

Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study:
A Coverage with Evidence Development Longitudinal Cohort Study

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List of Abbreviations and Acronyms

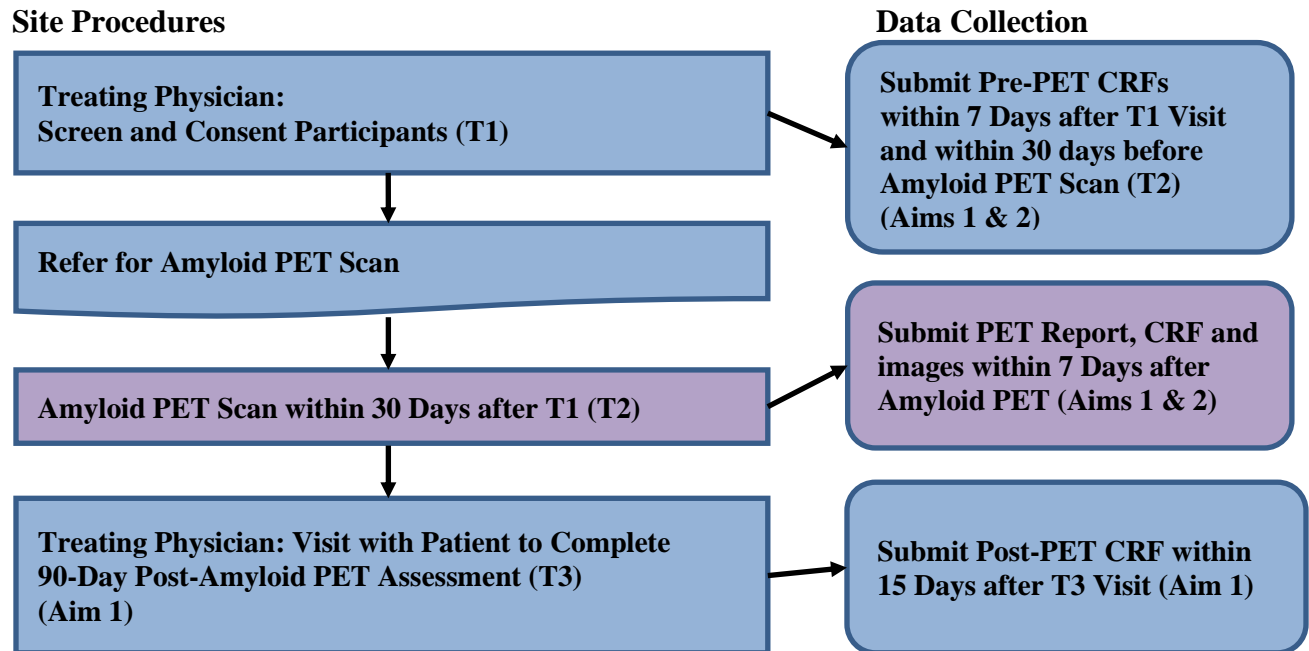
AAIC	Alzheimer’s Association International Conference
A β	Beta-Amyloid
ACR	American College of Radiology
ACRIN	American College of Radiology Imaging Network
AD	Alzheimer’s Disease
ADC	Apparent Diffusion Coefficient
AUC	Appropriate Use Criteria
BAA	Business Associate Agreement
BC	Biostatistics Center
BDMC	Biostatistics and Data Management Center
BGO	Bismuth Germanate
CBC	Complete Blood Count
CED	Coverage with Evidence Development
CMS	Centers for Medicare & Medicaid Services
CRF	Case Report Form
CT	Computed Tomography
DMC	Data Management Center
DVD	Digital Video Disk or Digital Versatile Disk
EC	Ethics Committee
FDA	Food and Drug Administration
FDG	F-18 fluorodeoxyglucose
FFS	Fee-For-Service
FTD	Frontotemporal Dementia
GCP	Good Clinical Practice
GSO	Gadolinium Oxyorthosilicate
HIPAA	Health Insurance Portability and Accountability Act
IAC	Intersocietal Accreditation Commission
ICD	International Classification of Diseases
ICF	Informed Consent Form
ICH	International Committee on Harmonisation
IRB	Institutional Review Board
KPNC	Kaiser Permanente Northern California
LSO	Lutetium Oxyorthosilicate
LYSO	Lutetium Yttrium Orthosilicate
MCI	Mild Cognitive Impairment
MDP	Multidisciplinary Dementia Program
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
N.A.	Not Applicable
NaF	F-18 Sodium Fluoride
NaI	Sodium Iodide
NCD	National Coverage Determination
NIH	National Institutes of Health
NOPR	National Oncology PET Registry
OHRP	Office for Human Research Protections
PET	Positron Emission Tomography
PET/CT	Positron Emission Tomography/Computed Tomography

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PET/MRI	Positron Emission Tomography/Magnetic Resonance Imaging
POLST	Physician Ordered Life-Sustaining Treatment
SOC	Standard of Care
SSDI	Social Security Death Index
U.S.	United States
TSH	Thyroid Stimulating Hormone

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SCHEMA: Longitudinal Cohort



Additional detail is provided in the Flow Chart provided in Appendix I.

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STUDY OBJECTIVES/SPECIFIC AIMS

The Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study will establish an open-label, longitudinal cohort study to assess the impact of amyloid PET on patient outcomes under Coverage with Evidence (CED) in patients meeting Appropriate Use Criteria (AUC) for amyloid PET (Johnson et al. 2013). Our hypothesis is that amyloid PET will decrease uncertainty and increase confidence in the underlying cause of cognitive impairment, that this will translate into earlier counseling and interventions in these domains, and that these interventions will lead to improved outcomes.

Aim 1: To assess the impact of amyloid PET on the management of patients meeting Appropriate Use Criteria (AUC). [Clinical Data to address Aim 1 will be collected for the first 11,050 participants in this study.]

Aim 2: To assess the impact of amyloid PET on hospital admissions and emergency room visits in patients enrolled in the study cohort (*amyloid PET-known*) compared to matched patients not in the cohort (*amyloid PET-naïve*) over 12 months. [CMS Claims Data to address Aim 2 will be collected from all participants registered to the longitudinal study cohort and from concurrent controls matched according to a validated algorithm.]

ELIGIBILITY (see Section 5.0 for details)

Participants must be Medicare beneficiaries referred by qualified dementia specialists who meet AUC for amyloid PET (Johnson et al. 2013). Specifically, patients must meet the following criteria:

- 1) Cognitive complaint verified by objectively confirmed cognitive impairment.
- 2) The etiologic cause of cognitive impairment is uncertain after a comprehensive evaluation by a dementia expert, including general medical and neurological examination, mental status testing including standard measures of cognitive impairment (e.g., Mini Mental State Examination [MMSE] or Montreal Cognitive Assessment), laboratory testing for toxic-metabolic disturbances and structural neuroimaging (CT or MRI).
- 3) Alzheimer’s disease (AD) is a diagnostic consideration.
- 4) Knowledge of amyloid PET status is expected to alter diagnosis and management.

Patients will be recruited into one of two sub-cohorts:

- 5) Progressive, unexplained mild cognitive impairment (MCI); and
- 6) Dementia of uncertain etiology.

SAMPLE SIZE

Aim 1. The projected prospectively-recruited sample size of *amyloid PET-known* participants for Aim 1 is **11,050** participants (assuming a distribution of 40% dementia and 60% MCI).

Aim 2. The projected prospectively-recruited sample size of *amyloid PET-known* participants for Aim 2 is **18,488** participants.

1.0 ABSTRACT

This protocol for a prospective human research study will be conducted according to United States and international standards of Good Clinical Practice (International Conference on Harmonisation [ICH] Guidelines), applicable government regulations (e.g., Title 45, Part 46 Code of Federal Regulations) and the American College of Radiology Imaging Network (ACRIN) research policies and procedures.

The IDEAS Study is an observational, open-label, longitudinal cohort study designed to assess the impact of amyloid PET on patient-oriented outcomes in Medicare beneficiaries with mild cognitive impairment (MCI) or dementia of uncertain etiology. The study falls under Centers for Medicare & Medicaid Services (CMS) Coverage with Evidence Development (CED) research. A total of 18,488 Medicare beneficiaries meeting Appropriate Use Criteria (AUC) to direct the recommendation for amyloid PET will be enrolled over 24 months at sites throughout the United States. Dementia specialists will team with PET facilities that have access to perform amyloid PET and with trained radiologists/nuclear medicine physicians, all of whom will consent to completing the data requirements and timelines for the study. Amyloid PET will be performed and interpreted at each facility with results provided to the ordering physician for support in further decision making, which will be captured for the study.

Our over-arching hypothesis is that in diagnostically uncertain cases, knowledge of amyloid status as determined by amyloid PET will lead to significant changes in patient management, and that this will translate into improved long-term outcomes. We will pursue two specific aims.

Aim 1 investigates the impact of amyloid PET on short-term patient management, by comparing pre-PET *intended* management (ascertained in a case report form [CRF] prior to PET) to post-PET *actual* management (CRF completed 90 days post-PET) in a cohort of *amyloid PET-known* patients. The primary objective will be to test whether amyloid PET testing leads to a $\geq 30\%$ change between intended and actual patient management plan within 90 days in a cumulative endpoint consisting of: AD drug therapy, other drug therapy, and counseling about safety and future planning. Secondary objectives will assess the impact of amyloid PET results on clinical diagnosis and prevention of unnecessary diagnostic procedures and treatments.

Aim 2 utilizes Medicare claims data to compare medical outcomes at 12 months for patients enrolled in the longitudinal cohort with from a matched control cohort of patients who have never undergone amyloid PET imaging (*amyloid PET-naïve*). The primary objective will be to determine if amyloid PET testing in the amyloid PET-known cohort of patients is associated with a $\geq 10\%$ reduction in hospitalizations and emergency room visits in comparison to the matched amyloid PET-naïve patients. Secondary objectives will examine whether knowledge of amyloid PET status reduces hospitalizations related to ambulatory-sensitive conditions, whether the association between amyloid PET knowledge and health outcomes varies by baseline cognitive status (MCI versus dementia) and amyloid status (amyloid positive versus negative). The amyloid PET-naïve cohort will be identified via a matching algorithm where each individual in the amyloid PET-known cohort will be matched to one individual with similar dementia diagnosis, pre-scan dementia-related resource utilization, age, race, gender, ethnicity, geographic location, and comorbid chronic conditions likely to impact cognition or the outcomes of interest seen at the same time as the amyloid PET-known patient (*concurrent control*).

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In pursuing these Aims, we will generate valuable observational data on clinical utility that will inform future use of this technology in diagnostic algorithms, and develop a cohort of patients who undergo amyloid PET and can serve as a foundation to address future research questions.

The Study Chair is Dr. Gil Rabinovici, Associate Professor of Neurology at the University of California, San Francisco, a behavioral neurologist with research expertise in amyloid PET. The leadership team includes Dr. Bruce Hillner from Virginia Commonwealth University and Dr. Barry Siegel from Washington University, the chair and co-chair, respectively, of the National Oncologic PET Registry (NOPR), one of the most influential registries developed in response to the CMS CED requirements. The data management and statistical analyses will be managed by the American College of Radiology (ACR)/ACRIN and Brown University, which were the data hosts for statistical evaluations in National Oncology PET Registry (NOPR) (under the leadership of Dr. Constantine Gatsonis). The study leadership team further includes Dr. Rachel Whitmer, a Senior Scientist and Epidemiologist at Kaiser Permanente Division of Research and an expert on population-based studies of dementia risk factors and outcomes. The protocol development has been coordinated by the Alzheimer's Association, under the leadership of Dr. Maria Carrillo, Vice President of Medical & Scientific Relations, and the ACR.

2.0 OBJECTIVES

Aim 1 investigates the impact of amyloid PET on short-term patient management, by comparing pre-PET *intended* management (documented in a case report form [CRF] prior to amyloid PET imaging) to post-PET *actual* management (CRF completed within 15 days of the T3 90-day visit [75-105 day allowable range] after PET scan.). (Data to address Aim 1 will be collected from the initial 11,050 participants registered in the longitudinal cohort.)

Aim 2 uses Medicare claims data from a total of 18,488 participants accrued in the longitudinal cohort and concurrent controls. Analyses in Aim 2 will be restricted to participants enrolled in fee-for-service (FFS) Medicare (i.e., excludes participants covered by Medicare Advantage). Participants in the longitudinal cohort (*amyloid PET-known*) who are FFS enrollees will be matched to concurrent controls (*amyloid PET-naïve*).

2.1 Aim 1

To assess the impact of amyloid PET on the management of patients meeting Appropriate Use Criteria (AUC)

2.1.1 Primary Objective

Test whether amyloid PET imaging will lead to a $\geq 30\%$ change between *intended* and *actual* patient management within 90 days (75-105 day allowable range) in a composite measure of at least one of the following:

- a) AD drug therapy;
- b) Other drug therapy; and
- c) Counseling about safety and future planning.

The hypothesis will be tested separately for MCI and dementia subgroups.

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2.1.2 Secondary Objectives

- 2.1.2.1 Estimate how frequently amyloid PET leads to a change in primary suspected etiological diagnosis (from AD to non-AD condition and vice versa).
- 2.1.2.2 Estimate the frequency of reduction in unnecessary diagnostic tests and AD drug therapy.

2.1.3 Exploratory Objectives

- 2.1.3.1 Assess the agreement between pre-PET suspected etiology (AD or non-AD condition) and amyloid PET results (positive or negative).
- 2.1.3.2 Identify specific diagnostic scenarios in which amyloid PET has the highest impact on patient management.
- 2.1.3.3 Evaluate the impact of amyloid PET on referrals to therapeutic trials for both AD and non-AD causes of cognitive impairment.

2.2 Aim 2

To assess the impact of amyloid PET on hospital admissions and emergency room visits in patients enrolled in the cohort (amyloid PET-known) compared to matched patients not in the cohort (amyloid PET-naïve) over 12 months

2.2.1 Primary Objective

- 2.2.1.1 Determine if amyloid PET is associated with a $\geq 10\%$ relative reduction in amyloid PET-known patients in comparison to matched amyloid PET-naïve patients in the following:
 - a) Inpatient hospital admissions over 12 months.
 - b) Emergency room visits over 12 months.

