EVALUATION OF THE ABILITY OF A NOVEL $^{18}$F AMYLOID LIGAND ($^{18}$F3'-F-PIB) TO DISTINGUISH PATIENTS WITH A CLINICAL DIAGNOSIS OF ALZHEIMER’S DISEASE FROM COGNITIVELY NORMAL ELDERLY INDIVIDUALS

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ACRIN PA 4004

EVALUATION OF THE ABILITY OF A NOVEL $^{18}$F AMYLOID LIGAND ($^{18}$F$^{3'}$-F-PIB) TO DISTINGUISH PATIENTS WITH A CLINICAL DIAGNOSIS OF ALZHEIMER’S DISEASE FROM COGNITIVELY NORMAL ELDERLY INDIVIDUALS

SCHEMA

ELIGIBILITY/REGISTRATION

People with Alzheimer’s disease and normal cognitive control participants ages 55 to 90 (inclusive) enrolled in the University of Pittsburgh’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 OR TWO DAYS

Two dynamic PET studies: the first using the $^{11}$CPIB amyloid imaging agent and, the second, using the experimental $^{18}$F$^{3'}$-F-PIB amyloid imaging agent—separated by a minimum of 120 minutes from the injection of $^{11}$CPIB to the beginning of the $^{18}$F$^{3'}$-F-PIB scan.

Safety assessment for $^{18}$F$^{3'}$-F-PIB will comprise pre- and post-imaging assessments of vital signs (blood pressure and pulse), as well as blood sampling for venous metabolites.

First/Second Day: Dynamic PET study using the $^{11}$CPIB agent

ORDER CAN BE REVERSED

First/Second Day: Dynamic PET studies using the experimental $^{18}$F$^{3'}$-F-PIB agent.

Safety assessment for $^{18}$F$^{3'}$-F-PIB 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 $^{[18F]}3'$-F-PIB compared to cognitively normal elderly individuals.

2. There will be no clinically meaningful difference in the amyloid retention performance characteristics of $^{[18F]}3'$-F-PIB and $^{[11C]}$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 15 to 18 months.
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 [11C]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 [18F] amyloid detection ligand ([18F]3’-F-PIB, also known as [18F]AH110690) with respect to its ability to distinguish patients with clinically-diagnosed probable Alzheimer’s disease from cognitively normal elderly participants and to independently compare its diagnostic performance characteristics with the ability of [11C]PIB to correctly categorize the same participants. At the University of Pittsburgh, 15 patients with a clinical diagnosis of probable Alzheimer’s disease and 15 cognitively normal elderly control participants will receive both [18F]3’-F-PIB and [11C]PIB to compare the diagnostic performance characteristics of each 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 [18F]-labeled amyloid ligand, 3’-F-PIB, that binds with high affinity to the amyloid-β (Aβ) 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 Aβ peptide may play an important role in the pathogenesis of the disease. Accumulation of Aβ 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 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 Aβ peptide leading to the formation of pathological aggregation of amyloid. 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. Finally, experimental treatments that reduce Aβ peptide production or increase the clearance of Aβ 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.

A variety of biomarkers for amyloid plaque accumulation have been proposed. In contrast to techniques designed to indirectly estimate levels of brain amyloid plaques from Aβ levels in cerebrospinal fluid, imaging techniques utilizing radiolabeled positron emission tomography (PET) tracers that bind to the aggregated Aβ 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, 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 Aβ pathology and consequent binding of PIB in the cortex of patients with Alzheimer’s disease.

[^18F] 3’-F-PIB

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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 $[^{18}F]3’$-F-PIB compared to cognitively normal elderly individuals.

3.1.2 There will be no clinically meaningful difference in the amyloid retention performance characteristics of $[^{18}F]3’$-F-PIB and $[^{11}C]PIB$ in the brains of normal individuals and participants with the clinical diagnosis of probable Alzheimer’s disease.

3.2 Primary Endpoints
To address the feasibility for further development of $[^{18}F]3’$-F-PIB. Specifically, to conduct a preliminary evaluation of $[^{18}F]3’$-F-PIB 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 3’-F-PIB in the brain can be used to correctly classify participants; and

3.2.2 Estimate the relationship between $[^{18}F]3’$-F-PIB and $[^{11}C]PIB$ among all participants.

3.3 Secondary Endpoints

3.3.1 To explore the SUV patterns from different regions of the brain between cognitively normal and probable Alzheimer’s disease participants.

3.3.2 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 4003 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: $[^{18}F]3'\text{-F-PIB}$ and $[^{11}C]\text{PIB}$ 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 15- to 18-month period, 15 patients with a clinical diagnosis of probable Alzheimer’s disease and 15 cognitively normal elderly participants, evaluated and enrolled through the University of Pittsburgh’s Alzheimer’s Disease Research 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, Aβ 1-42, (see Section 8.4.5) and an MRI using the Alzheimer’s Disease Neuroimaging Initiative (ADNI) protocol (see Section 10.1).
Each participant will have an $^{18}$F-$3'$-F-PIB 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 the administration of the $^{18}$F-$3'$-F-PIB agent. Blood sampling to assess for venous metabolites will be conducted during the experimental $^{18}$F-$3'$-F-PIB PET scan only.

The primary goals of the study (see Section 3) are:
1) To determine whether differences in the uptake and distribution of $^{18}$F-$3'$-F-PIB and $^{11}$C-PIB in the brain can be used to correctly classify participants; and
2) To estimate the relationship between $^{18}$F-$3'$-F-PIB 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 Pittsburgh 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 participant’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, blood tests, MRI, and other procedures if they need to be repeated;

**NOTE:** The cognitive tests and clinical dementia rating assessment must be completed within three (3) months prior to enrollment. The MRI will need to have been completed within the six (6) months prior to enrollment.

6.1.1.6 Able to be scheduled for first (and perhaps only) day of 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 University of Pittsburgh Alzheimer’s Disease Research Center consensus diagnosis of normal cognition;
6.1.2.2 Participant has been cleared of symptoms of clinically meaningful depression;
6.1.2.3 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 Participants with probable Alzheimer’s disease

6.1.3.1 University of Pittsburgh Alzheimer’s Disease Research Center consensus diagnosis of probable Alzheimer’s disease;

6.1.3.2 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 defaults or known structural brain abnormalities.

6.2.2 Neuroimaging: MRI brain scan with evidence of infection, clinically meaningful infarction, or other focal lesions. Participants 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
Pittsburgh’s Alzheimer’s Disease Center longitudinal clinical cohort. Cognitively normal participants 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. Participants 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 cognitively-normal control participants will complete the ACRIN PA 4004 amyloid imaging informed consent process and receive a standardized clinical evaluation at the respective performance sites.

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 for the $[^{18}\text{F}]3'$-F-PIB study);
- Lumbar puncture (optional procedure);
- MRI (per ADNI protocol minus the phantom image)—must be performed if not done within 6 months prior to enrollment;
- Either the study PI or a trained physician or nurse familiar with the protocol must see the participant prior to enrollment.

8.2A VISIT 2: When Both PET Scans Are Done on the Same Day
Within 28 days after enrollment, the participant must begin the imaging scans. However, if there are reasons for the participant to need two days to complete the imaging scans, 28 days maximum are allowed between the first imaging day and the second (see Section 8.2B for details). If the participant can complete both PET scans in a single day, then the following protocol will be followed. Details of the PET imaging protocols can be found below in Section 10.

- Safety examination: Vital signs (blood pressure and pulse for the $[^{18}\text{F}]3'$-F-PIB study);
- Two (2) intravenous catheters (one [1] for each arm) will be used to inject the two agents by bolus and for blood sampling (during the $[^{18}\text{F}]3'$-F-PIB PET scan only);
- $[^{11}\text{C}]$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 the $[^{11}\text{C}]$PIB and the beginning of the $[^{18}\text{F}]3'$-F-PIB scan.
• Following administration of $[^{18}F]3'$-F-PIB, 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 or nurse 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 Separate Days, $[^{11}C]PIB$ Followed by $[^{18}F]3'$-F-PIB or $[^{18}F]3'$-F-PIB Followed by $[^{11}C]PIB$)

If two days of imaging are necessary, they are permissible. The order in which the agents are introduced is not mandated. If the $[^{11}C]PIB$ agent is used, then only one [1] intravenous catheter should be placed on that day to introduce the bolus; if the $[^{18}F]3'$-F-PIB agent is used, then two [2] intravenous catheters will be used on that day, one to introduce the bolus and one to take several small blood samples for metabolite assessment. Other distinctions 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)

• 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;

• When the $[^{11}C]PIB$ PET scan is done, only one (1) intravenous catheter will be necessary—for the bolus injection.

• Either the study PI or a trained physician or nurse familiar with the protocol will see the participant prior to administration of study drug and prior to discharge.

If the $[^{18}F]3'$-F-PIB agent is used (first or second imaging day)

• Safety examination: Vital signs (blood pressure and pulse for the $[^{18}F]3'$-F-PIB study);

• Following administration of $[^{18}F]3'$-F-PIB, participants will have PET brain imaging as defined in the amyloid ligand–specific PET protocol detailed in Section 10;

• When the $[^{18}F]3'$-F-PIB PET scan is done, two (2) intravenous catheters (one [1] for each arm) will be inserted to inject the bolus and for blood sampling;

• 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 or nurse familiar with the protocol will see the participant prior to administration of study drug and prior to discharge.

