testing is still underway, but product MPRAGE at VB13 and beyond seems likely to be indistinguishable from the ADNI MPRAGE. However, if you wish to obtain access to the Siemens ADNI WIP (i.e., the actual ADNI pulse sequence(s) and protocol for Siemens systems), then you should contact Ravi Seethamraju PhD (ravi.seethamraju@siemens.com).

General Electric Systems– Two options exist for obtaining an ADNI or ADNI-like inversion prepared 3D T1-weighted pulse sequence.

Option: 1) use the GE product IR-SPGR sequence. The GE product imaging sequence which most closely resembles the ADNI MPRAGE is IR-FSPGR. GE has added enhancements needed to create a high quality ADNI-like IR-FSPGR to software version 14.0M4, which is scheduled for release in July 2006. The product IR-FSPGR sequence on pre-14.0M4 systems is incompatible with the ADNI protocol in several important ways. For this reason we do not recommend option 1 for employing pre-14.0M4 systems in studies attempting to incorporate ADNI-like MRI methods. IR-FSPGR parameters needed to reproduce an ADNI-like inversion prepared 3D T1-weighted sequence with 14.0M4 will soon be available at <http://www.loni.ucla.edu/ADNI/Research/Cores/> .

Option: 2) obtain the ADNI MPRAGE sequence on CD. This is a viable option for 1.5T systems running software levels 9.1, 11.0M4, 12.0M3A, 12.0M4, 14.0M3 and above. For studies interested in including 3T systems, the ADNI MPRAGE pulse sequence is available for software release VH3 M4, G3, E2, 12.0M4, and 14.0M3 and higher, as well. Matt Bernstein, PhD at Mayo Clinic, Rochester can distribute the ADNI MPRAGE CD compiled at the appropriate system level directly to study sites – but only when all of the following important provisions can be met: First, the MRI system must be run in research mode. Therefore, unless the MRI system already has research mode enabled, the site will need to work with Sandhya Parameswaran, PhD at GE to complete a research key agreement with GE. Second, the study will have to pay for expenses incurred by Matt Bernstein and Bret Borowski for providing support such as creating and sending the CD, answering support question by email, and associated paperwork. Third, the study will need to obtain prior permission from the University of Virginia (UVA) Intellectual Property Office for permission to use of MPRAGE for the study. This is because University of Virginia holds the MPRAGE patent. (Matt Bernstein can provide contact information for how to get that permission from UVA.) Finally, each of the GE sites participating in the

study will have to sign off on GE's standard site-to-site pulse sequence sharing letter agreement with Mayo. This site to site agreement must be signed as is, with no attempted one-of-a-kind modifications by individual sites. Contact information for option 2: Matt Bernstein, PhD (mbernstein@mayo.edu); and Sandhya Parameswaran, PhD (sandhya.parameswaran@med.ge.com).

IMAGE CORRECTIONS

In the actual ADNI study, three types of image non-ideality are corrected by ADNI after the images have been acquired. These are geometric distortion due to gradient nonlinearity, image intensity non-uniformity due to the non-homogeneous characteristics of some RF receiver coil designs, and image non-uniformity due to wave effects (i.e., the so-called “dielectric resonance”) at 3T. These three effects are addressed individually.

Gradient nonlinearity: On some MR systems linearity has been traded off for improved gradient performance characteristics. Gradient nonlinearity results in spatial distortion which should be corrected in all three spatial dimensions for high quality morphometric analyses.

Philips systems: The native images acquired without correction are sufficiently linear for the purposes of ADNI, so no non-linearity correction is employed in ADNI.

Siemens systems: 2D in plane distortion correction is offered as product (although not as the default operating mode) on systems operating at level VB11 and higher. 3D nonlinearity correction is available on Siemens systems at VB13 as a purchasable option.

GE systems: 2D in-plane distortion correction is the default operating mode of all current GE systems. 3D nonlinearity correction (i.e., correction in the slice direction as well) is currently not available as a product feature.

BRM gradient systems seem to require only minimal correction for nonlinearity. Although ADNI does incorporate 3D correction for images acquired on BRM systems, this might not be absolutely necessary, depending on the specific aims of the study. GE systems with TRM (i.e., TwinSpeed) gradients (operating in zoom mode as in the ADNI protocol) will require this correction in 3D.

Because correction for gradient nonlinearity contains proprietary information about gradient coil design, the correction methods cannot be distributed publicly. One option for obtaining 3D correction for gradient non-linearity of MPRAGE images acquired on GE or Siemens systems is to have Anders Dale, PhD (amdale@ucsd.edu) process the images in his laboratory.

Intensity non-uniformity due to non-homogeneous RF receiver coil profiles: For the ADNI imaging protocol, this non-uniformity generally presents itself as a dark center and bright periphery pattern on receive coils—especially multi-element phased arrays (also known as “matrix coils”, etc). Correction for this non-uniformity is available from the manufacturers. On Philips system the correction is called CLEAR, on GE systems PURE, and on Siemens systems PRESCAN NORMALIZE. CLEAR is present on all Philips systems that support multi array receiver coils. PURE is present on 1.5T GE systems at version 12.0 and beyond but is not yet available at 3.0T. PRESCAN NORMALIZE is present on all Siemens systems at the TIM level and beyond. Data from older MRI systems may be corrected for RF receiver coil non-uniformity by contacting Anders Dale (amdale@ucsd.edu) provided the appropriate B1-correction scans are acquired. Note that on some pre-VB13 Siemens systems this might require a WIPS pulse sequence.