2.2.2 Secondary Objectives

- 2.2.2.1 Determine if amyloid PET is associated with a reduction in preventable hospitalizations (as defined by ambulatory care-sensitive conditions) over 12 months.
- 2.2.2.2 Determine if the association between knowledge of amyloid PET status and outcomes varies by baseline cognitive status (MCI versus dementia).
- 2.2.2.3 Determine if the association between knowledge of amyloid PET status and outcomes will significantly vary by amyloid PET result (amyloid-positive vs. amyloid-negative).
- 2.2.2.4 Assess the impact of knowledge of amyloid PET status on aggregate healthcare resource utilization over 12 months.

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2.2.3 Exploratory Objective

2.2.3.1 To examine if components of the patient clinical management plan (AD drug therapy, non-AD drug therapy, counseling about safety and future planning) are differentially associated with medical outcomes (reduction in hospitalizations and emergency room visits) at 12 months within the longitudinal study cohort.

2.3 Image Collection

The IDEAS Study will collect and archive amyloid PET images from enrolled subjects, except those who specifically indicate that they do not consent to having their images collected and archived. The archived images will serve as a resource for future research.

3.0 INTRODUCTION/BACKGROUND

Alzheimer’s disease (AD) is the leading cause of dementia, affecting an estimated 5.2 million Americans, 96% of whom are age 65 or older (Thies and Bleiler 2013). The prevalence of AD is increasing with the aging population, and is expected to reach 13.8 million by 2050. AD is the sixth leading cause of death in the United States and the fifth leading cause of death in Americans 65 years or older. Medicare payments for beneficiaries with AD and other dementias are three times higher than for beneficiaries without these conditions, and total U.S. health care expenses associated with dementia were estimated in excess of \$200 billion dollars in 2013 (Thies and Bleiler. 2013).

3.1 Accurate Diagnosis of Dementia

Accurately diagnosing the cause of cognitive impairment helps direct rational pharmacologic therapy, and leads to a care plan that improves patient safety and minimizes the risk of preventable complications (Naylor et al. 2012). Establishing the diagnosis in the early stages of cognitive impairment enables patients to participate in care planning while they are still able, and thus adheres to core ethical principles of patient autonomy and absence of paternalism (Connell and Gallant. 1996; Klein and Karlawish. 2013). Studies suggest that most patients seeking a cognitive evaluation want to be informed if AD is the cause of their symptoms (Elson. 2006). Receiving a definitive diagnosis has a positive psychological impact on most patients who are experiencing symptoms and their caregivers (Carpenter et al. 2008).

The diagnosis of AD and other dementias is currently based on the patient’s history, physical examination, and cognitive testing. Laboratory data and brain imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) are used primarily to exclude non-neurodegenerative causes of cognitive impairment (Knopman et al. 2001). The limitations of this approach are increasingly evident. Studies repeatedly show that primary care providers are not comfortable diagnosing cognitive impairment or its cause, leading to diagnosis of fewer than 50% of patients with dementia in the primary care setting (Bradford et al. 2009). Even in the hands of experienced clinicians, diagnosing the cause of cognitive impairment on clinical grounds has limited accuracy compared to the gold standard of post-mortem diagnosis. In a recent study of 900 patients evaluated at U.S. Alzheimer’s Disease Centers and followed to

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autopsy, the expert clinical diagnosis of AD showed only 70% sensitivity and 70% specificity compared to neuropathology. Conversely, approximately 40% of patients who were clinically diagnosed with a non-AD dementia were found to have AD as the primary cause of dementia post-mortem (Beach et al. 2012).

The limited diagnostic accuracy of clinical assessment has negative implications for patient care. It is estimated that the majority of eligible patients do not receive cholinesterase inhibitors or memantine, drugs that have been shown to slow cognitive and functional decline in dementia due to AD (Zilkens et al. 2014). Conversely, AD drugs are often used off-label in patients with non-AD causes of dementia such as frontotemporal dementia (FTD) (Bei et al. 2010). For these people, use of these medications is associated with adverse outcomes (Mendez et al. 2007; Boxer et al. 2013). The lack of diagnostic accuracy also represents a barrier to developing and testing biologically specific therapies. In two recent Phase III trials of monoclonal antibodies targeting amyloid-beta ($A\beta$), approximately 20% of patients clinically diagnosed with mild-moderate AD dementia (and 35% of patients lacking the apolipoprotein E $\epsilon 4$ risk allele) did not show evidence of amyloid on PET scans, suggesting they were likely misdiagnosed and thus lacked the primary drug target (Doody et al. 2014; Salloway et al. 2014). From a cost perspective, the misdiagnosis of dementia leads to increased Medicare expenditures (Kirson et al. 2013), whereas an early diagnosis can reduce costs by decreasing acute care needs and delaying time to institutionalization (Geldmacher et al. 2014). For these reasons, improving early diagnosis was identified as a major goal of the National Alzheimer's Project Act passed by Congress in late 2010.

3.2 Amyloid PET Imaging as a Diagnostic Tool to Improve Outcomes

Amyloid PET imaging represents a potential major advance in the clinical assessment of cognitively impaired patients, enabling for the first time in vivo detection of neuritic plaques, a core element of AD neuropathology. The U.S. Food and Drug Administration (FDA) has approved three amyloid PET imaging radiopharmaceuticals for clinical use based on evidence that visual interpretations of PET scans performed during life were sensitive and specific for the presence of moderate to frequent neuritic plaques at autopsy: F-18 florbetapir (Amyvid™), F-18 flutemetamol (Vizamyl™), and F-18 florbetaben (Neuraceq™). Though amyloid PET has undoubtedly made a considerable contribution to AD research, data supporting its clinical utility are relatively sparse. Since amyloid scans can be positive in cognitively normal individuals and those with cognitive impairment due to causes other than AD, imaging results must be considered in the context of a full evaluation for cognitive impairment to avoid misdiagnosis.

To help allay concerns about potentially misleading clinical use of amyloid PET, a working group under the auspices of the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging developed appropriate use criteria (AUC) to guide clinicians (Johnson et al. 2013). The AUC indicate that amyloid PET should only be considered in patients with objective cognitive deficits when there is substantial diagnostic uncertainty after a comprehensive evaluation by a dementia specialist; and in whom scan results are expected to increase diagnostic certainty and alter patient management. Per AUC, amyloid PET may have greatest value in patients with either: (1) progressive, unexplained MCI; or (2) dementia of uncertain etiology (due to atypical or mixed clinical features, or unusually early age-of-onset).

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Although the AUC are based upon available evidence and expert opinion, there is no experience with their implementation in clinical practice.

3.3 Coverage with Evidence (CED) Development

In its 2013 National Coverage Decision on amyloid PET imaging in dementia and neurodegenerative disease (CAG-00431N), the CMS indicated that amyloid PET imaging would be considered under CED if subjects were enrolled in clinical studies designed to:

“(1) Develop better treatments or prevention strategies for AD, or, as a strategy to identify subpopulations at risk for developing AD, or

“(2) Resolve clinically difficult differential diagnoses (e.g., frontotemporal dementia (FTD) versus AD) where the use of PET A β imaging appears to improve health outcomes. These may include short-term outcomes related to changes in management as well as longer-term dementia outcomes.”

We believe the objectives identified by CMS are highly congruent with the principles guiding AUC. The AD field is moving towards early (i.e., pre-dementia) diagnosis and intervention, and patients with MCI who harbor AD pathology are increasingly becoming the focus of clinical trials of both pharmacologic and non-pharmacologic early interventions. Amyloid PET has the potential to improve patient outcomes by supporting an early and accurate diagnosis, thus enabling early interventions and appropriate use of AD medications (while reducing inappropriate use in patients unlikely to have AD). By optimizing the management of diagnostically challenging patients, amyloid PET also has the potential to improve long-term outcomes in these individuals.

3.4 Rationale for Aim 1

Amyloid PET does not in isolation establish a diagnosis of AD. Amyloid PET in this protocol is used as a diagnostic test for the presence or absence of moderate-frequent neuritic plaques, as established in the FDA-approved package inserts. In the appropriate clinical context, knowledge of amyloid status can alter the clinical diagnosis and suspected neuropathological substrate for cognitive impairment, as reflected in the NIA-AA consensus diagnostic criteria for MCI and AD dementia (Alberts et al. 2011; McKhann et al. 2011). The majority of studies examining the diagnostic utility of amyloid PET have assessed sensitivity and specificity versus a gold standard of expert clinical diagnosis or neuropathology. A limited number of studies have further examined the impact of amyloid PET on diagnosis and diagnostic confidence (Frederiksen et al. 2012; Ossenkoppele et al. 2013). However, to demonstrate that amyloid PET meets the CMS standard of “reasonable and necessary for the diagnosis or treatment of illness”, it is important to demonstrate an effect not only on diagnosis and diagnostic confidence, but also on physician recommendations, therapy, and ultimately on clinically meaningful outcomes.

To our knowledge, only two published studies have assessed changes in patient management related to amyloid PET in reasonably sized samples. Grundmann et al. ascertained intended changes in management based on F-18 florbetapir PET results in 229 patients included in the Avid A17 clinical trial, but clinicians were not allowed to incorporate the PET results into real clinical care as the tracer was not yet FDA approved (Grundman et al. 2013). This study found

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an overall 31% change in AD drug therapy, 7% change in non-AD drug therapy, and 16% change in clinical trial referrals. Sanchez-Juan et al. assessed observed changes in AD drug therapy after amyloid PET in 140 patients with dementia at a single center based on retrospective chart review, and found a 35% change in cholinesterase inhibitor or memantine use between the pre-PET and post-PET visit (Sanchez-Juan et al. 2014). Neither study provided a true prospective assessment of amyloid PET on observed patient management.

A number of studies presented at the recent 2014 Alzheimer’s Association International Conference (AAIC) evaluated the impact of amyloid PET on clinical care. Siderowf and colleagues from Avid Radiopharmaceuticals largely reproduced the results of Grundmann et al., but this time when examining actual rather than intended patient management in patients enrolled in the A17 trial. Zwan et al. assessed the impact of F-18 flutemetamol amyloid PET on clinical diagnosis and management of 80 diagnostically uncertain dementia patients evaluated at the VUMC Amsterdam dementia clinic. They found that amyloid PET led to a change in diagnosis in 20% of patients and to a change in the management plan in 52% of patients.

Changes in management included changes in diagnostic studies (15%), changes in medications (31%), and other changes in the care plan (10%). An important caveat is that this study focused on early-onset dementia (age > 70 was an exclusion). Finally, Ghosh and co-workers from UCSF prospectively evaluated the clinical impact of F-18 florbetapir PET in 50 patients with suspected AD or FTD. All patients in the study also underwent FDG-PET, currently reimbursed by CMS in this diagnostic dilemma. Overall, amyloid PET led to changes in diagnosis in 21% to 30% of patients (depending on the experience of the clinician) and to changes in management in 32% of patients (including changes in medications in 21%). Utilizing a balanced, step-wise disclosure design, the investigators found that the impact of amyloid PET on diagnosis and management was significantly higher than that of FDG-PET (~15% change in diagnosis, 13% change in management).

The primary objective of Aim 1 in this observational, longitudinal study tests whether amyloid PET leads to a cumulative $\geq 30\%$ change in three elements considered to be the most important items in the management plan: AD drug therapy, other drug therapy (herein categorized as non-AD drug modification, non-neuropsychiatric drugs impacting cognition, non-neurology/psychiatric therapies, for other neurologic conditions, and targeted therapies), and counseling about safety and future planning (which the literature suggests is under-emphasized in lieu of a specific diagnosis, yet is key to preventing the negative outcomes to be evaluated in Aim 2). The cumulative goal of $\geq 30\%$ was selected to detect a clinically meaningful impact of amyloid PET on these outcomes, and is considered feasible based on the limited preliminary data cited above.

Aim 1 will be powered to detect this change separately in MCI and dementia sub-groups. Secondary objectives assess the impact on etiologic diagnosis and unnecessary application of diagnostic tests and AD drug therapies. These objectives are in line with several elements of the CMS goals for CED, including: “develop better treatments... for AD” (by increasing the use of available treatments, increasing counseling), “resolve clinically difficult differential diagnoses... these may include short term outcomes related to management.” In addition, the changes in management recorded in Aim 1 will be critical to interpreting the impact of amyloid PET on the clinical outcomes assessed in Aim 2.

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Because the longitudinal cohort will provide information for both Aims 1 and 2, a group sequential design with early stopping for effect is not feasible. However, as described in Section 8.1, a futility analysis is incorporated into the design and will be carried out separately for the MCI and dementia subsets. If the futility boundary is crossed for both subsets, consideration will be given to curtailing further recruitment in Aim 1 and also curtailing plans to proceed with work for Aim 2.

3.5 Rationale for Aim 2

Patients with dementia have a two- to three-fold increased risk for hospitalization and emergency room visits compared to elderly individuals without dementia (Bynum et al. 2004; Schwarzkopf et al. 2012). Patients with MCI or dementia may have difficulty recognizing dangerous symptoms; effectively managing their self-care of chronic conditions; and communicating symptoms and changes in their health status. Patients with cognitive impairment also have a higher burden of certain chronic conditions including stroke, seizure, falls, fractures, and congestive heart failure, which by themselves increase risk of hospitalization (Toot et al. 2013). While hospitalization is a risky event for any elderly individual, the impact on patients with cognitive impairment is even greater. In comparison to non-demented elderly people, patients with dementia are significantly more likely to experience delirium, agitation, iatrogenic complications, decrease in functional ability, organ dysfunction, severe sepsis, death, a longer hospital stay, and transition from hospitalization to institutional care (Lyketsos et al. 2000; Phelan et al. 2012; Toot et al. 2013). Hospitalization also is associated with a substantially increased risk of death and shorter survival time for patients with dementia compared to those without dementia (Shen et al. 2012).

Because of the increased risk for negative sequelae during the hospital stay, and the increased risk of death for patients with dementia, it is critical to identify ways to reduce the risk of events that necessitate hospitalizations. Diagnostic clarity helps predict the patient's expected trajectory, and prompts patients and their families to develop targeted strategies to manage medical comorbidities and personal safety in the setting of cognitive impairment. Caregiver education and a defined care plan have the potential to reduce the risk of preventable hospitalizations, including ambulatory sensitive conditions such as falls, dehydration, bacterial pneumonia, and urinary tract infections.