8.3 FOLLOW UP: Next Day Following Imaging (Day 1)
Clinical team members (a physician or nurse) make phone contact to assess the participant’s 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 **Blood Tests:** Blood sampling will be taken during the experimental $[^{18}\text{F}]3'$-F-PIB PET scan to test venous metabolites.

8.4.3 **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.

8.4.4 **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 participant regarding potential AEs or other treatment issues.

8.4.5 **Lumbar Puncture (optional):** 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 $-80^\circ\text{C}$ 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 are excluded from this study.

8.6 Removal of Participants From Trial

Participants 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 participant to be removed from the trial. Participants 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

<table>
<thead>
<tr>
<th>PROCEDURES</th>
<th>VISIT 1: CLINICAL EVALUATION VISIT†</th>
<th>IMAGING VISIT(S) 2 AND 3—One- or Two-Day Imaging Sequence (Begin Within 28 Days After Enrollment; If Two Days of Scans Are Necessary, They Must Be Performed Within 28 Days of Each Other)</th>
<th>FOLLOW UP: DAY 1 POST IMAGING CONTACT(S)</th>
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<td>Informed Consent</td>
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<td>Eligibility checklist</td>
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<td>UDS demographic &amp; clinical data</td>
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<td>UDS cognitive evaluation</td>
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<td>LP for CSF*</td>
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<td>MRI (1.5T or 3T) – per ADNI protocol</td>
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<tr>
<td>Introduction of one (1) or two (2) intravenous catheters—see Sections 8.2A and 8.2B for details</td>
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<td>X</td>
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<tr>
<td>Vital signs assessment (heart rate and blood pressure) before and after administration of the [18F]3'-F-PIB agent</td>
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<tr>
<td>Blood sampling for venous metabolites (during [18F]3'-F-PIB imaging only)</td>
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<td>[18F]3'-F-PIB PET</td>
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<td>[11C]PIB PET</td>
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<tr>
<td>Post-study follow-up phone contact (or personal contact if two scanning days are immediately sequential)</td>
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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 Pittsburgh’s Alzheimer’s Disease Center 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 ACRIN 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

Participants will have a single intravenous access catheter placed in one arm for administration of the experimental ligand. Another intravenous catheter will be placed in the opposite arm for the determination of venous metabolites, but only on days when the \([^{18}\text{F}]3'\text{-F-PIB}\) agent PET scan is performed.

10.3 \([^{11}\text{C}]\text{PIB}\) PET Imaging Protocol

Approximately 40 minutes following the bolus intravenous injection of 15±1.5 mCi of \([^{11}\text{C}]\text{PIB}\) (administered over 10 to 20 seconds), participants will be placed in the PET scanner, positioned so that the entire brain is in the field of view. (If the dose falls below 8 mCi, the imaging study should be rescheduled and a new dose of the \([^{11}\text{C}]\text{PIB}\) will be needed.) The \([^{11}\text{C}]\text{PIB}\) PET scan will be acquired in dynamic, 3-D imaging mode for 20 minutes (4 x 5 minute frames) beginning 50 minutes (± 10 minutes) after injection of \([^{11}\text{C}]\text{PIB}\). No vital signs assessment will be performed for the \([^{11}\text{C}]\text{PIB}\) PET study, only for the \([^{18}\text{F}]3'\text{-F-PIB}\). Participants will receive 5 to 10 minute transmission scans following each PET scan.

*For same-day imaging only*: 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 \([^{11}\text{C}]\text{PIB}\) and the start of the second ligand image acquisition (i.e., 6 half-lives of \([^{11}\text{C}]\text{PIB}\)). A schematic indicating the PET scanning sequences is shown below (Figure 6) and is intended to be flexible enough to be sensitive to subject comfort but allow for complete data acquisition from participants who wish to complete the full protocol on the same day.

Figure 6. PET imaging protocol for \([^{11}\text{C}]\text{PIB}\) and \([^{18}\text{F}]3'\text{-F-PIB}\)
10.4 $[^{18}\text{F}]3'$-F-PIB PET Imaging Protocol

An intravenous catheter will be placed in one arm for the bolus injections of $[^{11}\text{C}]$PIB followed by $[^{18}\text{F}]3'$-F-PIB (or for $[^{11}\text{C}]$PIB or $[^{18}\text{F}]3'$-F-PIB alone if two [2] days of imaging are necessary). Another intravenous catheter will be placed in the opposite arm for the determination of venous metabolites, but only on days when the $[^{18}\text{F}]3'$-F-PIB agent PET scan is performed.

Approximately 80 minutes following administration of $[^{18}\text{F}]3'$-F-PIB by intravenous bolus injection, participants will be placed in the HR+ PET scanner, 10 minutes later (and between 90 and 120 minutes post-injection) brain imaging will be continuously performed for a period of 30 minutes (6 x 5 minute emission files). Following the 30-minute emission scan of $[^{18}\text{F}]3'$-F-PIB, a 5 to 10 minute transmission scan will be performed to permit attenuation correction. The subject will then be removed from the PET scanner.

Vital signs will be taken prior to administration of $[^{18}\text{F}]3'$-F-PIB for injection, immediately after $[^{18}\text{F}]3'$-F-PIB injection, and just prior to discharge from the PET suite;

Blood samples (venous) for metabolite evaluation will be taken after injection of $[^{18}\text{F}]3'$-F-PIB at the following approximate time intervals: 2, 5, 10, 15, 30, 60, 90, and 120 minutes after $[^{18}\text{F}]3'$-F-PIB administration.

Participants will be encouraged to void at the end of study to minimize bladder radiation dose.

10.5 PET Image Acquisition Technical Details

The PET data will be acquired on a Siemens/CTI ECAT HR+ scanner which utilizes BGO crystals in 3-D imaging mode without septa (63 parallel planes); axial field-of-view: 15.2 cm; in-plane resolution: 4.1 mm full-width at half-maximum; slice width: 2.4 mm). The scanner gantry is equipped with a Neuro-Insert (CTI PET Systems, Knoxville, TN) to reduce the contribution of scattered photon events. PET data will be reconstructed using filtered backprojection (Fourier rebinning and 2D backprojection with Hann filter: kernel FWHM = 3 mm). Data will be corrected for photon attenuation, scatter, and radioactive decay. The final reconstructed PET image resolution will be about 6 mm (transverse and axial) based on in-house point source measurements. After the emission data are acquired, post-injection transmission scans using a Ge-68 source will be obtained for attenuation correction. The emission and transmission data will be reconstructed using filtered backprojection methodology with appropriate ramp filters.

10.6 Quantitative and Qualitative Image Analyses

A quantitative analysis of the PET scan with each agent will be performed locally using methods well established at the site. For qualitative analysis, a 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 baseline diagnosis/participant cohort, but not 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.

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 4004 Images
American College of Radiology
1818 Market Street, Suite 1600
Philadelphia, PA 19103
Attn: Core lab ACRIN PA 4004

11.0 TISSUE SPECIMENS/BIOMARKERS

11.1 CSF Collection
Polypropylene tubes should be used for collection and storage, since Aβ 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 participants 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.

11.2 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 Intravenous Catheters—
the Injection Site:

➢ Pain;
➢ Bruising;
➢ Infection.

12.5.2 \[^{18}\text{F}]3’-F-PIB Investigational Agent—Known Potential Risks:

This section has been intentionally left blank.

12.5.3 \[^{11}\text{C}]\text{PIB Investigational Agent—Known Potential Risks:}

This section has been intentionally left blank.
12.5.4 Expected Adverse Events Associated With PET Scan:

- Discomfort;
- Claustrophobia.

12.5.5 Expected Adverse Events Associated With Lumbar Puncture:

- Pain, usually temporary and confined to the lower back;
- Parethesia and/or discomfort;
- Headaches occurring in fewer than 5% of elderly participants;
- 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.

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 the University of Pittsburgh, ACRIN, and the University of Pittsburgh/Avid (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, the University of Pittsburgh, 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 the University of Pittsburgh and ACRIN by telephone within 24-hours of first knowledge of the event. In the event that the SAE is [\(^{11}\)C]PIB related, the site will need to report to Avid’s SAE line in addition to the University of Pittsburgh and ACRIN within 24 hours of first knowledge of the event. In the case of a [\(^{11}\)C]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 participants’ concomitant medications. The University of Pittsburgh will review all SAEs. If the SAE meets expedited criteria, the University of Pittsburgh will work with the site to prepare a Council for International Organizations of Medical Sciences (CIOMS) form. The University of Pittsburgh will send a written report to the Food and Drug Administration (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. The University of Pittsburgh Hotline at (412) 692-2700
2. ACRIN SAE line at (215) 717-2763
3. In the event that the SAE is determined to be possibly related to $[^{11}C]$PIB, contact the Avid safety line at (609) 356-9955

**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:

- University of Pittsburgh Fax Number: (412) 692-2700
  University of Pittsburgh 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).
  - To confirm receipt of the SAE report, contact:
    Alzheimer’s Disease Research Center (412) 692-2700

- 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 $[^{11}C]$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 $[^{11}C]$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.