Intensity non-uniformity due to wave effects of 3T: The RF wavelength at 3T is half that at 1.5T. One consequence of this is an artifact known by various names, including wave effect or dielectric resonance. This presents as a bright center and dark periphery pattern in the head. At present no correction for this is offered by MR manufacturers to our knowledge. A correction for this has been incorporated in ADNI image pre-processing. When available the ADNI software application will be available under the heading “dielectric correction” at the following link <http://www.loni.ucla.edu/ADNI/Research/Cores/>. Note, that this application is a wrapper script written in perl and makes extensive use of publicly available packages including AIR, N3 and tools from the NIFTI initiative. ADNI MR Core makes the wrapper script and associated documentation freely available, however the ADNI MRI core cannot provide software support.

Appendix VI

Lumbar Puncture Safety Information

Lumbar Punctures

Spinal fluid will be obtained during a separately scheduled out-patient visit in the University of Pennsylvania Clinical and Translational Research Center (CTRC). The lumbar puncture (LP) will be done using a 25 gauge atraumatic Sprotte needle following methods compliant with the Alzheimer's Disease Neuroimaging Initiative (U01 AG02490) protocol. Individuals for whom a LP can not be completed satisfactorily in the Clinical Research Center will be taken to Radiology to have the procedure done under direct fluoroscopic visualization. To avoid even minor contamination from blood associated with needle insertion, the first 1-2 mL of CSF (or more if needed) will be discarded and the next 20 mL processed in the following manner: The first 3 mL will be used for routine tests (cell count, glucose, and total protein). The remaining fluid will be collected in sequential 5 mL volumes (to monitor possible biomarker gradients), transferred into labeled 1.0 mL plastic vials, bar code labeled, and placed in designated locations in a -80 °C freezer equipped with a liquid nitrogen backup.

The project database, in conjunction with a bar code reading system, will be used for inventory control. Bar code labels affixed to each sample vial will contain the following information: sample ID# (to preserve confidentiality), date of collection and processing, total initial volume collected, sample type (urine, plasma, serum, CSF), volume, aliquot number, freezer, shelf, rack, box, location in the box. The same bar code label will be used on the sample tracking form as is used by the technologist when processing and storing samples. This will be done to avoid manual sample number entry errors. When the data are entered into the database the bar code label is scanned in and the sample aliquots entered. Removals of samples will also be tracked on the database including the date removed. Backup safety measures will include alarm systems on each freezer, access to the hospital's emergency generator system for electrical power and CO₂ backup.

Potential Risks of Lumbar Puncture:

Lumbar puncture (LP) may be associated with pain during the procedure. This is usually temporary and confined to the lower back. LP associated headaches occur in fewer than 5% of elderly subjects. Less commonly, a persistent low-pressure headache may develop as a result of a post-LP CSF leakage. Lower rates of post-LP headache have been noted with the atraumatic (Sprotte) 25 gauge needle that will be used in this study. Potentially more serious, but very rare risks, include infection, damage to radicular nerves and bleeding into the lumbar CSF space. The risk of these procedure related complications is much less than 1%.

Penn Memory Center Protocol for Post Spinal Fluid Collection:

The following text is given to each patient at the time of his or her LP:

POST SPINAL FLUID COLLECTION INSTRUCTIONS for the next 48 Hours

How to take care of yourself after a spinal fluid collection

Drink plenty of fluids (avoiding alcohol) for 48 hours following the spinal fluid collection; drink liquids such as water, juice, and caffeinated beverages.

It is very important for you to RELAX. Do not exert yourself by engaging in any strenuous activities such as bending, lifting, vigorous walking, romantic encounters, housework, gardening, jogging, bike riding, tennis, or golf.

The amount of cerebrospinal fluid (CSF) that was collected will be replaced by your body in 1-2 hours.

Possible problems encountered after spinal fluid sampling

The most common problem is mild back soreness at the site of the procedure. You can put ice on your back and/or if you can take Tylenol, use it following the directions on the bottle.

A headache can occur.

It is possible but highly unlikely to experience vomiting, ringing in your ears or dizziness.

What to do if you get a headache following spinal fluid collection

If you get a mild headache following a spinal fluid sampling, LIE DOWN FLAT and drink plenty of fluid. Drink Coke, Coffee, tea, Mountain Dew or some other caffeinated beverage. If you can take Tylenol, use it following the directions on the bottle.

In case of a severe headache, call the appropriate numbers below. Post spinal fluid collection headaches are not life-threatening

In case of life-threatening emergency, dial 911.

How we treat severe post-spinal fluid collection headaches

In the rare event that you get a severe headache that lasts for several days, we can treat it by doing what is called a “blood patch”. This involves an injection of a small amount your own blood at the needle site, which generally provides quick relief. This is done at the hospital as an outpatient procedure.

For all medical concerns related to the spinal fluid collection procedure, please call:

Marianne Watson RN:
marianne.watson@uphs.upenn.edu
215-662-4373 office
215-401-8106 pager
215-662-7810 Penn Memory Center