Amyloid PET can help clarify the diagnosis in cases of MCI or dementia that have challenging and atypical presentations. It is crucial to determine if greater diagnostic certainty is associated with a benefit in medical outcomes. We hypothesize that regardless of amyloid status, patients enrolled in the PET-known contemporaneous cohort will have better outcomes compared to matched concurrent controls who did not undergo amyloid PET testing. Our hypothesis is based on evidence that a more definitive diagnosis results in more appropriate practice patterns, more effective clinical management and a defined care plan (Naylor et al. 2012). We hypothesize that amyloid PET will prompt subsequent changes in clinical management including a more tailored clinical management, a more targeted care plan and patient/caregiver education, and this will result in more effective patient management and, thus, fewer events that would lead to hospitalization or emergency room visits. The primary objective for Aim 2 was selected based on preliminary evidence from Kaiser Permanente Northern California (KPNC) demonstrating that

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patients with dementia who are evaluated at a multidisciplinary dementia program (MDP) that incorporates patient and caregiver education as well as a care plan have fewer hospitalizations and emergency room visits compared to age-, gender-, and race-matched patients who were not part of the MDP program as described below (Whitmer, unpublished).

Hospitalization and emergency room rates were compared with those of dementia patients seen at an MDP, compared according to age, gender, race, matched dementia patients who did not participate in the program. The MDP includes: 1) a Memory Disorder Class which covers topics of advance directive, end of life planning, legal issues, normal memory loss versus MCI versus dementia, diagnosis of dementia, delirium, expected progression, Physician Ordered Life-Sustaining Treatment (POLST), appropriate medication use, driving, and safety; 2) Team Evaluation; 3) Dementia Class; and 4) Caregiver Class (see Appendix VI).

Accurate diagnosis, telling patients and family what to expect, encouraging early calls for delirium with early intervention, effective home management of behavior problems, and proactively promoting early end of life planning discussions are hallmarks of the program.

3.5.1 Preliminary Data

A preliminary study of the care of dementia patients seen in the MDP memory disorder clinic has been performed. It demonstrated significantly reduced emergency room visits, hospitalizations, hospital days, medication use, and office visits in the cohort of patients with dementia seen in the program vs. patients seen in the same region with a diagnosis of dementia not seen in the program from November 2009 to October 2010 (Table 1).

In an ongoing matched cohort study of 612 patients with dementia being treated at an MDP, age, gender, race, and comorbidity matched to a cohort of 1733 patients with dementia being treated at a KPNC medical centers without a MDP program, there is preliminary evidence of MDP being associated with fewer events. Adjusting for utilization 5 years prior to baseline, Poisson regression was used to evaluate the association between MDP care and risk of emergency room and hospitalization. MDP patients had an 18% lower risk of emergency room visit (relative rate [RR] 0.89, 95% Confidence Interval [CI], 0.71, 0.96) and 11% lower risk of a hospitalization (RR 0.89, 95% CI, 0.66, 0.98) over a 12-month period (Whitmer, unpublished 2104).

Per these data, we propose that these elements of care, resulting from a more accurate diagnosis, are some of the mechanisms that will improve outcomes and reduce risk of emergency room visits and hospitalizations.

Table 1. Healthcare Utilization Profile in MDP and Non-MDP Programs

Healthcare Utilization	Memory Clinic Patients with Dementia	Non-Memory Clinic Patients with Dementia
Total Patients	839	215
Int Med Visits	3,322	1,899
Int Med Visits/Patient	4.0	8.8
ED Visits	628	476

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ED Visits/Patient	0.7	2.2
Hospital Admits	154	146
Hospital Admits/Patient	0.2	0.7

3.5.2 Assessing Aggregate Healthcare Utilization

Patients with dementia are much more likely to be hospitalized than age-comparable peers. For example, Phelan reported that in a large cohort of >3,000 patients who were tracked over 14 years (1994 to 2007), individuals with dementia had 1.41 times higher all-cause hospitalizations and 1.78 times higher preventable hospitalizations compared to individuals without dementia. Two-thirds of the preventable hospitalizations were due to bacterial pneumonia, congestive heart failure or urinary infections (Phelan et al. 2012).

Using data from the Health and Retirement Study linked with Medicare claims (n=12,420) from 2000–2008, Feng and colleagues found that among community-dwelling, elderly, FFS Medicare beneficiaries, those who had dementia (defined by dementia and related disorders diagnostic codes) were significantly more likely than those who did not to have a hospitalization (26.7% vs. 18.7%) or an emergency room visit (34.5% vs. 25.4%) per year (Feng et al. 2014).

It is more difficult to estimate the cost consequences associated with cognitive impairment without dementia. Health and Retirement Study results have found that cognitively impaired but not demented patients over a six year follow-up have slightly higher rates of hospitalization and duration compared to non-impaired controls but this may be due to progression from mild impairment to dementia (Fisher et al. 2011; Clark et al. 2013).

Measuring costs associated with the increasing patient dependence needs and delivered by extended family and partners—informal care (monetary value of unpaid caregiver’s time if replaced by professional caregivers) increases directly with the severity of cognitive impairment and can best be estimated from prospective cohort or randomized trial designs (Schaller et al. 2014; Hurd et al. 2013).

3.6 Scope and Limitations of the IDEAS Study

We strongly believe that an open-label, longitudinal cohort study is needed in order to address the key question posed by CMS in CAG-00431N, namely whether amyloid PET can improve patient-oriented outcomes in selected patients. In designing the study we strived to develop a protocol that generates valuable data about the clinical utility of amyloid imaging, yet is at the same time feasible to fund and implement. We determined early in the course of protocol development that to address our primary outcomes, a randomized controlled design would be impractical. By leveraging claims data to identify a control group and to determine 12 months outcomes in all subjects, we have developed a cost-efficient method to investigate the effects of amyloid PET on the types of outcomes that would justify a reconsideration of the National Coverage Determination (NCD). We will implement rigorous steps, as described in the research plan, in order to ensure the validity of our approach and subsequent inferences.

There are many interesting and clinically meaningful questions that can be posed regarding the translation of amyloid PET into practice, and we acknowledge that our study will not be able to address all of them. We will not be able to (nor is it our goal) to simulate a clinical trial or an

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academic observational study by collecting a plethora of standardized measures on patients and their caregivers. While our inclusion criteria mandate diagnostic uncertainty after completion of the current “standard of care” for the assessment of cognitive impairment (i.e., clinical assessment by an expert, full metabolic panel and structural brain imaging) (Knopman et al. 2001), our study will not directly compare the utility of amyloid PET to other candidate diagnostic tools, such as FDG-PET or cerebral spinal fluid biomarkers. Many of these additional questions are being pursued via other studies (e.g., the Alzheimer’s Disease Neuroimaging Initiative, studies in National Institutes of Health [NIH]-funded Alzheimer’s Disease Research Centers, ongoing industry-sponsored randomized control trials, etc.). That said, the detailed case report forms collected for Aim 1 will provide us with a high-resolution characterization of our cohort and the clinical implications of the scan in a larger and more clinically representative population than has ever been studied in the context of other investigations. Furthermore, we anticipate that the cohort imaged with amyloid PET under this protocol will help support additional, more focused sub-studies. The current design will accomplish all this while interfering very little with routine clinical care, which we believe will greatly accelerate site, clinician and patient recruitment and facilitate on-schedule study completion.

4.0 PATIENT ELIGIBILITY CRITERIA & REGISTRATION

4.1 Inclusion Criteria

- 4.1.1 65 and older;
- 4.1.2 Medicare beneficiary;
- 4.1.3 Diagnosis of MCI or dementia, according to DSM-IV and/or National Institutes of Aging-Alzheimer’s Association criteria, verified by a dementia specialist within 24 months (American Psychiatric Association. 2000; McKhann et al. 2011; Albert et al. 2011);
- 4.1.4 Meets AUC:
 - Cognitive complaint verified by objectively confirmed cognitive impairment;
 - The etiologic cause of cognitive impairment is uncertain after a comprehensive evaluation by a dementia specialist, including general medical and neurological examination, mental status testing including standard measures of cognitive impairment, laboratory testing, and structural neuroimaging as below;
 - Alzheimer’s disease is a diagnostic consideration;
 - Knowledge of amyloid PET status is expected to alter diagnosis and management.

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- 4.1.5 Head MRI and/or CT within 24 months prior to enrollment;
- 4.1.6 Clinical laboratory assessment (complete blood count [CBC], standard blood chemistry profile, thyroid stimulating hormone [TSH], vitamin B12) within the 12 months prior to enrollment;
- 4.1.7 Able to tolerate amyloid PET required by protocol, to be performed at a participating PET facility;
- 4.1.8 English or Spanish speaking (for the purposes of informed consent);
- 4.1.9 Willing and able to provide consent. Consent may be by proxy.

Note: All study procedures are considered standard practice.

4.2 Exclusion Criteria

- 4.2.1 Normal cognition or subjective complaints that are not verified by cognitive testing.
- 4.2.2 Knowledge of amyloid status, in the opinion of the referring dementia expert, may cause significant psychological harm or otherwise negatively impact the patient or family.
- 4.2.3 Amyloid status already known to patient or referring clinician based on prior amyloid imaging or cerebrospinal fluid analysis.
- 4.2.4 Current or previous enrollment in an anti-amyloid therapeutic trial.
- 4.2.5 Scan is being ordered solely based on a family history of dementia, presence of apolipoprotein E (APOE) 4, or in lieu of genotyping for suspected autosomal mutation carriers.
- 4.2.6 Scan being ordered for nonmedical purposes (e.g., legal, insurance coverage, or employment screening).
- 4.2.7 Cancer requiring active therapy (excluding non-melanoma skin cancer);
- 4.2.8 Hip/pelvic fracture within the 12 months prior to enrollment;
- 4.2.9 Body weight exceeds PET scanner weight limit;
- 4.2.10 Life expectancy less than 24 months based on medical co-morbidities;
- 4.2.11 Residence in a skilled nursing facility.

4.3 Dementia Specialist Eligibility

A **dementia specialist** is defined in AUC as a self-identified physician trained and board-certified in neurology, psychiatry, or geriatric medicine who devotes a substantial proportion ($\geq 25\%$) of patient contact time to the evaluation and care of adults with acquired cognitive impairment or dementia (Johnson et al. 2013). Each participating dementia specialist will be included in a contractual agreement with the ACR which will ensure eligibility and facilitate payment for submitted data.

4.4 PET Facility Eligibility & Registration Requirements

An eligible PET facility will have experience in PET brain imaging. Participating PET facility may be (1) free standing and accredited by either the American College of Radiology (ACR), the

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Intersocietal Accreditation Commission (IAC) or RadSite or (2) hospital based and accredited by a Medicare-approved hospital accrediting agency (for example, the Joint Commission) with or without additional accreditation by ACR, IAC or RadSite. The PET facility must document that it has experience performing brain PET, PET/CT or PET/MRI with one of the FDA-approved amyloid imaging agents or with F-18 fluorodeoxyglucose or with both. Only facilities with full-ring BGO, GSO, LSO or LYSO PET scanners are eligible to participate; partial-ring systems and dedicated NaI systems are not eligible for use in the IDEAS Study. The entity applying as a PET facility should be the entity that bills Medicare for either the technical charges or the global charges for PET studies. The PET facility must execute a business associate agreement (BAA) and contractual agreement for participating radiologists/nuclear medicine physicians with the American College of Radiology (ACR) before patient registration can begin. The required BAA is available via www.IDEAS-Study.org. Participating radiologists/nuclear medicine physicians reading images must be board certified and have completed vendor-provided reader training and consent to participating in the study and adhering to protocol procedures.

4.5 Recruitment & Screening

Screening and Responsibilities. All referrals to the study and for amyloid PET will come from dementia specialists. As articulated in AUC, substantial clinical expertise and experience are required to determine if amyloid PET is indicated, and to correctly interpret the results of amyloid PET in the context of a specific clinical syndrome, and after appropriate exclusion of alternative causes of cognitive impairment.

To meet inclusion criteria, patients will be required to have a diagnosis of MCI or dementia established within 24 months following a standard-of-care assessment for cognitive impairment as defined in the American Academy of Neurology practice parameter (Knopman et al. 2001). The standard assessment includes a medical and neurological history and physical examination, bedside mental status testing with formal neuropsychological testing if indicated, laboratory tests for systemic/reversible causes of cognitive impairment (at minimum CBC, standard blood chemistry profile, TSH, vitamin B12) within 12 months of enrollment, and structural neuroimaging (head CT or MRI) within 24 months. It is required that elements of the standard assessment be either performed or verified by the dementia specialist (i.e., no need to repeat tests that have been ordered prior to the dementia specialist's evaluation, but the data need to be reviewed prior to referral for amyloid PET).

The dementia specialist will be responsible for identifying patients with MCI and dementia who meet inclusion criteria, and for screening these candidates for exclusion criteria. Dementia specialists will be recruited through societies such as the International Association of Gerontology and Geriatrics, American Academy of Neurology, American Society of Neuroradiology, and clinician outreach through psychiatrists, members of the Alzheimer's Association, as well as media outreach. The referring dementia specialist will contact a participating PET facility to schedule the participant for amyloid PET. The amyloid PET will be read locally at the PET facility, which will provide the ACRIN Data Management Center (DMC) with the amyloid PET report text and an Amyloid PET Assessment Form completed by the radiologist/nuclear medicine physician who interpreted the study. The dementia specialist and PET facility will work closely to coordinate timing of imaging completion to within 30 days after pre-PET form submission. The dementia specialist will be responsible for completing the

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pre-PET CRF at the time of PET referral and after formulation of the patient's *intended* management plan, and the post-PET CRF within 15 days after the visit, which will be completed within 90 days (75-105 day allowable range) after amyloid PET, that describes the *actual* management plan as determined in an in-person follow-up clinical visit.