### 12.9.4 Completion of SAE Reports Associated With PET Scan

All SAEs considered **possibly, probably, or definitely related to the PET scan** 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. The SAE report must be handled by the following process:

- Telephone reporting within 24 hours of first knowledge of the event is required:
  - ACRIN SAE line at (215) 717-2763
- Submission of an expedited SAE report within three (3) calendar days of first knowledge of the event is required and must be sent to the following:
  - ACRIN SAE Fax Number: (215) 940-8819
  - Local IRB

**NOTE:** In addition to documentation listed above, the AE must also be documented in the participant’s chart and on an AE CRF in order to satisfy routine reporting requirements. 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.
If SAE is possibly related to \[^{11}C\]PIB
UPITT site personnel will notify the following within 24 hours of first knowledge of event:

University of Pittsburgh
[412-692-2700]

Avid Safety Line
[609-356-9955]

ACRIN-SAE Line
[215-717-2763]

UPITT will inform UPENN and/or Avid of SAE within 48-hours of first knowledge of event in cases where the SAE may adversely impact other human participants:

Avid Safety Line
[609-356-9955]

ACRIN PA 4004 SAE Reporting Process
If an SAE occurs at the University of Pittsburgh (UPITT) site

University of Pittsburgh
[412-692-2700]

ACRIN-SAE Line
[215-717-2763]

ACRIN PA 4004 PITT

If SAE is possibly related to \[^{18}F\]PIB
UPITT site personnel will notify the following within 24 hours of first knowledge of event:

Avid Safety Line
[609-356-9955]

ACRIN-SAE Line
[215-717-2763]

UPITT reviews the SAE report and determines whether or not expedited reporting is required.

Expedited reporting is NOT required:
UPITT prepares CIOMS form.

Expedited reporting IS required:
UPITT prepares CIOMS form.

Completed CIOMS will be sent to the FDA (7–15 days), ACRIN, and the UPITT IRB.

Completed CIOMS will be sent to ACRIN.

ACRIN
- ACRIN will add the AE form and SAE report to the calendar for web entry.
- Site will fax web entry confirmation of web entered forms or completed paper forms to UPITT (within 3 calendar days of first knowledge):
  412-692-2700
- ACRIN will be available for assisting the sites with form completion.
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, and ACRIN. 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 at several different time points: after first participant enrolled and during the conduct of the study. 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.

All participating institutions that enroll participants will be audited. The timing of the initial on-site audit will depend upon several factors, including the rate of accrual (both study-wide and site-specific), the number of evaluable participants enrolled at an individual site, the status of the protocol and pending amendments, and monitoring status. Generally, audits will be conducted after the number of evaluable participants reaches 20% of targeted accrual, either study-wide and/or site-specific. Audits are typically scheduled to occur at least 3 months after an institution has been monitored, providing that monitoring did not identify issues that mandate immediate auditing. This schedule may be altered in the event of pending protocol amendments. Closure of the study to accrual will trigger auditing of all participating institutions not yet audited. Additionally, site-specific circumstances may prompt an audit at any time.

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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REFERENCES


CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY
(Control Subject Consent)

TITLE: ACRIN PA 4004 EVALUATION OF THE ABILITY OF A NOVEL $^{18}$F AMYLOID LIGAND ($[^{18}F]3'$-F-PIB) TO DISTINGUISH PATIENTS WITH A CLINICAL DIAGNOSIS OF ALZHEIMER’S DISEASE FROM COGNITIVELY NORMAL ELDERLY INDIVIDUALS

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Research Project Coordinators

Conflict of Interest Statement: The University of Pittsburgh owns a patent application which covers portions of the technology used in this study. Rights to this technology have been licensed to GE Healthcare (formerly Amersham Health), a company that produces diagnostic imaging agents. Drs. Klunk and Mathis, co-investigators on this study, are listed as inventors on these University of Pittsburgh patent applications. Therefore, Drs. Klunk and Mathis have significant financial interest in the technology under study. A plan to manage this conflict of interest has been put into place according to University policy. This plan involves investigators who have no conflict of interest with the technology under study.
Source of Support: American College of Radiology Imaging Network (ACRIN)

[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). Local IRBs may choose to combine the authorization elements in the informed consent.]

The American College of Radiology Imaging Network (ACRIN) and the University of Pittsburgh are conducting a study known as a clinical trial. Your study doctor will explain to you what is involved in this clinical trial. Clinical trials include only people who choose to take part. Please take your time in deciding whether you want to be involved in this 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 informed consent form 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 what risks or benefits are 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 treating doctors. 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 Pittsburgh’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’ individual which means that your brain scans will be used as a comparison with the brain scans of a person that has Alzheimer’s disease.

**Why is this research being done?**

The study is being done to determine whether an investigational radioactive agent, or ‘radiotracer’ called \[^{18}\text{F}]3’-F-PIB\ (also known as \[^{18}\text{F}]\text{AH110690}\) or simply 3’-F-PIB\) in positron emission tomography (PET) scans will help doctors to diagnose and to identify progression of Alzheimer’s disease.

Currently for patients with Alzheimer’s disease, a radioactive agent called \[^{11}\text{C}]\text{PIB}\) (more commonly called “Pittsburgh Compound-B” or simply PIB\) is commonly used in PET scans.

The use of PIB radioactive agents requires specialized equipment that is available to about 1 out of 10 PET facilities around the world. This makes it difficult for people with Alzheimer’s disease to undergo this type of PET scan. This study will use the investigational radioactive agent, 3’-F-PIB, because it may
be more useful to more PET facilities, which would allow for more people with Alzheimer’s disease to have this type of PET scan.

**Who is being asked to take part in this study?**

You are being invited to take part in this study because you have been evaluated at the University of Pittsburgh Alzheimer Disease Research Center (ADRC) and have been given a diagnosis of “Cognitively Normal” (that is, your memory and thinking are normal for your age).

We wish to include a total of 30 individuals in this study. Fifteen of these individuals will have the diagnosis of probable Alzheimer's Disease, and 15 will be cognitively normal, healthy individuals called control participants. 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 participants can complete the full study.

**What procedures will be performed for research purposes?**

To participate in this study, you will be asked to read and sign this informed consent form before you are enrolled to participate in this study. All study visits and tests will be performed at the ADRC 4-West, University of Pittsburgh Medical Center (UPMC) Montefiore or the Lilliane Kaufmann Building. For this study, you are being asked to undergo one PET scan with the PIB radioactive agent and one PET scan with the 3’-F-PIB radioactive agent. Your study doctor and research staff will make sure that you are safe while these images are being done.

**Screening procedures:** 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 prior 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 brain 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 MRI 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.) Research staff in the MRI center will ask you questions regarding your past jobs, activities, and/or hobbies that may cause you to have metal(s) in your body. If you think that metal may be present in your body, you will need to have an x-ray to make sure there is no metal(s). You will be asked to sign an additional consent form to have the x-ray.

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.

4. You will need to agree to release results from previous tests to the doctors conducting this study.

I agree to release my most recent ADRC evaluation results to the doctors conducting this study.

☐ YES  ☐ NO  ___________ Participant’s Initials

Lumbar puncture—this is an optional procedure: You are also being asked to have a lumbar puncture, sometimes called a “spinal tap.” This is an optional procedure in this study, so you may choose to be in the study but not to have the lumbar puncture. If you agree to have the lumbar puncture, your spinal fluid will be sent to and 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 shared and stored. Your spinal fluid sample will be labeled with an identification number, but your name will not be provided.

About Lumbar Puncture (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 choose to have the procedure, you will be asked to lie on your side and curled up in a ball, or to sit up and bend forward, whichever is easier for you.

Your study doctor will clean the lower part of your back with antiseptic and then inject a numbing agent, called lidocaine 1%, into the skin of your lower back. When your back is numb, a very thin, long needle will be inserted into your spinal canal in your lower back, below where the spinal cord ends. The research team will be monitoring your condition throughout the procedure.

About 15 milliliters or 1 tablespoon of spinal fluid will be removed for analysis. Your body replaces this spinal fluid within 1 to 2 hours. After the lumbar puncture is completed, you will remain in the clinic 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 24 hours after the lumbar puncture. 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.

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.

I agree to participate in the Lumbar Puncture/Spinal Tap portion of this study.

☐ YES  ☐ NO  ___________ Participant’s Initials

**Imaging procedures:** All PET imaging scans will be performed at the PET Facility on the 9th floor of UPMC at Presbyterian University Hospital (directly above the MR Research Center).

If you decide to take part in this study, you will be asked to come in to UPMC for a single visit lasting about 5 hours for two PET scans. The first PET scan would be done with the PIB agent and the second with the investigational radiotracer, 3’-F-PIB. However, if you cannot complete both PET scans in a single day, you can ask the research staff to schedule two separate days for the two PET scans. If you have the imaging scans on two different days, it does not matter whether you get PIB or 3’-F-PIB first.

You will receive the investigational radiotracers PIB and 3’-F-PIB. These two radiotracers are currently not approved by the Food and Drug Administration (FDA). The use of PIB and 3’-F-PIB in this study has been reviewed and is considered to be generally safe and effective by the FDA in accordance with its regulations.

**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.

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

1. Before you have the PET scans, your study nurse will place two (2) plastic tubes (called intravenous [i.v.] catheters) in your arms: one in a vein in your left arm and one in a vein in your right arm. The i.v. catheters allow the research staff to take a small amount of blood from one arm and inject the radiotracers PIB and 3’-F-PIB into the other.
You will have your blood taken at different time points during the PET scan using the investigational radiotracer 3’-F-PIB. For this study, a total of 6 1/2 tablespoons (no more than 100 milliliters) of blood will be taken from you.

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 PIB. The PIB radiotracer will be injected into the i.v. catheter in your arm. Fifty (50) minutes after the 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 what is called a transmission scan. The transmission scan will take about 10 to 15 minutes and is done to make sure the equipment is set properly.

c. At least two (2) hours after the PIB injection, the investigational 3’-F-PIB will be injected into the i.v. catheter in your arm. Ninety (90) minutes (1.5 hours) after the 3’-F-PIB is injected, you should already be placed in the PET scanner. The PET scan will last about 30 minutes. During this scan, a blood sample will be taken from the i.v. catheter in your other arm at several different timepoints.

   NOTE: If you have the two (2) PET scans done on the same day, there will be 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.

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

If You Choose to Have Your PET Scans on Two (2) Separate Days
If you and your doctor choose to have the PET scans completed on two separate days, it will not matter which PET scan is completed first. The 3’-F-PIB PET scan (or PIB PET scan) can be done at a second visit as long as it is within 28 days after your first PET scan. In the case of two scanning days, just one (1) i.v. catheter will be needed on the day of the PIB PET scan. But two (2) i.v. catheters will be needed to perform the 3’-F-PIB PET scan. The PIB and 3’-F-PIB PET scanning procedures would otherwise be identical to the processes described above.

Monitoring/follow-up procedures: Procedures performed to ensure your safety and evaluate the safety and effectiveness of the research procedures are called “monitoring” or “follow-up” procedures. For this study, the monitoring/follow-up procedures include:

1. To help cleanse your body and decrease your radiation exposure, you will be asked to drink several glasses of water after each PET scan session and to urinate immediately after the scan session is finished.
2. You will be asked to remain at the PET center for 30 minutes following the PET scan for observation.

3. If you have both PET scans on the same day, your study doctor or nurse will contact you by phone the next day to see how you are doing. If you have two (2) separate days of PET imaging, then you will receive a phone call following each day of imaging. However, if the second imaging day happens to fall on the day right after the first PET scan, the study doctor or nurse will ask how you are doing in person prior to your next PET scan.
### Chart of Visits

<table>
<thead>
<tr>
<th>Visit 1: At the Baseline/Screening Visit</th>
<th>Visit 2: When Both PET Scans Are Completed the Same Day (Within 28 Days After Enrollment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sign the informed consent form;</td>
<td>Within 28 days after enrollment, you will need to go for your PET scan. (The two PET scans can be done either in one [1] day, per the scenario below, or in two [2] days as described below for Visit 3 [Optional].)</td>
</tr>
<tr>
<td>• Have a physical examination, including tests for behavior, mood, and function;</td>
<td>If you are having two PET scans on the same day:</td>
</tr>
<tr>
<td>• Have a test for cognitive skill level (meaning your ability to think, reason, and remember) and presence of dementia—these tests may not be done if you have had cognition testing within three (3) months prior to enrollment:</td>
<td>• Have your vital signs taken as safety measures;</td>
</tr>
<tr>
<td>• Have a lumbar puncture to remove some spinal fluid, if you choose to have it completed (this is an optional procedure);</td>
<td>• Have two (2) i.v. catheters inserted—one (1) in a vein in one arm, one (1) in a vein in the other. This is to inject the PIB and then the 3’-F-PIB agents and to take blood samples during the 3’-F-PIB PET scan only;</td>
</tr>
<tr>
<td>• Have an MRI scan of the brain, if one has not been done within six (6) months prior to enrollment.</td>
<td>• Have PIB injected into one (1) intravenous catheter;</td>
</tr>
<tr>
<td></td>
<td>• Fifty (50) minutes after the PIB injection, have a PET scan for about 30 minutes;</td>
</tr>
<tr>
<td></td>
<td>• Wait at least two (2) hours after the first PET scan;</td>
</tr>
<tr>
<td></td>
<td>• Have 3’-F-PIB injected into an i.v. catheter at least two (2) hours after the first PET scan;</td>
</tr>
<tr>
<td></td>
<td>• Have small blood samples taken at different time points from the other i.v. catheter;</td>
</tr>
<tr>
<td></td>
<td>• Ninety (90) minutes after the 3’-F-PIB injection, have the second PET scan for about 30 minutes;</td>
</tr>
<tr>
<td></td>
<td>You will be monitored throughout the PET scans and for at least 30 minutes after the scans are completed. Your study doctor or nurse will check in on you prior to being released from the center.</td>
</tr>
</tbody>
</table>
Visit 3: (Optional) When the PET Scans Are Done on Two (2) Separate Days (Second Imaging Day Must Occur Within 28 Days of First Imaging Day)

If you cannot or choose not to have both PET scans in the same day, a second visit will be scheduled to complete the second PET scan. The second scan must be completed within 28 days after the first scan:

- Have the second imaging scan using either PIB or 3’-F-PIB, depending on which was done on the first scan day (see details above);
- If the second PET scan uses the PIB agent, then only one (1) i.v. catheter will be placed in your arm to inject the PIB;
- If the second day of scanning involves the 3’-F-PIB agent, then two (2) i.v. catheters will be needed so that blood sampling can be done during the PET scan.

You will be monitored throughout the PET scans and for at least 30 minutes afterward the scan is complete. Your study doctor or nurse will check in on you prior to being released from the center.

Follow Up: The Day After the Second PET Scan

The day after the PET scans (or the day after each PET scan), your study doctor or a nurse will call you to ask how you are doing. If the second PET scan is done on the day immediately after the first PET scan, then the study doctor or a nurse will ask you how you are doing in person prior to the next scan.

How long will I be in the study?

If you choose to participate, you will be in the study for about three (3) months. After your initial baseline/screening visit, you will be scheduled for two (2) PET scans. You will have the two (2) PET scans on the same day. However, if that is not possible, your first PET scan will be scheduled within 28 days after your baseline/screening visit; then, the second PET scan will be scheduled within 28 days after the first PET scan.

Of course, you can refuse to do any of the scans at any time and your participation in the study will be terminated.

What are the possible risks, side effects, and discomforts of this study?

Possible risks and side effects during this study are related to collecting blood, mood and behavior tests, the placement of i.v. catheters, the lumbar puncture (if you choose to have this procedure done), the MRI, the x-ray (if required), the radiation exposure from the scans and the PIB and 3’-F-PIB radiotracers, the PET scans, and/or having to lie still during the imaging scans. Research staff members are involved in this trial have been trained to minimize any risks. As with any investigational study, some side effects of 3’-F-PIB may be unknown, and it is possible that certain unknown risks could be serious.
**Risks of the cognitive skill level tests:** The tests for mood and mental status may be slightly frustrating or produce fatigue and/or boredom.

**Risks of the lumbar puncture/spinal tap (optional):** If you agree to have the optional lumbar puncture/spinal tap, approximately 1 tablespoon (15 milliliters) of spinal fluid may be taken for this study. Your body will make up for the fluid that was taken within one-to-two hours. 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 1%, 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 of the local anesthetic 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 in the past (such as when you were visiting the dentist).

**Rare**
- Vomiting;
- Infection;
- Temporary weakness of the eye muscles 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 reactions. To minimize these risks, the lumbar puncture procedure will be done by a neurologist who is trained and experienced in the procedure.
**Risks of the placement of the i.v. catheters:**

*Likely*

Ten (10) to 25 out of 100 people getting intravenous (i.v.) catheters will experience bruising and soreness from the placement of the catheter in an arm vein and repeated drawing of blood.

*Rare*

Fewer than 1 out of 100 people experience fainting, bleeding, or infection associated with catheter placement in the vein and repeated drawing of blood.

**Risks of MRI:** The potential risk from MRI is that the machine attracts metal. Research staff in the MRI center will ask you questions regarding your past jobs, activities, and/or hobbies that may cause you to have metal(s) in your body. If you think that metal may be present in your body, you will need to have an x-ray to make sure there is no metal(s). You will be asked to sign an additional consent form to have the x-ray. If you have metal within your body (e.g., aneurysm clips or pacemakers), you will not be able to take part in the study. Participants with dental fillings can take part in the study without these risks.

*Likely*

About 10 to 25 out of every 100 people who have an MRI experience claustrophobia. Claustrophobia means you are anxious or frightened because you are in a small space. For the MRI, you will be asked to lie with your head and neck inside a narrow scanner tube. If you have had claustrophobia before, you should tell your study doctor or study nurse. If you feel claustrophobic during the study or feel that you cannot stay in the scanner, the MRI scan can be stopped and you will be able to rest outside of the scanner. You will be in voice contact with the research staff at all times during the MRI.

**Risks of X-ray:** If an X-ray is required to see if you have metal fragments, the risks can be found in the additional consent form that you will be asked to review and sign.

**Risks of PET scan:** The risks from the PET scans include discomfort and claustrophobia. Claustrophobia means you are anxious or frightened because you are in a small space. For the PET scan, you will be asked to lie with your head and neck inside a narrow scanner tube. If you have had claustrophobia before, you should tell your study doctor or study nurse. If you feel claustrophobic during the study or feel that you cannot stay in the scanner, the PET scan can be stopped and you will be able to rest outside of the scanner. You will be in voice contact with the research staff at all times during the PET scan.

**Risks of radiation exposure, including PET scans and the PIB and 3’-F-PIB radioactive agents:**

Participating in this study will involve exposure to radiation from the PET scans and the radioactive agents PIB and 3’-F-PIB.

You will receive one injection of PIB (15 mCi), one 3’-F-PIB injection (10 mCi), and two PET scans. The radiation exposure from these procedures fall 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 PIB and 3’-F-PIB PET scans to further reduce your radiation exposure.

PIB and 3’-F-PIB are investigational agents and are not currently approved by the Food and Drug Administration (FDA); however their use in this study is considered to be generally safe and effective as approved by the FDA in accordance with its regulations (21 CFR 361.1).