Participant and Physician Consent. The referring dementia specialist and/or authorized designee will obtain informed consent (see template consent forms in Appendix II, III, and IV). All participants, or a proxy as appropriate, will provide written consent to allow access to their healthcare data to complete study CRFs as well as to their Medicare administrative claims for up to three years for follow-up purposes. All participating physicians—dementia specialists and radiologists/nuclear medicine physicians reading amyloid PET scans—will complete a separate physician consent to allow for participation and for collection and research use of the data on the CRFs they complete. Only participants who have been enrolled in FFS Medicare for the full 12 months of follow up will be included in the primary analysis for Aim 2. Data for those in FFS Medicare less than 12 months will be collected and used in an exploratory descriptive analysis.

Case Registration. The referring dementia specialist (or an authorized designee) will register the participant in the database, including documentation that participant consent has been obtained. Registration is processed via a secure Web-based application when identifying information about the patient and dementia specialist is introduced on the Patient Registration Form. The database will issue a unique study case number for that patient and send a confirmation e-mail to the dementia specialist and the PET facility.

4.6 Inclusion of Women and Minorities

Both men and women, English- and Spanish-speaking people, and members of all ethnic groups are eligible for this study.

5.0 STUDY WORKFLOW

The IDEAS Study is an observational, open-label, longitudinal cohort study collecting participant clinical information and dementia specialist intended management plan (pre-PET CRF), amyloid PET result (report text and scan assessment CRF), clinical information and actual management 90 days (75-105 day allowable range) after amyloid PET (post-PET CRF), and Medicare claims data from standard practice procedures. Each dementia specialist (or institution acting on behalf of one or more dementia specialists) invited to participate will complete qualification procedures and contracting requirements. Referring treatment facilities will require dementia specialists and research staff to work closely with a PET facility capable of performing and interpreting amyloid PET examinations. All referring dementia specialists will be required to provide written consent authorizing research use of the data they provide for the study and to document that they agree to comply with the study procedures, Federal and local human subjects' protections, and data submission timelines for all participants in the study. All radiologists/nuclear medicine physicians who interpret amyloid PET studies will be required to provide similar written consent and agreement to comply with study requirements. Referrals for amyloid PET will come from dementia experts; all providers will be provided educational materials about amyloid PET that highlight the fact that amyloid pathology is not synonymous with clinical or neuropathological AD. Each individual patient will be asked to provide written consent allowing his or her data collected for the study to be used for research purposes; if the

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patient is unable to provide consent, a proxy may consent on his or her behalf. Templates for each of these consent forms are available in Appendix II, III, and IV.

5.1 Patient Eligibility Review, Consent, & Registration

- 5.1.1 Referring dementia specialist confirms eligibility criteria.
- 5.1.2 Patient or proxy provides written consent.
- 5.1.3 Participant is registered to the study.

5.2 VISIT 1: Clinical Assessment—Completion of Pre-PET CRF Reporting *Intended Management*

An e-mail confirming participant registration will be sent to the dementia specialist and the affiliated PET facility. The referring dementia specialist must complete and sign the electronic Pre-PET Forms; the PET facility will be electronically informed that the Pre-PET Forms are completed.

The Pre-PET Form will collect the following information: (1) the specific reason for the PET study referral; (2) the patient's working clinical assessment/provisional diagnosis; (3) the referring physician's documentation or assessment of prior evaluation and treatment for cognitive impairment; and (4) the referring physician's intended management if PET were not available.

5.2.1 Pre-PET Case Report Forms

Referring dementia specialists will complete online CRFs prior to amyloid PET. Data elements to be collected include the following:

- Patient education level, marital status, and living arrangements
- Certification of inclusion (AUC)/exclusion criteria
- The pre-PET clinical diagnosis:
 - 1) MCI or dementia
 - 2) Suspected etiologic cause/s (as a differential diagnosis)
 - 3) Previous evaluation
 - 4) AD drug therapy
- The *intended* management plan including:
 - 1) Watchful waiting
 - 2) Intended changes in AD therapy (cholinesterase inhibitors and/or memantine)
 - 3) Intended changes in other relevant medications, including psychiatric drugs, drugs that can negatively impact cognition, drugs to treat medical conditions that can impact cognition (e.g. cardiovascular disease, diabetes), other neurological conditions, and targeted therapies
 - 4) Guidance about safety and planning
 - 5) Referral to family support systems (Alzheimer's Association for care plans, legal and safety education)
 - 6) Additional diagnostic procedures

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- 7) Referral to non-pharmacologic interventions
- 8) Plans to refer individuals to clinical trials (for AD or non-AD dementia)

5.3 VISIT 2: Amyloid PET and Report/PET Forms Submission

The PET scan must be completed within 30 days after completion of the Pre-PET Forms. The PET facility will be informed electronically when the Pre-PET Forms are completed. If the amyloid PET is delayed for more than 30 days from the time of pre-PET form submission and documentation of intended management, the registration will be cancelled, and the PET facility will be notified that this has occurred. If the amyloid PET is still to be performed at a later date, it will be necessary for the patient to be registered again, with the expectation that the information on the pre-PET form will be updated, as necessary, and then re-entered into the database. When the amyloid PET has been completed, the PET facility documents this by submitting the Amyloid PET Completion Form via the Web site by midnight on the day the scan was performed. Within 7 days of the scan, the PET Facility must upload a copy of the full PET report to the IDEAS data base and must upload the amyloid PET images to the ACR image archive (see Section 5.6), unless the patient has withheld consent for image collection and archival. The radiologist/nuclear medicine physician who interprets the amyloid PET will be required to complete the online Amyloid PET Assessment Form within 7 days of the scan.

- 5.3.1 Participating PET facilities will follow Society of Nuclear Medicine and Molecular Imaging guidelines for amyloid PET (to be finalized in 2015).

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5.3.2 **Subjectivity of Amyloid PET Interpretation:** As part of the FDA approval process, each of the vendors was required to demonstrate the reliability of dichotomous qualitative reads (positive or negative). Each radiologist and nuclear medicine physician who interprets amyloid PET images as part of the IDEAS Study is required to have completed the vendor-provided in-person or online training courses specific to the amyloid imaging agent (or agents) used at his or her participating PET facility for IDEAS Study participants. Each vendor already has in place and will continue to provide for IDEAS Study research, consultative resources to assist PET facilities with technical aspects of amyloid imaging, including patient preparation and positioning, dosing and administration, imaging acquisition and reconstruction, and scanner and image quality. Each vendor already has in place and will continue to provide for the IDEAS Study consultative resources to assist with image interpretation. The availability of these vendor-supported resources, which are part of standard amyloid imaging practices, are expected to ensure that amyloid imaging quality and interpretations for the IDEAS Study meet the standard of care.

5.4 VISIT 3 (T3) : 90 Days (75-105 day allowable range) After Amyloid PET Scan — Completion of Post-PET CRF Reporting *Actual* Management

- 5.4.1 A mandatory 90-day (75-105 day range allowable from day of PET) clinical office follow-up is required. The same dementia specialist will complete both the Pre- and Post-PET Forms. The Post-PET Form is due within 15 days after the 90-day (T3) visit. Exceptions reflecting subsequent study exclusion are: a) if patients have had subsequent events leading to prolonged care in a skilled nursing facility or b) death. The Post-PET form must be completed even in these circumstances, however, to document the reason the visit was not completed.
- 5.4.2 At this 90-day visit, the actual patient management (according to the dementia specialist or others) will be documented and characterized. Management actions include further diagnostic testing/consultation, imaging, laboratory or genetic analysis, referrals and counseling for non-pharmaceutical care, and a detailed documentation of pharmaceutical treatments (started, continued, or stopped) by drug categories.
- 5.4.3 Emergency room visits, and all cause hospitalizations during this 90-day interval also will be collected.

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- 5.4.4 If 90-day follow-up cannot be completed because the patient died, withdrew from care by the dementia specialist, withdrew consent, or was lost to follow-up, the specific reasons must be recorded on the post-PET CRF.
- 5.4.5 For any patients who are deceased, the dementia specialist will state the cause of death. Any death also will prompt a direct call from the study team to the dementia specialist to further ascertain the circumstances of death.
- 5.4.6 We will ask the dementia specialist to note on the post-PET CRF any adverse effects reported by the patient or caregiver that are attributable to learning amyloid status.
- 5.4.7 Accrual for Aim 1 will be completed after **11,050** participants are enrolled; the post-PET form will not be required for completion during further accrual for the full longitudinal cohort.

5.5 Case Completion & Reimbursement

After all Pre- and Post-PET CRFs have been completed and all data uploaded to the ACRIN DMC within the required time windows by the dementia specialist, reimbursement will be made. Upon completion of the Amyloid PET scan, forms completion, and all data uploaded to the ACRIN DMC within the required windows by the PET facility, claim(s) for the amyloid PET study may be submitted for reimbursement.

5.6 Digital Image Submission

Brain amyloid PET scans will be collected for this study for all subjects, except those who have specifically opted out of image collection during the study consent process. Images will be submitted to the American College of Radiology (ACR) archive within 7 days of scan acquisition using the web-based TRIAD™ application.

5.6.1 Digital Image Submission Using TRIAD™

TRIAD™ is the ACR image exchange application. It provides participating PET facilities a secure method to transmit subject images. TRIAD™ anonymizes and validates the images as they are transferred.

Site radiology/nuclear medicine staff who will submit images through TRIAD™ will need to be registered as site users in the TRIAD™ system to enable use of the application.

5.7 CMS Claims Data Collection for the 12 Months After VISIT 1

ACRIN DMC and Brown University will coordinate CMS claims data collection and analysis for the longitudinal cohort of **18,488** participants for Aim 2. The data provided by participating sites will be used for coordinating collection of CMS claims data from the prospective observational study as well as matching these participants with the concurrent controls for comparisons of claims data.

5.8 Institutional Review Board (IRB) Approval for IDEAS Study Participation

The primary entity charged with operationalizing this study is the IDEAS Study team, described on the cover page of this document; the IDEAS Study team intends to use the data it is collecting for research purposes in accordance with the consent for such use provided by the patient, the patient’s treating doctor (the dementia specialist), and the radiologist/nuclear medicine physician interpreting the patient’s amyloid PET scan. Dementia specialists and radiologists/nuclear medicine physicians will need to consent once—prior to first patient on-study in their respective practices—and will continue to participate in the IDEAS Study unless written withdrawal is provided to ACR. The ACR IRB and either a local IRB or a central IRB will be charged with reviewing and approving the consent forms prior to study activation at the referring physician’s site. Templates of consents specific to each of these participants are available in Appendix II, III, and IV. Each site must provide a copy of the final consent form to ACR, and must notify ACR if any revisions are made to the consent during the study. Each site must also provide ACR with a copy of its IRB letter of approval, if the site uses a local IRB.

5.9 Role of CMS in the IDEAS Study

While CMS is not conducting research, submission of data for the IDEAS Study (clinical assessment, pre- and post-PET [*intended* versus *actual*] management plans, PET scan reports and interpretations introduced into CRFs) is required by CMS for payment for PET studies for all Medicare beneficiaries participating in the study. CMS will be involved in facilitating access to CMS claims data for algorithm development and validation, and on IDEAS Study participants and matched controls towards Aim 2 of the project.

5.10 IDEAS Study Oversight

The ACRIN Biostatistics and Data Management Center (BDMC) will monitor participant accrual and data submission. Total target accrual for this study is **18,488** participants.

Organization Structure. The IDEAS-Study organization structure has been modeled after other successful studies of this type, and attempts to provide the optimal balance between tight control and broad engagement. The combination of a Steering Committee (with associated subcommittees), Operations Center, and Stakeholder Group create an effective structure which will promote rapid completion of the study while ensuring maximum data integrity.

Images Quality Assurance. Quality assurance procedures for IDEAS imaging interpretation and application will include vendor-specific training and testing. See Section 5.3.2 above. Vendors will have expert consultants available to local readers for cases that might require additional assistance in interpretation.

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5.11 Study Calendar

Study Procedure	Eligibility/ Registration	VISIT 1 (T1) : Pre-PET Clinical Assessment (Complete <i>Intended</i> Management)	VISIT 2 (T2) : Amyloid PET Imaging (Within 30 Days after Pre-PET Form Completion)	VISIT 3 (T3): Post-PET Office Visit 90 Days (75-105 Day Allowable Range) after date of PET Imaging (Complete <i>Actual</i> Management)
Screening/Eligibility Review	X			
Informed Consent (Allowable by Proxy)	X			
IDEAS Web Registration	X			
Pre-PET Form Completion Reporting Intended Management ¹		X		
Schedule Amyloid PET Scan		X		
Amyloid PET Scan at Participating PET Facility ²			X	
Submit PET Scan to ACRIN via TRIAD TM 2			X	
Post-PET Form Completion Reporting Actual Management ³				X

¹The Pre-PET Form completed by Dementia Specialist is required to be submitted to ACRIN DMC within 7 days after the visit/assessment.

²PET Completion Form completed by PET Facility staff is required to be submitted to ACRIN DMC by midnight on the day the scan is performed. Amyloid PET Assessment Form completed by the radiologist/nuclear medicine physician and PET Report uploaded by PET Facility staff are required to be submitted to ACRIN DMC within 7 days after the scan. PET images must be uploaded to ACR Image Archive via TRIADTM within 7 days after scan completion.

³The Post-PET Form completed by Dementia Specialist is required to be submitted to ACRIN DMC within 15 days after the visit/assessment.

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5.12 IDEAS Study and CMS-Suggested Design Specifications

As noted earlier, in its decision memo (CAG-00431N), CMS will cover one amyloid PET scan per patient through coverage with evidence development (CED), under §1862(a)(1)(E) of the Act, in clinical studies that meet certain specific criteria.

The primary endpoint of interest to CMS is that clinical studies under the CED program must address one or more aspects of the following questions.

For Medicare beneficiaries with cognitive impairment suspicious for AD, or who may be at risk for developing AD:

- 1) Do the results of amyloid PET lead to improved health outcomes? Meaningful health outcomes of interest include: avoidance of futile treatment or tests; improving, or slowing the decline of, quality of life; and survival.
- 2) Are there specific subpopulations, patient characteristics or differential diagnoses that are predictive of improved health outcomes in patients whose management is guided by the amyloid PET?
- 3) Does using amyloid PET in guiding patient management, to enrich clinical trials seeking better treatments or prevention strategies for AD, by selecting patients on the basis of biological as well as clinical and epidemiological factors, lead to improved health outcomes?

This study will collect data that directly address the first two of these questions. The third question is beyond the scope of the current study, though data regarding clinical trials referrals will be collected in the post-PET CRF for participants in Aim 1.