**Rare**
As with the administration of any drug, fewer than 1 out of 100 people will experience an allergic reaction, and you will be monitored for any reactions. The PET Facility provides a fully equipped medical cart, and a physician will always be available.

**Reproductive risk:** The risk of the investigational radioactive agents to an unborn child 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.

**What are possible benefits from taking part in this 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 3’-F-PIB 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 for you 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 in the brain and therefore help with the care of patients with AD in the future.

**What treatments or procedures are available if I decide not to take part in this study?**
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.

**If I agree to take part in this study, will I be told of any new risks that may be found during the course of 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.

**Who will be charged for the costs of procedures performed as part of this study?**

None of the study services and/or procedures (clinical tests, blood work, MRI scan, lumbar puncture, or PIB and 3’-F-PIB PET scan studies) will be billed to you or your health insurance. If you get a bill or believe your health insurance has been billed for something that is part of the study, notify a member of the research team or UPMC Patient Billing Services.

**Will I be paid if I take part in this study?**

You will be paid a total of $250.00 if you complete all the study visits to pay for your time and travel. In addition, any parking fees related to participation in this study will be paid for by the study.

If you do not complete the study visits, you will receive partial payment for the portion(s) of the study visits you have completed. If, for whatever reason, you complete only part but not all of the study, the terms of this payment will be as follows: 1) Fifty dollars ($50.00) will be paid for completion of Visit 1, 2) One hundred dollars ($100.00) for completion of the Visit 2/3—for the PIB scan, and 3) One hundred dollars ($100.00) for completion of the Visit 2/3—the 3’-F-PIB PET scan. If you have a lumbar puncture/spinal tap, you will be paid an additional $200.00 for the completion of Visit 1 and the lumbar puncture.

Payment according to the above schedule 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).

**Who will pay if I am injured as a result of taking part in this study?**

University of Pittsburgh researchers and their associates who provide services at the UPMC recognize the importance of your voluntary participation in their research studies. These individuals and their staff will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research. If you believe that you are injured as a result of the research procedures being performed, please immediately contact the Principal Investigator, Dr. James Mountz, or a co-investigator listed on the first page of this form.

Emergency medical treatment for injuries solely and directly related to your participation in this study will be provided to you by the hospitals of the UPMC. It is possible that the UPMC may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care unless otherwise specifically stated below. There is no plan for monetary compensation if you are injured. You do not, however, waive any legal rights by signing this form.
How will my medical records be kept private? Who will know about my participation in this study?

Any information about you obtained from or for this study will be kept as private as possible according to the law. Although it is highly unlikely, there is still the possibility that information on your identity could be linked back to your research information. All paper records that could identify your involvement in this study will be stored in a locked file cabinet. All electronic records that could identify your involvement will be stored in password-protected files. Your identity on these records will be indicated by a case number rather than by your name.

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. 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 and 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.

About Your Privacy: Spinal Fluid Sample

All of your personal information will be removed from the spinal fluid sample collected during the lumbar puncture/spinal tap before it is shared and stored. Your spinal fluid sample will be labeled with an identification number, but your name will not be provided. Your identity will remain confidential. The spinal fluid sample will be sent and stored at the University of Pennsylvania. Data will be stored in a locked file and in a computer with restricted access. Any information that could be used to identify you in the computer will be stored in a separate file and encrypted or coded to preserve your privacy. Only the University of Pennsylvania investigators and their research assistants will have access to the original research data.

Data from your spinal fluid test will not be revealed to family members, insurance companies, employers, or other individuals or organizations. Any information gained from this research will be reported in anonymous summary form. The samples will be retained indefinitely. No information regarding the biomarker research will be entered into your regular medical record. Study investigators will maintain and be responsible for deciding how your samples and the information obtained from them will be used.

Only de-identified data, which does not include anything that might directly identify you, will be shared with ACRIN members and the general scientific community for research purposes.

Access to your research records will be limited to the researchers listed on the first page of this form. Authorized representatives of ACRIN, the Center for Statistical Sciences at Brown University, the FDA, the University of Pittsburgh’s Human Use Subcommittee (HUSC) of the Radioactive Drug Research
Committee (RDRC), the Institutional Review Board (IRB) of the University of Pittsburgh, GE and Avid (for safety purposes only) and other groups or organizations 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. 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.

**Will this study involve the use or disclosure of my identifiable medical information?**

Yes. This study will involve the recording of current and/or future identifiable medical information from your hospital and/or other (e.g., Alzheimer Disease Research Center evaluation) records. The information that will be recorded will be limited to information concerning your diagnosis, age, level of education, memory test results (neuropsychological testing), past medical and psychiatric history, previous MRI, PET, or CT scans, and results of any blood tests. This information will be used for the purpose of identifying whether you meet the conditions for participation in this study, to compare your memory tests to the findings from this study and, if possible, to use your previous MRI exam results in place of or in addition to the MRI exam needed for this study.

This study may result in identifiable information that will be placed into your medical records held at the UPMC.

**Who will have access to identifiable information related to my participation in this study?**

In addition to the investigators listed on the first page of this authorization (informed consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this study:

The staff of the UPMC PET facility will have access to your identifiable research information (which may include your identifiable medical information) for the purpose of performing the PET studies done as part of this protocol.

Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office and ACRIN may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this study.

In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical information) related to your participation in this study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.
Authorized representatives of the U.S. FDA may review and/or obtain identifiable information (which may include your identifiable medical information) related to your participation in this study as a result of this agency’s oversight of the radiotracers, PIB and 3’-F-PIB. While the U.S. FDA understands the importance of maintaining the privacy of your identifiable research and medical information, the University of Pittsburgh and UPMC cannot guarantee the confidentiality of this information after it has been obtained by the U.S. FDA.

Authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this study?
The investigators may indefinitely continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this study.

May I have access to my medical information that results from my participation in this study?
In accordance with the UPMC Notices of Privacy Practices document, you are permitted access to information (including information resulting from your participation in this study) contained within your medical records filed with your health care provider unless otherwise specifically stated below. 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.

Is my 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 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 Pittsburgh, UPMC hospital or affiliated health care provider, or your current or future relationship with a health care insurance provider.

Your doctor may be involved as an investigator in this study. As both your 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 doctor.

**May I withdraw, at a future date, my consent for participation in this study?**

You may withdraw, at any time, your consent for participation in this study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable information for the purposes described above, you will also be withdrawn from further participation in this study.) Any identifiable research or medical information recorded for, or resulting from, your participation in this study prior to the date that you formally withdraw your consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for participation in this study, you should provide a written and dated notice of this decision to your study doctor and/or study team at the address listed on the first page of this form.

Your decision to withdraw your consent for participation in this study will have no effect on your current or future relationship with the University of Pittsburgh. Your decision to withdraw your consent for participation in this study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

**If I agree to participate in this study, can I be removed from the study without my consent?**

It is possible that you may be removed from the study by the investigators 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.
VOLUNTARY CONSENT

All of the information above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form.

Any questions I have about my rights as a research participant will be answered by the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh 1-866-212-2668. By signing this form, I agree to participate in this study. A copy of this consent form will be given to me.

Participant’s Signature*       Date

CERTIFICATION OF INFORMED CONSENT: I certify that I have explained the nature and purpose of this research to the above individual(s) and/or their proxy representative, and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise.

Printed Name of Person Obtaining Consent       Role in Study

Signature of Person Obtaining Consent       Date
CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY
(AD Subject Consent)

TITLE: ACRIN PA 4004 EVALUATION OF THE ABILITY OF A NOVEL $^{18}$F AMYLOID LIGAND ($^{18}$F$^{3'}$-F-PIB) TO DISTINGUISH PATIENTS WITH A CLINICAL DIAGNOSIS OF ALZHEIMER’S DISEASE FROM COGNITIVELY NORMAL ELDERLY INDIVIDUALS

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Conflict of Interest Statement: The University of Pittsburgh owns a patent application which covers portions of the technology used in this study. Rights to this technology have been licensed to GE Healthcare (formerly Amersham Health), a company that produces diagnostic imaging agents. Drs. Klunk and Mathis, co-investigators on this study, are listed as inventors on these University of Pittsburgh patent applications. Therefore, Drs. Klunk and Mathis have significant financial interest in the technology under study. A plan to manage this conflict of interest has been put into place according to University policy. This plan involves investigators who have no conflict of interest with the technology under study.
Source of Support: American College of Radiology Imaging Network (ACRIN)

[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). Local IRBs may choose to combine the authorization elements in the informed consent.]

The American College of Radiology Imaging Network (ACRIN) and the University of Pittsburgh are conducting a study known as a clinical trial. Your study doctor will explain to you what is involved in this clinical trial. Clinical trials include only people who choose to take part. Please take your time in deciding whether you want to be involved in this 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 informed consent form 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 what risks or benefits are 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 treating doctors. 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 Pittsburgh’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’ individual which means that your brain scans will be used as a comparison with the brain scans of a person that has Alzheimer’s disease.

Why is this research being done?
The study is being done to determine whether an investigational radioactive agent, or ‘radiotracer’ called \([^{18}F]3’-\text{F-PIB}\) (also known as \([^{18}F]\text{AH110690}\) or simply \(3’-\text{F-PIB}\)) in positron emission tomography (PET) scans will help doctors to diagnose and to identify progression of Alzheimer’s disease.