In addition, CMS requires that any approved clinical study must adhere to the following standards of scientific integrity and relevance to the Medicare population. These are listed in Table 2 and include comments on how the IDEAS Study will address it.

Table 2. CMS National Coverage Standards of Scientific Integrity and Relevance to Medicare Beneficiaries for CED Assessments

Element	IDEAS Study
The principal purpose of the research study is to test whether a particular intervention potentially improves the participants' health outcomes.	Yes. See Aim 2 and statistical plan (Section 8.0).
The research study is well supported by available scientific and medical information or it is intended to clarify or establish the health outcomes of interventions already in common clinical use.	Yes. Evidence indicates that amyloid PET will lead to more accurate diagnosis of the cause of MCI or dementia, with resultant appropriate change in management that is hypothesized to reduce hospitalizations and emergency room visits.
The research study does not unjustifiably duplicate existing studies.	Yes.
The research study design is appropriate to answer the research	Yes.

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Element	IDEAS Study
question being asked in the study.	
The research study is sponsored by an organization or individual capable of executing the proposed study successfully.	Yes. The investigators and organizations managing this study have extensive prior experience with large CED studies (NOPR for FDG-PET and for NaF-PET).
The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found at 45 CFR Part 46. If a study is regulated by the Food and Drug Administration (FDA), it must be in compliance with 21 CFR parts 50 and 56.	Yes. The study protocol and consent documents will be approved by the ACR IRB and a central IRB, and by each participating site's IRB if required by that site before accrual at the site begins.
All aspects of the research study are conducted according to appropriate standards of scientific integrity (see http://www.icmje.org).	Yes.
The research study has a written protocol that clearly addresses, or incorporates by reference, the standards listed here as Medicare requirements.	Yes.
The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Trials of all medical technologies measuring therapeutic outcomes as one of the objectives meet this standard only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.	Yes. The clinical research study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals.
The clinical research study is registered on the ClinicalTrials.gov website by the principal sponsor/investigator prior to the enrollment of the first study subject.	Yes. The study has been registered and assigned identifier NCT02420756.
The research study protocol specifies the method and timing of public release of all pre-specified outcomes to be measured including release of outcomes if outcomes are negative or the study is terminated early. The results must be made public within 24 months of the end of data collection. If a report is planned to be published in a peer reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors (http://www.icmje.org). However a full report of the outcomes must be made public no later than three (3) years after the end of data collection.	Yes. These reporting standards were all achieved in our prior work with the NOPR.
The research study protocol must explicitly discuss subpopulations affected by the treatment under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria effect enrollment of these populations, and a plan for the retention and reporting of said populations on the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of	Yes. This study will address two major subpopulations of patients who may potentially benefit from amyloid imaging: patients with MCI and those with dementia of uncertain cause after conventional diagnostic evaluation.

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underrepresented populations, the protocol must discuss why these criteria are necessary.	
The research study protocol explicitly discusses how the results are or are not expected to be generalizable to the Medicare population to infer whether Medicare patients may benefit from the intervention. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.	Yes. The study will exclusively enroll patients who are Medicare beneficiaries for a minimum of 24 months.

5.13 IDEAS Study Web Site and Data Collection

The IDEAS Study Web site (www.IDEAS-Study.org) is the portal for all facility registrations, case registrations, and data entry of the CRFs. Instructional and informational material are available for downloading from the Web site by participating facilities and other interested parties.

Table 3. Case Report Form (CRF) Data Collection Timelines

Form	Completed By:	Due Date Requirements
Case Registration Form	Dementia Specialist	After consent
Pre-PET Forms (Medical History and Clinical Assessment Forms)	Dementia Specialist	No more than 30 days before amyloid PET scan
Amyloid PET Completion Form	PET Facility	No later than midnight on the day the study was performed
Amyloid PET Report Submission Form	PET Facility	Within 7 days after completion of amyloid PET
Amyloid PET Assessment Form	Radiologist/Nuclear Medicine Physician	Within 7 days after completion of amyloid PET
Post-PET Form (Clinical Assessment Form)	Same Dementia Specialist as Completed Pre-PET Forms	Within 15 days after completion of the Post-PET 90-Day (75-105 day allowable range) Visit (The Post-PET Form will be required only for the first 11,050 participants.)

6.0 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 ACR policy) must fully disclose the nature of the conflict of interest in accordance with [IDEAS Conflict of Interest policies](#) and applicable federal, state, and local laws and regulations.

7.0 PUBLICATION & DATA SHARING POLICIES

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 IDEAS Study leadership. Any investigator involved in this study is obligated to provide ACR with complete test results and all clinical data obtained from the participants in this protocol. Investigators will follow the IDEAS Publication Policy (to be available online at www.IDEAS-Study.org).

The IDEAS Study will be open to and encourage data sharing of the resources collected during this project. The Data Access Policy provides information and guidelines for individuals and corporations wishing to request access to clinical data archived during the IDEAS study. A current version of the Data Access Policy will be maintained on the IDEAS Study Web site (www.IDEAS-Study.org).

8.0 STATISTICAL CONSIDERATIONS

This study will employ two modes of data collection, prospective study and CMS claims, and will address two groups of questions organized as Aims 1 and 2. Aim 1 will examine the change in patient management following amyloid PET and be addressed using data from the prospective data collection (longitudinal cohort). Aim 2 will examine the impact of amyloid PET on subsequent health care utilization and will be addressed using CMS claims data for longitudinal cohort participants and an appropriately constructed control cohort of patients receiving concurrent care (concurrent cohort).

Aim 1: To assess the impact of amyloid PET on the management of patients meeting Appropriate Use Criteria (AUC)

The primary objective of Aim 1 tests whether amyloid PET leads to a cumulative $\geq 30\%$ change in a composite endpoint consisting of three elements considered to be the most important items in the management plan: a) AD drug (b) other drug therapy (herein categorized as non-AD drug modification, non-neuropsychiatric drugs impacting cognition, non-neurology/psychiatric therapies, for other neurologic conditions, and targeted therapies), or c) counseling about safety and future planning. A change in any of the three items listed above will be counted towards the composite endpoint. The cumulative goal of $\geq 30\%$ change between intended and actual patient management plan within 90 days (75-105 day allowable range) was selected to detect a clinically meaningful impact of amyloid PET on these outcomes, and is considered feasible based on the limited preliminary data cited above.

Secondary objectives assess the impact amyloid PET testing has on etiologic diagnosis and subsequent care, including unnecessary application of diagnostic tests and AD drug therapies.

8.1 Primary Objective

Test whether amyloid PET imaging will lead to a $\geq 30\%$ change between intended and actual patient management within 90 days in a composite measure consisting of the following:

- a) AD drug therapy;*
- b) Other drug therapy; or*

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c) Counseling about safety and future planning.

In this analysis, *implemented, recommended and pending* changes in management between the pre-PET and post-PET CRFs in the categories “AD drugs”, “Other drugs” and “Counseling for safety, planning, and social support” will be included in the primary endpoint. A change in *any* of these categories will be included in the composite endpoint.

The primary hypothesis will be tested using a one-sided test, separately for MCI and dementia participants. In a secondary analysis, the proportion of change for each of the three components of care will be estimated using Wilson intervals for binomial proportions. In addition, hierarchical regression modeling will be used to examine the relation between change in management patient characteristics, such as level of cognitive impairment (as measured by MMSE) and provider characteristics, such as specialty and practice type. To account for patient clustering, physician practice will be used as a level in the hierarchical model structure.

8.2 Secondary Objectives

8.2.1 Estimate how frequently amyloid PET leads to a change in primary suspected etiological diagnosis (from AD to non-AD condition and vice versa).

A change in primary suspected etiological diagnosis will be defined as a change between the Pre-PET CRF and the Post-PET CRF from AD (or mixed AD) to a non-AD diagnosis (or vice versa) as the most likely suspected diagnosis listed. The probability of change in each direction will be estimated using Wilson intervals for binomial proportions. In a secondary analysis, hierarchical regression modeling will be used to examine the relation of patient and provider characteristics on the probability of change in primary suspected diagnosis.

8.2.2 Estimate the frequency of reduction in unnecessary diagnostic tests and AD drug therapy.

For this Aim, unnecessary AD drug treatment is defined as treatment with AD symptomatic drugs given in the pre-PET period that is discontinued post-PET or AD drug treatment included in the pre-PET management plan that was not initiated post-PET. The proportion of patients with each type of unnecessary treatment will be estimated using a Wilson interval for binomial proportions. Unnecessary diagnostic tests are defined as tests that were included as parts of the intended management in the Pre-PET CRF but were not included in the Post-PET CRF. The proportion of patients with at least one unnecessary test will be estimated using a Wilson interval for binomial proportions.

8.3 Exploratory Objectives

8.3.1 Assess the agreement between pre-PET suspected etiology (AD or non-AD condition) and amyloid PET results (positive or negative).

In this analysis, patients will be cross-classified by suspected etiology (dichotomized as AD/non-AD) and amyloid PET results (dichotomized as positive/negative). The 2x2 table

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will be used to derive a kappa coefficient and to estimate the proportion of concordant pairs as a measure of overall agreement and the conditional probabilities of positive test results if the suspected etiology is AD and negative test results if the suspected etiology is non-AD. In an elaboration of this analysis, we will use ordinal regression modeling to examine the relation between the full range of suspected etiology and the full range of results from the amyloid PET interpretation.

- 8.3.2 Identify specific diagnostic scenarios in which amyloid PET has the highest impact on patient management.

In this analysis, we will use hierarchical regression modeling to examine amyloid PET results as predictor of management change. In addition to PET results, predictor variables will include patient and provider characteristics.

- 8.3.3 Evaluate the impact of amyloid PET on referrals to therapeutic trials for both AD and non-AD causes of cognitive impairment.

In this analysis, we will use hierarchical regression modeling to examine amyloid PET results as predictor of referral to therapeutic trials. In addition to PET results, predictor variables will include the pre-PET suspected etiology, and other patient and provider characteristics.

Aim 2: To assess the impact of amyloid PET on hospital admissions and emergency room visits in patients enrolled in the cohort (amyloid PET-known) compared to matched patients not in the cohort (amyloid PET-naïve) over 12 months

The primary objective in Aim 2 is to compare rates of key components of health care utilization between individuals undergoing amyloid PET and matched controls of individuals who did not undergo amyloid PET. The primary objective will be to compare rates of: a) inpatient hospital admissions over 12 months, and b) emergency room visits over 12 months. A threshold of 10% relative reduction was chosen to represent a magnitude of reduction that is clinically meaningful. Secondary objectives include a comparison of total inpatient and outpatient CMS costs in patients imaged with amyloid PET and in amyloid PET naïve patients, as well as an assessment of the impact of amyloid PET results on outcomes of patients in the longitudinal cohort arm.

8.4 Description of Matching Criteria for Aim 2

Aim 2 objectives will utilize a matched cohort design:

- 1) Individuals in the *amyloid PET-known* cohort (that is the cohort of longitudinal study participants) will be compared to *amyloid PET-naïve* controls.
- 2) *Amyloid PET-naïve* controls will be identified and matched 1:1 to individuals in the amyloid PET-known contemporaneous cohort using Medicare claims data.
- 3) Claims data will be used to ascertain outcomes.

In order to assess the impact of amyloid PET imaging on the occurrence of inpatient hospital admissions, preventable hospitalizations, and emergency room visits, we will compare outcomes

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for our cohort of patients who receive amyloid PET imaging (*amyloid PET-known*) with a matched cohort of patients gathered from the CMS data files (*amyloid PET-naïve*).

First, we will divide the IDEAS Study cohort into: 1) a Mild Cognitive Impairment (MCI) cohort, and 2) a dementia of unknown etiology (dementia) cohort based on the dementia specialist's diagnosis at accrual into the study. For each participant in each of these cohorts, we will match controls with comparable diagnoses. The criteria are described in Appendix V.

These matching criteria should provide a sample comparable to the amyloid imaging cohort, with the exception that the control cohort had no amyloid PET. We are matching on factors related to both the receipt of amyloid PET and the outcomes of interest to avoid confounding the association between amyloid PET and patient outcomes.

For the MCI cohort comparison, we restrict our case definition to CMS patients based on the first listed claim using ICD-9 code 331.83 (MCI). Patients from the CMS data files (*amyloid PET-naïve*) identified using (alternative) additional ICD-9 codes may be included in the control group if we find other codes consistently used for the MCI cohort cases prospectively accrued to the study (*amyloid PET-known*). If other codes are consistently used, *amyloid PET-known* patients will be matched with CMS data file patients by ICD-9 code.

For the dementia cohort comparison, our initial plan will be to match CMS patients with more than two different categories of dementia codes from two or more different providers **or** more than two claims of non-specific dementia codes (senile dementia and/or organic brain syndrome) that are new (none in the preceding 24 months) and clustered with 24 months. As in the MCI group, it is difficult to anticipate *a priori* what spectrum of ICD-9 codes will be linked to patient in the dementia cohort, and we will adapt our strategy if needed as dementia patients enroll in the cohort.

Second, for both the MCI and dementia groups, in addition to matching on diagnosis and to ensure comparability of *amyloid PET-known* participants and CMS *amyloid PET-naïve* control patients, we plan to require structural brain imaging (brain CT or MRI) of matches (Table 1, line 2) within the past 24 months. To avoid potential confounding associated with other pathologies, we will exclude CMS patients with cancers and/or hip fracture listed in Table 1, lines 3 and 4. To create a comparison group that is comparable to the *amyloid PET-known* cohort with respect to the risk of outcomes of interest, we will match the *amyloid PET-known* prospective cohort and CMS *amyloid PET-naïve* controls on factors detailed in Table 2, as well as morbidities detailed in Tables 3 and 4. These co-morbidities were selected based on suspected associations with either subject selection for amyloid PET and/or the outcomes of interest. For example, a patient with severe comorbidities may be less likely to have amyloid imaging because of other potential explanations for the observed cognitive symptoms and because they are more likely to be hospitalized or appear in an emergency room.

Each of the matching covariates was selected because it is a potential confounder of the association between amyloid imaging (yes or no) and outcomes of interest.

8.5 Timeline for Matching Procedures

8.5.1 Pilot Phase

- A comprehensive set of variables will be analyzed during the pilot phase to create a refined set.
- During year 1 of the IDEAS Study, we will analyze Medicare claims and modify our algorithms for identifying and selecting claims characteristics for the CMS claims through a pilot phase.
- Upon accrual of the first few hundred cases to the study, we will pilot the actual matching algorithm for adjustment.

8.5.2 Selection of Control Concurrent Cohort

- The construction of the final cohort will be timed to align as closely with the completion of study accrual as feasible based on CMS data availability. A match will be sought for each amyloid PET study case accrued in as real-time as possible during the course of study conduct.
- Results will be reported to CMS and revisions to the protocol will be made to explain the final matching procedures.

8.6 Primary Objective

Determine if amyloid PET is associated with a $\geq 10\%$ relative reduction in amyloid PET-known patients in comparison to matched amyloid PET-naïve patients in the following:

- a) Inpatient hospital admissions over 12 months.*
- b) Emergency room visits over 12 months.*

In the primary analysis for this objective, the proportions of patients with hospital admissions and with emergency room visits will be compared between longitudinal study participants and controls. Separate comparisons will be made for each component of care, using McNemar's test to account for matching and the Bonferroni correction to account for the two comparisons. In an elaboration of this analysis, conditional logistic regression modeling will be used to compare the two study arms while controlling for provider characteristics.

8.7 Secondary Objectives

- ### 8.7.1 Determine if amyloid PET is associated with a reduction in preventable hospitalizations (as defined by ambulatory care-sensitive conditions) over 12 months.

The analytic approach to this aim will involve a comparison of the proportions of patients experiencing preventable hospitalizations in the two arms of the study, using McNemar's test, as well as a conditional regression analysis, controlling for provider characteristics.

- ### 8.7.2 Determine if the association between knowledge of amyloid PET status and outcomes varies by baseline cognitive status (MCI versus dementia).

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The analysis for this objective will use data from participants in the longitudinal study cohort. Hierarchical regression modeling will be used to compare the probabilities of the two components of the primary endpoint between participants with MCI or dementia baseline status, while controlling for other patient and provider characteristics.

- 8.7.3 Determine if the association between knowledge of amyloid PET status and outcomes will significantly vary by amyloid PET result (amyloid-positive vs. amyloid-negative).

The analysis for this objective will use data from participants in the longitudinal cohort of the study. Hierarchical regression modeling will be used to compare the probabilities of the two components of the primary endpoint between participants positive and negative amyloid PET status, while controlling for other patient and provider characteristics.

- 8.7.4 Assess the impact of knowledge of amyloid PET status on aggregate healthcare resource utilization over 12 months.

The analysis for this objective will assess the differences in medical care costs between *amyloid PET-known* vs. *amyloid PET-naïve* groups. Cost will be quantified as the aggregate direct medical care payments by Medicare over 12 months. The Medicare Provider Analysis and Review files will be used to assess payments overall, costs for hospitalizations, costs for preventable hospitalizations (>80% are for congestive heart failure, bacterial pneumonia, urinary infection, chronic obstructive lung disease or dehydration) (AHRQ, 2009; Lyketsos, 2012), and emergency room visits. A signed rank test will be used compare costs between longitudinal cohort participants and matched controls.

8.8 Exploratory Objective

- 8.8.1 To examine if components of the patient clinical management plan (AD drug therapy, non-AD drug therapy, counseling and care plan) are differentially associated with medical outcomes (reduction in hospitalizations and emergency room visits) at 12 months within the longitudinal study cohort.

This analysis will involve the longitudinal study cohort and will utilize data from the observational Aim 1 study and from CMS claims. Regression modeling will be used to examine the relation of each of the two components of the primary outcome to variables indicating the type of the post-PET clinical management plan.

8.9 Validation Assessment and Sensitivity Analyses

- 8.9.1 In order to assess the validity of Medicare claims information in the identification of patients with MCI or dementia we will compare the diagnostic information in claims data to the classification of MCI or dementia made of the longitudinal study cohort. The objective of this analysis will be to assess the ability of individual claims based features (e.g., diagnostic codes) and combinations of them to distinguish MCI from dementia cases. We will also assess the agreement between the pre-PET assessment of medical history and clinical status information, such as the presence of heart disease, diabetes and psychiatric disease, to the corresponding information obtained from the Medicare claims.
- 8.9.2 In order to assess whether differences in hospitalizations and emergency room use detected between *amyloid PET-known* participants and their concurrent CMS controls was attributable to differences between geriatric centers with amyloid PET available and those without amyloid PET (*amyloid PET-naïve*), we will do a sensitivity analysis in which we select a second group of controls selected from the CMS data for the period preceding the introduction of amyloid PET. This second group of controls will be seen at the same centers as *amyloid PET-known* participants, but will have been seen prior to the availability of amyloid PET. Controls will be matched to *amyloid PET-known* participants on similar dementia diagnosis, pre-scan dementia-related resource utilization, age, race, gender, ethnicity, geographic location, and comorbid chronic conditions likely to impact cognition or the outcomes of interest.

8.10 Sample Size/Accrual Rate

Aim 1. The primary objective in Aim 1 calls for the assessment of the rate of change between intended and actual management of longitudinal study participants in a composite measure indicating change in at least one of three domains, (a) AD drug therapy, (b) other drug therapy, or (c) counseling about safety and future planning. For the composite measure, we will test the hypothesis that the rate of change exceeds a threshold of 30% separately for the MCI and dementia subgroups. To account for multiple comparisons, a Bonferroni correction will be used and each hypothesis will be tested at level $0.05/2 = 0.025$.

We used the PASS11 software (Hintze. 2011) to compute the required sample size in order to achieve power 80% using a one-sided test of level 0.025. The table below shows the results of these calculations for several possible values of the true rate (P1). The table shows the number of cases, with completed data, required to achieve power 80%.

Power	N	P0	P1	P1 - P0	Alpha
0.80	4197	0.30	0.32	0.02	0.025
0.80	1881	0.30	0.33	0.03	0.025
0.80	1076	0.30	0.34	0.04	0.025

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Assuming 5% of cases with missing or incomplete information, a (fixed) sample size of 4420 per subgroup will be required. Assuming a 40:60 split between dementia and MCI, the total (fixed) sample size needed to address the primary objective of Aim 1 will be approximately 11,050. The total accrual to the cohort will be larger in order to address the needs for Aim 2 as detailed below. Accrual to the cohort will be completed in 2 years.

Futility Analyses. Because the cohort of longitudinal study participants will provide information for both Aims 1 and 2, a group sequential design with early stopping for effect is not feasible. However, a futility analysis is incorporated into the design for Aim 1. The futility analysis will be used to inform a decision of whether to continue with the remaining data collection in Aim 1 and with the work for Aim 2. Specifically, we plan to use a futility boundary corresponding to an O'Brien-Fleming spending function and two interim looks for futility for each subset (MCI and dementia). The interim looks will be conducted when 1/3 and 2/3 of the information is available. As in the sample size computations above, the boundaries were developed assuming a one-sided test of level 0.025 for each subset and a value 0.032 for the proportion of change under the alternative hypothesis. Computations were performed using the East 5.4 software (East 5.4. Cytel Corporation. 2010). We will consider curtailing further data collection for Aim 1 and work for Aim 2 only if futility is declared in both subsets. Decisions related to revisions to the protocol based on the futility analyses will be made in consultation with CMS.

Aim 2. The primary aim comprises two separate comparisons of proportions of patients in the longitudinal study and the control arm, the proportions of patients who experience an in-patient hospital admission or emergency room admission.

We computed the required sample size to achieve power of 90% for each comparison, using a McNemar's two-sided test, at level $0.05/2=0.025$ to account for the simultaneous comparisons.

Power	N1	N2	Study rate	Control rate	Ratio (Study/Control)
0.90	13484	13484	0.135	0.15	0.9
0.90	9614	9614	0.180	0.20	0.9
0.90	4504	4504	0.315	0.35	0.9
0.90	3660	3660	0.360	0.40	0.9

Based on an analysis in the Health and Retirement Study cohort (<http://hrsonline.isr.umich.edu>) and an analysis at KPNC of 12 month rates of hospitalization and emergency room visits for patients with a diagnosis of MCI, we propose 12-month rates of 20% and 35% respectively would be reasonable to assume. Allowing for 20% of cases with incomplete or missing information, the required sample size to detect a 10% relative reduction in hospitalizations will be 12017 per arm. The sample size for a 10% reduction in emergency room visits will be 5630/arm. We also adjusted the sample size to account for cases that will not have adequate claims data information, as needed for the analysis of Aim 2. We assumed that 35% of cases enrolled in the longitudinal cohort will be participating in Medicare Advantage or may not have 2 years of Medicare coverage at enrollment. Thus, an overall sample size of 18,488 cases will be sufficient for the longitudinal cohort arm in order to address the needs of both Aim 2 components

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of the primary endpoint. For the concurrent control arm, 12,017 cases with claims data will be sufficient.

We will monitor the proportion of dementia and MCI cases enrolled in the longitudinal cohort and consider modifications to the sample size projections if there are significant deviations from our postulated 40:60 ratio (dementia:MCI). In addition, we monitor the actual rates of hospitalization and ER visits as determined by Medicare claims data for patients in the longitudinal study cohort and the control cohort. We expect that for patients enrolled during the first four months of the study the information on hospitalization and ER visits will be available near the end of the second year of accrual. If significant deviations from the postulated frequencies of hospitalization and ER visits are encountered we will consider modifications to the sample size projections.

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Appendix I: Study Flow Chart

IDEAS Study Flow

Referring Physician	PET Facility	IDEAS Operations Center (ACRIN)
<ul style="list-style-type: none"> Registers to participate in IDEAS study Obtains IRB approval Executes contract with ACR Dementia Specialist establishes IDEAS Portal login and uploads informed consent (one per Dementia Specialist) 	<ul style="list-style-type: none"> Registers to participate in IDEAS study Executes Contract & Business Assoc. Agreement Physician establishes logon and uploads informed consent (one per participating physician) Establishes escrow account Accesses TRIAD™ for anonymized image submission to ACR archive 	<ul style="list-style-type: none"> Reviews Referring Physician site readiness/regulatory documentation Reviews PET Facility site readiness/regulatory documentation Sends notification of site activation
<ul style="list-style-type: none"> Screens and consents participants (Visit 1) Refers and schedules participant for PET scan 		<ul style="list-style-type: none"> Sends automated e-mail notification of patient registration
<ul style="list-style-type: none"> Dementia Specialist completes and submits Pre-PET Clinical Assessment eCRF via IDEAS Portal no more than 30 days prior to Amyloid PET Scan¹ 		<ul style="list-style-type: none"> Sends automated e-mail notification to PET Facility confirming receipt of Pre-PET eCRF, indicating that PET Facility may image participant within 30 days
	<ul style="list-style-type: none"> Performs PET imaging (Visit 2) Submits Amyloid PET Completion eCRF via IDEAS Portal by midnight on the day of imaging 	
	<ul style="list-style-type: none"> Provides radiologist report to Referring Physician 	
	<ul style="list-style-type: none"> Radiologist/Nuclear Medicine Physician submits Amyloid PET Assessment eCRF via IDEAS Portal¹ Submits Amyloid PET Report eCRF¹ Submits PET scan via TRIAD™ to ACR archive¹ 	<ul style="list-style-type: none"> Sends automated e-mail notification to PET Facility that case documentation is complete and CED requirements are met
	<ul style="list-style-type: none"> Submits claim to CMS per CED requirements 	<ul style="list-style-type: none"> Stores images and data for analysis
<ul style="list-style-type: none"> Performs post-PET consultation at 90 days (Visit 3) Completes and submits Post-PET eCRF (Clinical Assessment Form) via IDEAS portal² 		<ul style="list-style-type: none"> Requests CMS claims (12 months after last Visit 1)
		<ul style="list-style-type: none"> Performs study analysis

¹ To be submitted within 7 days of visit
² To be submitted within 15 days of 90-day visit
eCRF = electronic Case Report Form

Appendix II: Model Informed Consent - Potential Study Participant

Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study:

A Coverage with Evidence Development Longitudinal Cohort Study

ClinicalTrials.gov Identifier: NCT02420756

National Study Principal Investigator: Gil Rabinovici, M.D.
University of California, San Francisco (UCSF)

Local Site Principal Investigator:

Site of Investigation:

Sponsor: American College of Radiology Imaging Network

You are being asked to take part in a research study. The study will be done based on rules set by the Federal government and the State. Under these rules, a researcher will first explain the study and what is expected of you, and then he or she will ask you if you are willing to participate. You will be asked to sign this consent form, which states that the study has been explained, that your questions have been answered, and that you agree to participate. This process is called informed consent.

Then, if you decide to be in the study, you will sign and date this form in front of the person who explained the study to you. You will be given a copy of this form to keep.

Schulman Associates Institutional Review Board, Inc. (Schulman) [*may be replaced with local IRB information*] has approved the information in this consent document and has given approval for the study doctor(s) to do the study. An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. This does not mean the IRB has approved your participation in the study. You must think about the information in this consent document for yourself. You must then decide if you want to be in the study.

What is the purpose of this study?

The purpose of this research study, called the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study, is to examine how brain imaging helps guide your doctors in how to treat your condition, and whether these changes in treatment lead to better medical outcomes. Increased amyloid plaques in the brain have been linked with Alzheimer’s disease and related brain disorders. The study is being run by experienced researchers, the Alzheimer’s Association, and the American College of Radiology Imaging Network (ACRIN). The research component is to study if the brain imaging will help your doctor treat you; the brain imaging itself is not part of the research, but a procedure recommended by your doctor as part of clinical care.

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The brain imaging, called an *amyloid PET scan*, will look at the build-up of “amyloid plaques” in the brain. Amyloid plaques can clump together and block signals in the brain, which has been linked to Alzheimer’s disease. The brain imaging will highlight the amyloid plaques in the brain using positron emission tomography, known as PET imaging. A drug called a *radioactive tracer*, or radiopharmaceutical, that has been approved by the U.S. Food and Drug Administration (FDA) will be injected into your body to highlight the amyloid plaques. The brain imaging has been requested by your physician as part of your usual care (in other words, the brain imaging is not for research); the actual “research” part of the study is to examine how the brain imaging helps your doctor plan your treatment. Medicare has agreed to cover the cost of the amyloid PET scans (brain imaging) of participants in the IDEAS Study so that the researchers can evaluate whether the scans lead to improved patient outcomes. The program that allows Medicare to pay for the brain imaging is called Coverage with Evidence Development; Medicare “covers” the brain imaging cost while the research is in progress.