Currently for patients with Alzheimer’s disease, a radioactive agent called \([^{11}C]\text{PIB}\) (more commonly called “Pittsburgh Compound-B” or simply PIB) is commonly used in PET scans.
The use of PIB radioactive agents requires specialized equipment that is available to about 1 out of 10 PET facilities around the world. This makes it difficult for people with Alzheimer’s disease to undergo this type of PET scan. This study will use the investigational radioactive agent, 3’-F-PIB, because it may be more useful to more PET facilities, which would allow for more people with Alzheimer’s disease to have this type of PET scan.

Who is being asked to take part in this study?
You are being invited to take part in this study because you have been evaluated at the University of Pittsburgh Alzheimer Disease Research Center (ADRC) and have been given a diagnosis of probable Alzheimer’s Disease.

We wish to include a total of 30 individuals in this study. Fifteen of these individuals will have the diagnosis of probable Alzheimer's Disease, and 15 will be cognitively normal, healthy individuals called control participants. 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 participants can complete the full study.

What procedures will be performed for research purposes?
To participate in this study, you will be asked to read and sign this informed consent form before you are enrolled to participate in this study. All study visits and tests will be performed at the ADRC 4-West, University of Pittsburgh Medical Center (UPMC) Montefiore or the Lilliane Kaufmann Building. For this study, you are being asked to undergo one PET scan with the PIB radioactive agent and one PET scan with the 3’-F-PIB radioactive agent. Your study doctor and research staff will make sure that you are safe while these images are being done.

Screening procedures: 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 prior magnetic resonance imaging (MRI) scan.

If you have not had an MRI scan of your brain within the 6 months prior to 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 brain 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 MRI 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.) Research staff in the MRI center will ask you questions regarding your past jobs, activities, and/or hobbies that may cause you to have metal(s) in your body. If you think that metal may be present in your body, you will need to have an x-ray to make sure there is no metal(s). You will be asked to sign an additional consent form to have the x-ray.

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.

4. You will need to agree to release results from previous tests to the doctors conducting this study.

I agree to release my most recent ADRC evaluation results to the doctors conducting this study.

☐ YES  ☐ NO  ___________ Participant’s Initials

Lumbar puncture—this is an optional procedure: You are also being asked to have a lumbar puncture, sometimes called a “spinal tap.” This is an optional procedure in this study, so you may choose to be in the study but not to have the lumbar puncture. If you agree to have the lumbar puncture, your spinal fluid will be sent to and 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 shared and stored. Your spinal fluid sample will be labeled with an identification number, but your name will not be provided.

About Lumbar Puncture (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 choose to have the procedure, you will be asked to lie on your side and curled up in a ball, or to sit up and bend forward, whichever is easier for you.
Your study doctor will clean the lower part of your back with antiseptic and then inject a numbing agent, called lidocaine 1%, into the skin of your lower back. When your back is numb, a very thin, long needle will be inserted into your spinal canal in your lower back, below where the spinal cord ends. The research team will be monitoring your condition throughout the procedure.

About 15 milliliters or 1 tablespoon of spinal fluid will be removed for analysis. Your body replaces this spinal fluid within 1 to 2 hours. After the lumbar puncture is completed, you will remain in the clinic 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 24 hours after the lumbar puncture. 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.

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.

I agree to participate in the Lumbar Puncture/Spinal Tap portion of this study.

☐ YES ☐ NO ___________ Participant’s Initials

**Imaging procedures:** All PET imaging scans will be performed at the PET Facility on the 9th floor of UPMC at Presbyterian University Hospital (directly above the MR Research Center).

If you decide to take part in this study, you will be asked to come in to UPMC for a single visit lasting about 5 hours for two PET scans. The first PET scan would be done with the PIB agent and the second with the investigational radiotracer, 3’-F-PIB. However, if you cannot complete both PET scans in a single day, you can ask the research staff to schedule two separate days for the two PET scans. If you have the imaging scans on two different days, it does not matter whether you get PIB or 3’-F-PIB first.

You will receive the investigational radiotracers PIB and 3’-F-PIB. These two radiotracers are currently not approved by the Food and Drug Administration (FDA). The use of PIB and 3’-F-PIB in this study has been reviewed and is considered to be generally safe and effective by the FDA in accordance with its regulations.
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.

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

1. Before you have the PET scans, your study nurse will place two (2) plastic tubes (called intravenous [i.v.] catheters) in your arms: one in a vein in your left arm and one in a vein in your right arm. The i.v. catheters allow the research staff to take a small amount of blood from one arm and inject the radiotracers PIB and 3’-F-PIB into the other.

You will have your blood taken at different time points during the PET scan using the investigational radiotracer 3’-F-PIB. For this study, a total of 6 1/2 tablespoons (no more than 100 milliliters) of blood will be taken from you.

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 PIB. The PIB radiotracer will be injected into the i.v. catheter in your arm. Fifty (50) minutes after the 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 what is called a transmission scan. The transmission scan will take about 10 to 15 minutes and is done to make sure the equipment is set properly.

c. At least two (2) hours after the PIB injection, the investigational 3’-F-PIB will be injected into the i.v. catheter in your arm. Ninety (90) minutes (1.5 hours) after the 3’-F-PIB is injected, you should already be placed in the PET scanner. The PET scan will last about 30 minutes. During this scan, a blood sample will be taken from the i.v. catheter in your other arm at several different time points.

NOTE: If you have the two (2) PET scans done on the same day, there will be 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.

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

If You Choose to Have Your PET Scans on Two (2) Separate Days
If you and your doctor choose to have the PET scans completed on two separate days, it will not matter which PET scan is completed first. The 3’-F-PIB PET scan (or PIB PET scan) can be done at a second visit as long as it is within 28 days after your first PET scan. In the case of two scanning days, just one (1) i.v. catheter will be needed on the day of the PIB PET scan. But two (2) i.v. catheters will be needed to perform the 3’-F-PIB PET scan. The PIB and 3’-F-PIB PET scanning procedures would otherwise be identical to the processes described above.

**Monitoring/follow-up procedures:** Procedures performed to ensure your safety and evaluate the safety and effectiveness of the research procedures are called “monitoring” or “follow-up” procedures. For this study, the monitoring/follow-up procedures include:

1. To help cleanse your body and decrease your radiation exposure, you will be asked to drink several glasses of water after each PET scan session and to urinate immediately after the scan session is finished.

2. You will be asked to remain at the PET center for 30 minutes following the PET scan for observation.

3. If you have both PET scans on the same day, your study doctor or nurse will contact you by phone the next day to see how you are doing. If you have two (2) separate days of PET imaging, then you will receive a phone call following each day of imaging. However, if the second imaging day happens to fall on the day right after the first PET scan, the study doctor or nurse will ask how you are doing in person prior to your next PET scan.
**Chart of Visits**

<table>
<thead>
<tr>
<th>Visit 1: At the Baseline/Screening Visit</th>
<th>Visit 2: When Both PET Scans Are Completed the Same Day (Within 28 Days After Enrollment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sign the informed consent form;</td>
<td>Within 28 days after enrollment, you will need to go for your PET scan. (The two PET scans can be done either in one [1] day, per the scenario below, or in two [2] days as described below for Visit 3 [Optional].)</td>
</tr>
<tr>
<td>• Have a physical examination, including tests for behavior, mood, and function;</td>
<td>If you are having two PET scans on the same day:</td>
</tr>
<tr>
<td>• Have a test for cognitive skill level (meaning your ability to think, reason, and remember) and presence of dementia—these tests may not be done if you have had cognition testing within three (3) month prior to enrollment:</td>
<td>• Have your vital signs taken as safety measures;</td>
</tr>
<tr>
<td>• Have a lumbar puncture to remove some spinal fluid, if you choose to have it completed (this is an optional procedure);</td>
<td>• Have two (2) i.v. catheters inserted—one (1) in a vein in one arm, one (1) in a vein in the other. This is to inject the PIB and then the 3'-F-PIB agents and to take blood samples during the 3'-F-PIB PET scan only;</td>
</tr>
<tr>
<td>• Have an MRI scan of the brain, if one has not been done within six (6) months prior to enrollment.</td>
<td>• Have PIB injected into one (1) intravenous catheter;</td>
</tr>
</tbody>
</table>

You will be monitored throughout the PET scans and for at least 30 minutes after the scans are completed. Your study doctor or nurse will check in on you prior to being released from the center.
Visit 3: (Optional) When the PET Scans Are Done on Two (2) Separate Days (Second Imaging Day Must Occur Within 28 Days of First Imaging Day)

If you cannot or choose not to have both PET scans in the same day, a second visit will be scheduled to complete the second PET scan. The second scan must be completed within 28 days after the first scan:

- Have the second imaging scan using either PIB or 3’-F-PIB, depending on which was done on the first scan day (see details above);
- If the second PET scan uses the PIB agent, then only one (1) i.v. catheter will be placed in your arm to inject the PIB;
- If the second day of scanning involves the 3’-F-PIB agent, then two (2) i.v. catheters will be needed so that blood sampling can be done during the PET scan.

You will be monitored throughout the PET scans and for at least 30 minutes afterward the scan is complete. Your study doctor or nurse will check in on you prior to being released from the center.

Follow Up: The Day After the Second PET Scan

The day after the PET scans (or the day after each PET scan), your study doctor or a nurse will call you to ask how you are doing. If the second PET scan is done on the day immediately after the first PET scan, then the study doctor or a nurse will ask you how you are doing in person prior to the next scan.