Your doctor has already discussed the potential benefits and other concerns that you might have regarding having an amyloid PET scan, but you should ask detailed questions of your doctor should you have additional concerns. You should only consider participating in the study if you are interested in knowing your amyloid status.

Why am I being asked to join this study?

You are being asked to join this study because you are age 65 or older, you have been diagnosed with mild cognitive impairment (MCI) or dementia, you have Medicare as your primary medical coverage, and your referring doctor has determined that an amyloid PET scan will help to guide your care. MCI may be diagnosed if you are experiencing memory loss or trouble thinking but are able to function daily on your own. People with MCI are at increased risk for Alzheimer’s disease and other types of dementia, but may also get better instead of worse. People with dementia have problems with memory and thinking that interfere with some aspects of independent daily function. Dementia can be due to a variety of causes, including Alzheimer’s disease. Amyloid PET may help your doctors diagnose the cause of your symptoms, or help rule out Alzheimer’s disease as a cause.

Participating in the IDEAS Study is your choice. Your participation in the research component for data collection is voluntary. You may choose not to participate. The cost of the PET scan your doctor is recommending is covered by Medicare if you agree to participate in the IDEAS Coverage with Evidence Development program. Should you decide not to participate in the research project, you may still have an amyloid PET scan but Medicare will not pay for the scan and you would need to pay for it if your other current insurance does not. If you agree to participate, you may discontinue participation at any time. If you withdraw from the study, no new data will be collected from you for research purposes.

If you agree to participate, researchers will use information about your health care and personal information you provide for research purposes.

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What am I being asked to do for the project?

For this study, you are being asked to consent to the following:

- a) Allow information about your health and your brain imaging to be collected for up to three years (36 months);
- b) Give researchers your name, address, social security number (SSN), Medicare identification number, and date of birth so the researchers can request information from Medicare about your medical care after the scan; only trained research staff will have access to your personal information; and
- c) Allow your amyloid PET scan, which will be stripped of all identifying information, to be collected and archived at the ACR for future research, unless you indicate in a later section of this consent form that you do not want your images collected and used for future research which will not affect your participation in the rest of the study.

How long will I be in the study? What will happen during the study?

An anticipated 18,488 people will join the study over approximately two years (24 months); you will have an amyloid PET scan and follow-up with your referring doctor as part of your ongoing medical care; your referring doctor will complete two forms about your diagnosis and treatment plan: one before the amyloid PET scan and one 90 days after the scan; claims submitted to Medicare to cover your health care will be collected for up to three years.

What are the risks?

The amyloid PET imaging test performed as described in this consent form is not experimental and is considered part of your clinical care. However, there are risks associated with this imaging test that may be discussed with you or may be addressed in a separate consent form at the center where you have it done. These risks include exposure to low doses of radiation equal to 10-15% of the amount a person who works with radiation is allowed to have in one year. The injection of the radiotracer may cause pain at the injection site and rarely may cause allergic reactions. During the scan, you will be in an enclosed space and this may cause some people to experience claustrophobia (fear of being in a small space). You will be carefully monitored to minimize all of these effects.

The known risk of participating in this type of study is release of your personal health information. The research team is taking extra precautions to mitigate this risk. For the study database, you will be identified only by a unique number; your name and other personal information will not be included. Your personal information will be accessed only by trained research staff personnel who need it to make requests for your Medicare claims.

Any new important information that is discovered during the study and which may influence your willingness to continue participation in the study will be made available to you.

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How will I benefit from the study?

The direct benefit to you from joining the study is that your treating physician will receive the results of your amyloid PET examination and may use that information in planning your future care. Additionally, you may benefit from increased knowledge about amyloid PET's influence on clinical decision making and medical outcomes when the study results are available. In the future, the knowledge learned during this study could help guide the appropriate use of amyloid PET imaging in patients whose conditions are difficult to diagnose.

Will it cost me anything to participate?

Your amyloid PET scan will be paid for by Medicare as a covered benefit as part of the Coverage with Evidence Development program. As with any medical service covered by Medicare, you will still be responsible for any deductible or co-payment required for the service. The amount you would have to pay will depend on whether or not you have supplemental insurance or other coverage for your deductible and co-payments.

Who is funding the study?

The IDEAS Study is sponsored by the American College of Radiology and ACRIN, with funding that is being provided by the Alzheimer's Association, the American College of Radiology, and the manufacturers of the FDA-approved radiopharmaceuticals for amyloid imaging.

The doctor (or his or her practice, hospital or university) who is referring you for an amyloid PET scan and has asked you to participate in the IDEAS Study will be reimbursed by ACRIN for the work your doctor and his or her research staff are doing as part of this research.

What happens if I decide to withdraw from the study?

The decision to participate is voluntary. You can choose to not participate or you may withdraw from the study for any reason without penalty or loss of benefits to which you are otherwise entitled and without any effect on your future medical care. You can inform the study team in writing to the address listed on page 1 of this form. Any data collected before then will belong to the study, and may be used for research. You may choose to have an amyloid PET scan at the advice of your doctor, without participating in the IDEAS Study.

The study doctor or sponsor can stop your participation at any time without your consent for the following reasons: if it appears to be medically harmful to you, if you fail to follow directions for participating in the study, if it is discovered that you do not meet the study requirements, if the study is canceled, or for administrative reasons.

What are my alternatives?

This research study is for research purposes only. The only alternative is to not participate in this study. The amyloid PET scan can be obtained outside the study.

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How will my privacy be protected?

We will do our best to make sure that your health and management information collected during the course of this research study will be kept private. However, we cannot guarantee total privacy. Records of your participation on this study, your progress and data from the images submitted while you are on the study will be kept in a confidential form at the headquarters of the American College of Radiology Imaging Network (ACRIN) . All data sent to ACRIN over the internet will be coded so that other people cannot read it. Your personal information will be stored separately from the study data that will be analyzed. Study information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Who will be allowed to see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. However, the researchers will do their best to make sure that any information that is released will not identify you. There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The American College of Radiology Imaging Network (ACRIN) to include the Operations Center and the Center for Statistical Sciences located at Brown University
- The Centers for Medicare & Medicaid Services (CMS); and
- The Institutional Review Board (IRB), a group of people who review the research with the goal of protecting the people who take part in the study.

Specifically, the principal investigator <<*referring physician*>>, the statistical team coordinating collection of claims data from CMS, and members of the IRB at Schulman Associates IRB <<*or use local institution IRB*>> will have access to the records. De-identified information may be provided as required by law.

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

If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, you should write to Schulman Associates Institutional Review Board, Inc. 4445 Lake Forest Drive - Suite 300, Cincinnati, Ohio 45242, or call toll-free 1-888-557-2472 during business hours Monday - Friday 8:00 a.m. to 6:00 p.m. EST<<*or local institution IRB location*>>.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This website will not include information that can identify you. At most, the website site will include a summary of the results. You can search this website at any time

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How will confidentiality be maintained?

The IDEAS Study analysis database and image archive will contain only unique identifiers (your own ID that is not linked to your name or any other personal health information) for you to protect your identity. This database will be used to learn about the data and meet the study's aims.

Your amyloid PET scan will be collected and archived at ACR, stripped of all identifying information, for use in future research. Should you not wish for your PET images to be collected and used in future research, you may opt out by initialing below. Your decision to opt out of the image collection will not affect your participation in other elements of the IDEAS Study.

_____ **(insert participant or *legally authorized representative (LAR) initials)** No, I do NOT want my de-identified PET images to be collected and used in future research.

The IDEAS Study is collaborating with additional research studies investigating amyloid, cognitive decline, Alzheimer's disease and other types of dementia.

Below, please let us know if you are willing to be contacted about other research studies for which you may be a candidate.

_____ **(insert participant or LAR initials)** YES, I am willing to be contacted about other research studies.

_____ **(insert participant or LAR initials)** NO, I am not willing to be contacted about other research studies.

(Authority of Legally Authorized Representative to act on behalf of Subject)

*Authority to act on behalf of another includes, but is not limited to parent, guardian, or durable power of attorney for health care.

Your decision to not be contacted will not affect your participation in the IDEAS study.

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My signature for participating in the IDEAS study

I have read this consent form or had it read to me. I have discussed it with the study team as necessary, and my questions have been answered to my satisfaction. I voluntarily agree to participate in this study until I decide otherwise. I do not give up any of my legal rights by signing this consent document. I will be given a signed copy of this form. I agree to take part in the study.

Participant's name/signature

Date of signature_____

(Depending on the person's mental health, another person, a legally authorized representative (LAR), may need to make the decision to allow for the data collection needed for the study, and may need to provide some information for the study about the participant's care. In these cases, have that person provide a signature below.)

Participant LAR's signature

Date of signature_____

(The following signature and date lines for the person(s) conducting the discussion may be included at the discretion of the study sponsor.)

Signature of person(s) conducting the informed consent discussion

Date of signature_____

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Appendix III: Model Informed Consent - Dementia Specialist

Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study: A Coverage with Evidence Development Longitudinal Cohort Study

National Study Principal Investigator: Gil Rabinovici, M.D.
University of California, San Francisco (UCSF)

Local Site Principal Investigator:

Site of Investigation:

Sponsor: American College of Radiology Imaging Network

<<To be completed by all certified referring dementia specialists consenting patients and completing Case Report Forms related to their diagnosis and care considerations at participating specialty institutions. Single consent is designed to cover conduct throughout the IDEAS Study project; written notification will be required to cease participation in the project.>>

Schulman Associates Institutional Review Board, Inc. (Schulman) [*may be replaced with local IRB information*] has approved the information in this consent document and has given approval for the study doctor to do the study. An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. This does not mean the IRB has approved your participation in the study. You must think about the information in this consent document for yourself. You must then decide if you want to be in the study.

The purpose of the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study is to examine prospectively how the use of amyloid PET impacts the management and outcomes of patients with mild cognitive impairment (MCI) or dementia of unknown etiology.

The Centers for Medicare & Medicaid Services (CMS) is providing coverage for the amyloid PET performed for this project under a program known as “coverage with evidence development” (CED). As a condition of payment for the PET scan, CMS requires that you, as a participating dementia specialist, provide specific patient information to record your *intended* care for your patient before the PET scan and then to record the *actual* care your patient has received in the 90 days after the results of the amyloid PET are known. The information is entered into a secure database maintained by the IDEAS Study.

Participating in the IDEAS Study as a dementia specialist is your choice. Your participation in the research component is voluntary. You may choose not to participate. If you agree to participate, you may discontinue participation at any time. If you withdraw from the study, no new data will be collected from you for research purposes. Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are otherwise entitled, other than the inability to order amyloid PET scans performed as part of the

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IDEAS Study for future patients. If you agree to participate, the IDEAS Study investigators will use the information you provide for research purposes. Your patient and the radiologist/nuclear medicine physician reading the amyloid PET for the study also will be asked to consent to study procedures.

You are being asked to sign this document to show you agree to the following: a) adequately consenting your patients to allow for their data collection; and b) following the procedures and timelines of the IDEAS Study. If after choosing to sign this consent you no longer wish to participate in the IDEAS Study, you will need to provide written notification to the research team documenting removal of your consent.

What are the purposes of the study?

There are two main purposes of this study:

1. To assess how amyloid PET results impact the management of patients who qualify for amyloid PET based on standardized Appropriate Use Criteria. This will be assessed largely on the basis of data you will supply before and after amyloid PET.
2. To assess the rates of hospital admissions and emergency room visits over 12 months in subjects enrolled in the main IDEAS Study cohort (who have had amyloid PET) compared with a matched control group (who have not had amyloid PET). This will be assessed by use of CMS claims, both for patients enrolled in the study who undergo amyloid PET and matched controls who do not.

Additional data collected during the IDEAS Study will allow for multiple secondary and exploratory aims related to diagnosis, costs, and overall patient management.

What am I being asked to do for the project?

You are being asked to participate in this project because you are a specialist in diagnosing and treating people with dementia and mild cognitive impairment. Because you or members of your staff will be obtaining consent from the patients you enroll in the IDEAS Study, you are considered to be engaged in the research. Additionally, because the goal of assessing how the amyloid PET results impact your planned and actual management of your patients, you are also considered a research subject.

If you choose to participate, you will need to obtain informed consent from your patients who are being referred for amyloid PET and you will need to complete case report forms before and approximately 90 days after PET describing your patient's clinical profile and management. These activities are necessary components of the IDEAS Study required Medicare payment of the amyloid PET scans ordered on your eligible patients. If you choose to participate in the research study, the information you provide will become part of the research data. The Pre-PET Form, which must be completed before the PET scan, will ask you questions related to your intended management plan for your patient before PET results are available. The Post-PET Form will ask you to report the current management for your patient and any adverse effects reported by the patient or family/caregiver. By signing this consent, you are agreeing to complete and submit the required forms within the timelines prescribed in the study protocol.

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The IDEAS Study will compensate your (or your practice, hospital, or university) for the time and effort you and your staff spend identifying and consenting patients for the IDEAS Study and for completion of the required case report forms.

How long will I be in the study? What will happen during the study?

The IDEAS Study is expected to enroll 18,488 patients with MCI or dementia over a period of 24 months. You will be a participating dementia specialist for as long as you choose to remain in the study or until patient accrual is finished.

What are the risks?

There are no known risks of participating in this type of study other than the potential loss of confidentiality. You may find participating in this study, viewing web-based educational content, attending meetings associated with the study conduct, and completing the electronic case report forms for the study to be additional work added to your clinical responsibilities. The information collected for the study will be de-identified at time of collection.

How will I benefit from the study?

There may be no direct benefit to you. However, you may benefit from increased knowledge about amyloid PET's influence on clinical decision making when the results are available. In the future, the knowledge learned during this study could help guide the appropriate use of amyloid PET in patients whose conditions are difficult to diagnose.

What happens if I do not choose to join the study?