How long will I be in the study?

If you choose to participate, you will be in the study for about three (3) months. After your initial baseline/screening visit, you will be scheduled for two (2) PET scans. You will have the two (2) PET scans on the same day. However, if that is not possible, your first PET scan will be scheduled within 28 days of your baseline/screening visit; then, the second PET scan will be scheduled within 28 days of the first PET scan.

Of course, you can refuse to do any of the scans at any time and your participation in the study will be terminated.

What are the possible risks, side effects, and discomforts of this study?

Possible risks and side effects during this study are related to collecting blood, mood and behavior tests, the placement of i.v. catheters, the lumbar puncture (if you choose to have this procedure done), the MRI, the x-ray (if required), the radiation exposure from the scans and the PIB and 3’-F-PIB radiotracers, the PET scans, and/or having to lie still during the imaging scans. Research staff members are involved in this trial have been trained to minimize any risks. As with any investigational study,
some side effects of 3’-F-PIB may be unknown, and it is possible that certain unknown risks could be serious.

**Risks of the cognitive skill level tests:** The tests for mood and mental status may be slightly frustrating or produce fatigue and/or boredom.

**Risks of the lumbar puncture/spinal tap (optional):** If you agree to have the optional lumbar puncture/spinal tap, approximately 1 tablespoon (15 milliliters) of spinal fluid may be taken for this study. Your body will make up for the fluid that was taken within one-to-two hours. 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 1%, 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 of the local anesthetic 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 in the past (such as when you were visiting the dentist).

**Rare**
- Vomiting;
- Infection;
- Temporary weakness of the eye muscles 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 reactions. To minimize these risks, the lumbar puncture procedure will be done by a neurologist who is trained and experienced in the procedure.

**Risks of the placement of the i.v. catheters:**

*Likely*

Ten (10) to 25 out of 100 people getting intravenous (i.v.) catheters will experience bruising and soreness from the placement of the catheter in an arm vein and repeated drawing of blood.

*Rare*

Fewer than 1 out of 100 people experience fainting, bleeding, or infection associated with catheter placement in the vein and repeated drawing of blood.

**Risks of MRI:** The potential risk from MRI is that the machine attracts metal. Research staff in the MRI center will ask you questions regarding your past jobs, activities, and/or hobbies that may cause you to have metal(s) in your body. If you think that metal may be present in your body, you will need to have an x-ray to make sure there is no metal(s). You will be asked to sign an additional consent form to have the x-ray. If you have metal within your body (e.g., aneurysm clips or pacemakers), you will not be able to take part in the study. Participants with dental fillings can take part in the study without these risks.

*Likely*

About 10 to 25 out of every 100 people who have an MRI experience claustrophobia. Claustrophobia means you are anxious or frightened because you are in a small space. For the MRI, you will be asked to lie with your head and neck inside a narrow scanner tube. If you have had claustrophobia before, you should tell your study doctor or study nurse. If you feel claustrophobic during the study or feel that you cannot stay in the scanner, the MRI scan can be stopped and you will be able to rest outside of the scanner. You will be in voice contact with the research staff at all times during the MRI.

**Risks of X-ray:** If an X-ray is required to see if you have metal fragments, the risks can be found in the additional consent form that you will be asked to review and sign.

**Risks of PET scan:** The risks from the PET scans include discomfort and claustrophobia. Claustrophobia means you are anxious or frightened because you are in a small space. For the PET scan, you will be asked to lie with your head and neck inside a narrow scanner tube. If you have had claustrophobia before, you should tell your study doctor or study nurse. If you feel claustrophobic during the study or feel that you cannot stay in the scanner, the PET scan can be stopped and you will be
able to rest outside of the scanner. You will be in voice contact with the research staff at all times during the PET scan.

**Risks of radiation exposure, including PET scans and the PIB and 3’-F-PIB radioactive agents:**
Participating in this study will involve exposure to radiation from the PET scans and the radioactive agents PIB and 3’-F-PIB.

You will receive one injection of PIB (15 mCi), one 3’-F-PIB injection (10 mCi), and two PET scans. The radiation exposure from these procedures fall 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 PIB and 3’-F-PIB PET scans to further reduce your radiation exposure.

PIB and 3’-F-PIB are investigational agents and are not currently approved by the Food and Drug Administration (FDA); however their use in this study is considered to be generally safe and effective as approved by the FDA in accordance with its regulations (21 CFR 361.1).

**Rare**
As with the administration of any drug, fewer than 1 out of 100 people will experience an allergic reaction, and you will be monitored for any reactions. The PET Facility provides a fully equipped medical cart, and a physician will always be available.

**Reproductive risk:** The risk of the investigational radioactive agents to an unborn child 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.

**What are possible benefits from taking part in this 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 3’-F-PIB 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 for you 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 in the brain and therefore help with the care of patients with AD in the future.

**What treatments or procedures are available if I decide not to take part in this study?**
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.

**If I agree to take part in this study, will I be told of any new risks that may be found during the course of 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.

**Who will be charged for the costs of procedures performed as part of this study?**
None of the study services and/or procedures (clinical tests, blood work, MRI scan, lumbar puncture, or PIB and 3'-F-PIB PET scan studies) will be billed to you or your health insurance. If you get a bill or believe your health insurance has been billed for something that is part of the study, notify a member of the research team or UPMC Patient Billing Services.

**Will I be paid if I take part in this study?**
You will be paid a total of $250.00 if you complete all the study visits to pay for your time and travel. In addition, any parking fees related to participation in this study will be paid for by the study.

If you do not complete the study visits, you will receive partial payment for the portion(s) of the study visits you have completed. If, for whatever reason, you complete only part but not all of the study, the terms of this payment will be as follows: 1) Fifty dollars ($50.00) will be paid for completion of Visit 1, 2) One hundred dollars ($100.00) for completion of the Visit 2/3—for the PIB scan, and 3) One hundred dollars ($100.00) for completion of the Visit 2/3—the 3'-F-PIB PET scan. If you have a lumbar puncture/spinal tap, you will be paid an additional $200.00 for the completion of Visit 1 and the lumbar puncture.

Payment according to the above schedule 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).
**Who will pay if I am injured as a result of taking part in this study?**

University of Pittsburgh researchers and their associates who provide services at the UPMC recognize the importance of your voluntary participation in their research studies. These individuals and their staff will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research. If you believe that you are injured as a result of the research procedures being performed, please immediately contact the Principal Investigator, Dr. James Mountz, or a co-investigator listed on the first page of this form.

Emergency medical treatment for injuries solely and directly related to your participation in this study will be provided to you by the hospitals of the UPMC. It is possible that the UPMC may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care unless otherwise specifically stated below. There is no plan for monetary compensation if you are injured. You do not, however, waive any legal rights by signing this form.

**How will my medical records be kept private? Who will know about my participation in this study?**

Any information about you obtained from or for this study will be kept as private as possible according to the law. Although it is highly unlikely, there is still the possibility that information on your identity could be linked back to your research information. All paper records that could identify your involvement in this study will be stored in a locked file cabinet. All electronic records that could identify your involvement will be stored in password-protected files. Your identity on these records will be indicated by a case number rather than by your name.

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. 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 and 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.

**About Your Privacy: Spinal Fluid Sample**

All of your personal information will be removed from the spinal fluid sample collected during the lumbar puncture/spinal tap before it is shared and stored. Your spinal fluid sample will be labeled with an identification number, but your name will not be provided. Your identity will remain confidential. The spinal fluid sample will be sent and stored at the University of Pennsylvania. Data will be stored in
a locked file and in a computer with restricted access. Any information that could be used to identify you in the computer will be stored in a separate file and encrypted or coded to preserve your privacy. Only the University of Pennsylvania investigators and their research assistants will have access to the original research data.

Data from your spinal fluid test will not be revealed to family members, insurance companies, employers, or other individuals or organizations. Any information gained from this research will be reported in anonymous summary form. The samples will be retained indefinitely. No information regarding the biomarker research will be entered into your regular medical record. Study investigators will maintain and be responsible for deciding how your samples and the information obtained from them will be used.

Only de-identified data, which does not include anything that might directly identify you, will be shared with ACRIN members and the general scientific community for research purposes.

Access to your research records will be limited to the researchers listed on the first page of this form. Authorized representatives of ACRIN, the Center for Statistical Sciences at Brown University, the FDA, the University of Pittsburgh’s Human Use Subcommittee (HUSC) of the Radioactive Drug Research Committee (RDRC), the Institutional Review Board (IRB) of the University of Pittsburgh, GE and Avid (for safety purposes only) and other groups or organizations 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. 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.

**Will this study involve the use or disclosure of my identifiable medical information?**

Yes. This study will involve the recording of current and/or future identifiable medical information from your hospital and/or other (e.g., Alzheimer Disease Research Center evaluation) records. The information that will be recorded will be limited to information concerning your diagnosis, age, level of education, memory test results (neuropsychological testing), past medical and psychiatric history, previous MRI, PET, or CT scans, and results of any blood tests. This information will be used for the purpose of identifying whether you meet the conditions for participation in this study, to compare your memory tests to the findings from this study and, if possible, to use your previous MRI exam results in place of or in addition to the MRI exam needed for this study.

This study may result in identifiable information that will be placed into your medical records held at the UPMC.
Who will have access to identifiable information related to my participation in this study?

In addition to the investigators listed on the first page of this authorization (informed consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this study:

The staff of the UPMC PET facility will have access to your identifiable research information (which may include your identifiable medical information) for the purpose of performing the PET studies done as part of this protocol.

Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office and ACRIN may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this study.

In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical information) related to your participation in this study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

Authorized representatives of the U.S. FDA may review and/or obtain identifiable information (which may include your identifiable medical information) related to your participation in this study as a result of this agency’s oversight of the radiotracers, PIB and 3’-F-PIB. While the U.S. FDA understands the importance of maintaining the privacy of your identifiable research and medical information, the University of Pittsburgh and UPMC cannot guarantee the confidentiality of this information after it has been obtained by the U.S. FDA.

Authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this study?

The investigators may indefinitely continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this study.
May I have access to my medical information that results from my participation in this study?

In accordance with the UPMC Notices of Privacy Practices document, you are permitted access to information (including information resulting from your participation in this study) contained within your medical records filed with your health care provider unless otherwise specifically stated below. 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.

Is my 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, 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 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 Pittsburgh, UPMC hospital or affiliated health care provider, or your current or future relationship with a health care insurance provider.

Your doctor may be involved as an investigator in this study. As both your 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 doctor.

May I withdraw, at a future date, my consent for participation in this study?

You may withdraw, at any time, your consent for participation in this study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable information for the purposes described above, you will also be withdrawn from further participation in this study.) Any identifiable research or medical information recorded for, or resulting from, your participation in this study prior to the date that you formally withdraw your consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for participation in this study, you should provide a written and dated notice of this decision to your study doctor and/or study team at the address listed on the first page of this form.
Your decision to withdraw your consent for participation in this study will have no effect on your current or future relationship with the University of Pittsburgh. Your decision to withdraw your consent for participation in this study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

**If I agree to participate in this study, can I be removed from the study without my consent?**
It is possible that you may be removed from the study by the investigators 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.

******************************************************************************
VOLUNTARY CONSENT

All of the information above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form.

Any questions I have about my rights as a research participant will be answered by the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh 1-866-212-2668. By signing this form, I agree to participate in this study. A copy of this consent form will be given to me.

________________________________   __________________
Participant’s Signature*     Date

ACRIN PA 4004 PITT   Page 93   Participant’s initials:______
*USE THE FOLLOWING ONLY WHEN APPLICABLE

Participant’s Name (Print)

The above-named participant is unable to provide direct consent for study participation because:___________________________________________________________

_____________________________________________________________________

Therefore, by signing this form, I give my consent for his/her participation in this research study.

Representative’s Name (Print)  Representative’s Relationship to Participant

Representative’s Signature  Date

Witness’ Signature  Date

ACKNOWLEDGEMENT OF RELATIVE OR CAREGIVER: I certify that I have read the preceding or it has been read to me and that I understand its contents. Any questions I have pertaining to the participation of ___________________________ (Name of Participant) have been and will be answered by Dr. Mountz and/or his designee. Any questions I have regarding the rights of ___________________________ (Name of Participant) as a research participant will be answered by the Human Subjects Protection Advocate, Institutional Review Board at 1-866-212-2668. A copy of this consent form will be given to me. My signature below means that I have freely agreed to the participation of ___________________________ (Name of Participant) in this study.

Date  Signature  Relationship
VERIFICATION OF EXPLANATION

I certify that I have carefully explained the purpose and nature of this research to

in appropriate language. He/she has had an opportunity to discuss it with me in detail. I have answered all of his/her questions and he/she provided affirmative agreement (i.e., assent) to participate in this research.

________________________________   __________________
Investigator’s Signature     Date

CERTIFICATION OF INFORMED CONSENT: I certify that I have explained the nature and purpose of this research to the above individual(s) and/or their proxy representative, and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise.

__________________________________________ ________________________
Printed Name of Person Obtaining Consent   Role in Study

__________________________________________ ________________________
Signature of Person Obtaining Consent   Date
ADDENDUM CONSENT FORM
ADDITIONAL X-RAY EXAM FOR MRI STUDY
CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: ACRIN PA 4004 EVALUATION OF THE ABILITY OF A NOVEL [18F] AMYLOID LIGAND ([18F]3'-F-PIB) TO DISTINGUISH PATIENTS WITH A CLINICAL DIAGNOSIS OF ALZHEIMER’S DISEASE FROM COGNITIVELY NORMAL ELDERLY INDIVIDUALS

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Participant’s initials:_______
The University of Pittsburgh is owner of a patent application which covers portions of the technology used in this research study. Rights to this technology have been licensed to GE Healthcare (formerly Amersham Health), a company that produces diagnostic imaging agents. Drs. Klunk and Mathis, co-investigators on this study, are listed as inventors on these University of Pittsburgh patent applications. Therefore, Drs. Klunk and Mathis have significant financial interest in the technology under study. A plan to manage this conflict of interest has been put into place according to University policy. This plan involves investigators who have no conflict of interest with the technology under study.

SOURCE OF SUPPORT: American College of Radiology Imaging Network (ACRIN)

DESCRIPTION:

You have consented to participate in a research study entitled, “ACRIN PA 4004.” As addressed in the consent form for this research study, you have agreed to undergo a brain imaging procedure called Magnetic Resonance Imaging (MRI). The MRI scanner uses a strong magnet to obtain a picture of the brain. Because of the powerful magnet, metal objects within your body could move, and this movement could result in your injury. Based on the medical or occupational history that you have provided, there is a possibility that some foreign metal object(s) may be present in your body or around your eyes. In order to determine whether any foreign metal exists within your body, you will need to have an additional X-ray exam prior to receiving the MRI study. This X-ray exam will be performed in the Radiology department of UPMC at Presbyterian University Hospital on the first floor and will take approximately 20 minutes.

RISKS and BENEFITS:

Risks of X-Ray:
The additional X-ray exam involves exposure to radiation. The maximum amount of radiation exposure that you will receive from the additional X-ray exam is approximately 0.3 rem (a unit of radiation exposure) to the area of the body evaluated, with minimal exposure of other areas of your body. For comparison, this is a small fraction (about 1% to 2%) of the annual radiation exposure (20 rems) permitted to the most sensitive organs of radiation workers by federal regulations. There is no minimal level of radiation exposure that is recognized as being totally free of the risk of causing genetic mutations (abnormal cells) or cancer. However, the risk associated with the amount of radiation exposure that you will receive from this additional X-ray exam is considered to be low and comparable to everyday risks.

RIGHT to WITHDRAW:
I understand that, in order for me to have the MRI scan and continue to participate in the main research study, I will need to have the additional X-ray exam. I understand that I may refuse to participate in the additional X-ray exam which will also result in my withdrawal from the main research study. As addressed in the consent form for the main research study, I understand that such refusal to participate in the additional X-ray exam will have no effect on my current or future medical care or any other benefits to which I am otherwise entitled.

**COSTS and PAYMENTS:**

None of the procedures (X-ray) you receive during this research study will be billed to you or your health insurance. If you get a bill or believe your health insurance has been billed for something that is part of the study, notify a member of the research team or UPMC Patient Billing Services.

**VOLUNTARY CONSENT:**

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form.

Any questions I have about my rights as a research participant will be answered by the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh (866-212-2668). By signing this form, I agree to participate in this research study. A copy of this consent form will be given to me.

________________________________   __________________
Participant’s Signature*     Date

*USE THE FOLLOWING ONLY WHEN APPLICABLE

__________________________________________
Participant’s Name (Print)

The above-named participant is unable to provide direct consent for study participation because:_________________________________________________________________
________________________________________________________________________

Therefore, by signing this form, I give my consent for his/her participation in this research study.
ACKNOWLEDGEMENT OF RELATIVE OR CAREGIVER: I certify that I have read the preceding or it has been read to me and that I understand its contents. Any questions I have pertaining to the participation of ________________________________ (Name of Participant) have been and will be answered by Dr. Mountz and/or his designee. Any questions I have regarding the rights of ________________________________ (Name of Participant) as a research participant will be answered by the Human Subjects Protection Advocate, Institutional Review Board at 1-866-212-2668. A copy of this consent form will be given to me. My signature below means that I have freely agreed to the participation of ________________________________ (Name of Participant) in this study.

Date Signature Relationship

VERIFICATION OF EXPLANATION
I certify that I have carefully explained the purpose and nature of this research to

in appropriate language. He/she has had an opportunity to discuss it with me in detail. I have answered all of his/her questions and he/she provided affirmative agreement (i.e., assent) to participate in this research.

Investigator’s Signature Date

CERTIFICATION OF INFORMED CONSENT: I certify that I have explained the nature and purpose of this research to the above individual(s) and/or their proxy representative, and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise.
<table>
<thead>
<tr>
<th>Printed Name of Person Obtaining Consent</th>
<th>Role in Research Study</th>
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<tr>
<td>Signature of Person Obtaining Consent</td>
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Appendix II

ACRIN PA 4004 Eligibility Checklist

The ACRIN PA 4004 Eligibility Checklist is available on the ACRIN web site at ACRIN PA 4004 web page (www.acrin.org/4004_protocol.aspx). For more detailed information, contact the ACRIN PA 4004 Data Manager at ACRIN. The contact information can also be found on the above-mentioned web page.
Appendix III

ACRIN PA 4004 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 4004 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 4004). The complete Protocol-Specific Application is on the ACRIN web site at www.acrin.org/4004_protocol.aspx.
Appendix IV

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/4004_protocol.aspx under the Imaging Materials section.
Appendix V
ADNI MRI Methods

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 properties, 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/](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](http://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 NORMAL-IZE 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.