The decision to participate or not is your own (in coordination with your employer, if required). No matter what decision you make, and even if your decision changes, there will be no penalty to you. You can choose to stop at any time by informing the study team in writing. If you choose not to participate, you will be unable to refer eligible Medicare patients for amyloid PET under the IDEAS Study.

How will my privacy be protected?

We will do our best to make sure that the patient and management information obtained during the course of this research study is kept private. However, we cannot guarantee total privacy. Study information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

How will confidentiality be maintained?

The IDEAS Study database will contain only unique identifiers for you and your patients to protect your identities. The study investigators will need to know your patients' identities in

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order to coordinate collection of Medicare claims data for the study. Your patients will consent to the release of this information, and the protected health information (PHI) required for this part of the study will be kept in a database dedicated to PHI, which will be separately housed from the primary database used for analysis purposes.

Who will be allowed to see de-identified data?

You, the dementia specialist, the ACRIN data management center, the statistical team coordinating collection of claims data from CMS, and members of the IRB will have access to the records. De-identified information may be provided as required by law.

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

If you have questions, concerns, or complaints regarding your participation in this study, or if you have any questions about your rights as a participating dementia specialist, you should speak with the study Principal Investigator or contact the IDEAS Study project management office at www.IDEAS-Study.org.

If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, you should write to Schulman Associates Institutional Review Board, Inc. 4445 Lake Forest Drive - Suite 300, Cincinnati, Ohio 45242, or call toll-free 1-888-557-2472 during business hours Monday - Friday 8:00 a.m. to 6:00 p.m. EST. <<*or local institution IRB location*>>.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This website will not include information that can identify you. At most, the website site will include a summary of the results. You can search this website at any time

My signature for participating in the study

I have read this consent form. I have had the opportunity to discuss this consent with the study team, as necessary, and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the study.

Participant's signature

Date of signature_____

Appendix IV: Model Informed Consent - Radiologists/Nuclear Medicine Physician

**Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study:
A Coverage with Evidence Development Longitudinal Cohort Study**

<<To be provided to all radiologist/nuclear medicine physicians interpreting amyloid PET studies at participating PET facilities. Single consent is designed to cover conduct throughout the IDEAS Study project; written notification will be required to cease participation in the project.>>

Schulman Associates Institutional Review Board, Inc. (Schulman) [*may be replaced with local IRB information*] has approved the information in this consent document and has given approval for the study doctor to do the study. An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. This does not mean the IRB has approved your participation in the study. You must think about the information in this consent document for yourself. You must then decide if you want to be in the study

The purpose of the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study is to prospectively examine how the use of amyloid PET scans impacts the management and outcomes of patients with mild cognitive impairment (MCI) or dementia of unknown etiology.

The Centers for Medicare & Medicaid Services (CMS) is providing coverage for the amyloid PET performed for this project under a program known as “coverage with evidence development” (CED). As a condition of payment for amyloid PET, CMS requires that the imaging be completed within 30 days after submission of the Pre-PET Form by the referring dementia specialist, that your PET report and a completed electronic case report form related to your findings be submitted within 7 days after amyloid PET, and that the referring dementia specialist submit case report forms before and approximately 90 days after the amyloid PET. The information is entered into a secure database maintained by the IDEAS Study. The IDEAS Study will notify you and the PET facility that performed the amyloid PET when all required data are received, indicating that is appropriate to submit a claim for payment to CMS.

Participating in the IDEAS Study is your choice. Your participation in the research component is voluntary. You may choose not to participate. If you agree to participate, you may discontinue participation at any time. If you withdraw from the study, no new data will be collected from you for research purposes. Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are otherwise entitled, except for inability to perform professional interpretations of amyloid PET scans performed on patients enrolled in the IDEAS Study. If you agree to participate, the IDEAS Study investigators will use the information you provide for research purposes. The patient and the referring dementia specialist also will be asked to allow their information to be used for the same research purposes.

You are being asked to sign this document to show you agree to the following: a) completing the amyloid PET interpretation and completing the Amyloid PET Assessment Form within the defined timeline; and b) following the procedures for submitting results information to the IDEAS Study database. If after choosing to sign this consent you no longer wish to participate in

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the IDEAS Study, you will need to provide written notification to the research team documenting removal of your consent.

What are the purposes of the study?

There are two main purposes of this study:

1. To assess how amyloid PET results impact the management of patients who qualify for amyloid PET based on standardized Appropriate Use Criteria. This will be assessed largely on the basis of data you will supply before and after amyloid PET.
2. To assess the rates of hospital admissions and emergency room visits over 12 months in subjects enrolled in the main IDEAS Study cohort (who have had amyloid PET) compared with a matched control group (who have not had amyloid PET). This will be assessed by use of CMS claims, both for patients enrolled in the study who undergo amyloid PET and matched controls who do not.

Additional data collected during the IDEAS Study will allow for multiple secondary and exploratory aims related to diagnosis, costs, and overall patient management.

What am I being asked to do for the project?

You are being asked to participate in this project because you have experience and training in brain amyloid PET.

If you choose to participate, you will need to complete an Amyloid PET Assessment Form and submit your PET report, which are necessary for the IDEAS Study and for Medicare payment of the PET scan. If you choose to participate in the research study, the information you provide will become part of the research data. The Amyloid PET Assessment Form, which must be completed within 7 days after the PET scan, will ask you questions about the imaging study that will be entered into the database for study analysis. By signing this consent, you are agreeing to complete and submit the required form within the timelines prescribed in the study protocol.

How long will I be in the study? What will happen during the study?

The IDEAS Study is expected to enroll 18,488 patients with MCI or dementia over a period of 24 months. You will be a participating radiologist/nuclear medicine physician for as long as you choose to remain in the study or until patient accrual is finished.

What are the risks?

There are no known risks of participating in this type of study other than the potential for loss of confidentiality. You may find participating in this study, viewing web-based educational content, attending meetings associated with the study conduct, and completing the electronic case report forms for the study to be additional work added to your routine clinical responsibilities. The information collected for the study will be de-identified at time of collection.

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How will I benefit from the study?

There may be no direct benefit to you. However, you may benefit from increased knowledge about amyloid PET's influence on clinical decision making when the results are available. In the future, the knowledge learned during this study could help guide the appropriate use of amyloid PET in patients whose conditions are difficult to diagnose.

What happens if I do not choose to join the study?

The decision to participate or not is your own. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You can choose to stop at any time by informing the study team in writing. If you choose not to participate you will be unable to interpret amyloid PET scans for Medicare patients enrolled in the IDEAS Study.

How will my privacy be protected?

We will do our best to make sure that the patient and management information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Study information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

How will confidentiality be maintained?

The IDEAS Study database will contain only unique identifiers for you and your patients to protect your identities. The study investigators will need to know your patients' identities in order to coordinate collection of Medicare claims data for the study. Your patients will consent to the release of this information, and the personal health information (PHI) required for this part of the study will be kept in a database dedicated to PHI, which will be separately housed from the primary database used for analysis purposes.

Who will be allowed to see de-identified data?

You, the radiologist/nuclear medicine physician, the ACRIN data management center, the statistical team coordinating collection of claims data from CMS, and members of the IRB. will have access to the records. De-identified information may be provided as required by law.

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

If you have questions, concerns, or complaints regarding your participation in this study, or if you have any questions about your rights as a participating radiologist/nuclear medicine physician, you should speak with the study Principal Investigator or contact the IDEAS Study project management office at www.IDEAS-Study.com.

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If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, you should write to Schulman Associates Institutional Review Board, Inc. 4445 Lake Forest Drive - Suite 300, Cincinnati, Ohio 45242, or call toll-free 1-888-557-2472 during business hours Monday - Friday 8:00 a.m. to 6:00 p.m. EST. <<*or local institution IRB location*>>.

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This website will not include information that can identify you. At most, the website site will include a summary of the results. You can search this website at any time

My signature for participating in the study

I have read this consent form. I have had the opportunity to discuss this consent with the study team, as necessary, and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the study.

Participant’s signature

Date of signature_____

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Appendix: V: Matching Criteria for IDEAS Study

The following tables outline the preliminary set of criteria that will be used during the pilot phase of algorithm development for the matching component of that statistical plan (Aim 2). See Section 8.5 of the protocol for additional information.

Table 1. Inclusion/Exclusion Criteria

	Criterion	Factors/Examples	Time
1	New Diagnosis of MCI or Dementia*	CMS claims related to dementia and MCI in the 24 mo. prior to IDEAS Study initiation; aim is to avoid prevalent cases	≥24 mo.
1A	MCI CODE	331.83 Mild cognitive impairment - include other ICD9 codes upon retrospective sensitivity analysis	
1B	DEMENTIA CODE: Prior to structural imaging Inconsistent claims patterns*	≥2 different categories of dementia codes or >2 claims with exclusively limited to non-specific dementia codes (senile dementia and/or organic brain syndrome) occurring within a two year (24 month) time interval	
2	Minimal Structural Brain Tests Minimal Blood Laboratory w/u	Head MRI or CT (+/-) CBC, standard blood chemistry profile, TSH, vitamin B12	<12 mo.
3	Exclude cases with unanticipated brain pathology on intake MRI/CT	Such as primary or metastatic cancers at time of match and at baseline for contemporaneous cohort	
4	Exclude cases with the following conditions: - All Non-Skin Cancers, Lymphomas, and Hematologic Malignancies - Hip/Pelvic Fracture		<12 mo.

Note: Same criteria apply to Contemporaneous and Historical Controls

* Cases will be suppressed and a new match will be found for all deaths within 12 mo., which would indicate diagnosis other than MCI or dementia.

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Table 2. Matching Criteria

	Criterion	Factors/Examples	Time
1	Age	Minimal age of 66 to 67 years to allow review of preceding 12 to 24 mo. of claims	+/- 24 mo.
2	Gender		N.A.
3	Marital status		N.A.
4	Ethnicity		N.A.
5	Location/Service Area	Hospital Referral Region (n=306) If too tight match by state	N.A.
6	Match Chronic Condition Warehouse per table below: Focus is on conditions related to hospitalizations	Match on number or specifics of associated CMS Codes. Non-CHF heart disease is an aggregate of Acute MI, A fib., HTN, and CAD/IHD), CKD, COPD, diabetes	<24 mo.
7	Match for Chronic Neurological Conditions, not included in Warehouse, per table below.	Prior stroke, TIA, PD, MS, epilepsy, TBI	<24 mo.
8	Hospitalization/Emergency Room Visits	Dementia or delirium	<12 mo.
9	Medicare/Medicaid Eligibility	Single or dual eligibility	N.A.

Notes: Potentially also match on AD Directed drugs, anti-depressants, psychotics prior to brain imaging. Excluding deaths within the 12 mo. prior to AI study initiation.

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Table 3. Chronic Conditions Warehouse for Matching

Chronic Condition[†] Medicare Beneficiaries (n=51,717,260)	Match	Reference Time Period Years	Condition Prevalence %, 2012
Congestive Heart Failure	Match	1	15
Other heart disease: Atrial fibrillation, acute myocardial infarction, ischemic heart disease, and/or hypertension	Match	1	~60
Chronic Kidney Disease	Match	2	16
Chronic Obstructive Pulmonary Disease	Match	1	12
Depression, Bipolar, Schizophrenia, Affective Disorder	Match separately	1	16
Diabetes	Match	2	28
Stroke / Transient Ischemic Attack	Match Separately	1	4

Table 4. Non-Warehouse Conditions for Matching

Chronic Condition[†] Medicare Beneficiaries (n=51,717,260)	Match	Reference Time Period Years	Condition Prevalence %, 2012
Epilepsy/seizure disorders	Match	2	
Parkinson's disease	Match	2	
Cerebrovascular disease without stroke	Match	2	

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Table 5. ICD-9 (+/- 10) Diagnosis Relevant for Matching

Diagnostic Categories for Suspected Dementia/MCI	2013 ICD-9 Codes	2015 ICD-10 Codes	Description
AD Neurodegenerative		To be added	
Mild cognitive impairment	331.83	G31.84	Mild cognitive impairment
Alzheimer’s Disease*	331.0*		Alzheimer’s disease (usually used in <u>combination</u> with ICD9 290s or 294s)
AD, clinically typical (memory-predominant)	290.0		Senile dementia, uncomplicated
Only for age<65	290.1		Pre-senile dementia, uncomplicated
	290.20		Senile dementia with delusional features
	290.21		Senile dementia with depressive features
	290.23		Senile dementia with delirium
AD, clinically atypical non-amnestic			ICD10 will include typical pathologies
AD plus mixed pathologies			ICD10 will include mixed pathologies
Primary AD w mixed pathology			
Mixed AD/cerebrovascular			
Mixed AD/Lewy body disease			
Mixed AD/vascular/Lewy			
Mixed AD/frontal temporal			
Non-AD neurodegenerative			
Diffuse Lewy Body Disease	331.82		Dementia w Lewy bodies
Parkinson’s	331.82 + 294.10		Dementia w Parkinsonism + conditions classified elsewhere w/out behavioral disturbance
Frontotemporal lobar degeneration	331.19		Frontotemporal dementia
Hippocampal sclerosis	348.81		Temporal sclerosis
Prion disease	46.79		Unspecified prion disease of CNS
Vascular dementia†	290.40		Vascular dementia, uncomplicated
	290.41		Vascular dementia, with delirium
	290.42		Vascular dementia, with delusions
	290.43		Vascular dementia w depressive features
Brain neoplasm	191 225.0		Malignant neoplasm of brain Benign neoplasm of brain
Chronic traumatic encephalopathy	348.30 + 907.0		Encephalopathy NOS
Prior traumatic brain injury (excluding skull fractures)	907.0 854,310.2		Late effect of intracranial injury without mention of skull fracture Post-concussion syndrome
Hydrocephalus	331.4 331.5		Obstructive hydrocephalus Normal pressure hydrocephalus

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Primary psychiatric			
Major depression	311		Depressive disorder, not elsewhere classified
Bipolar disorder (needs psychiatry review)	296 300.4		Episodic mood disorders (bipolar, mania and depression + recurrent episodes) Dysthymic disorders
Schizophrenia	295		Schizophrenic disorders
Toxic metabolic encephalopathies	292 + 304		Drug induced mental disorders Drug dependence
	292.82 292.83		Drug induced persisting dementia Drug induced persisting amnestic disorder
Alcohol	291.x		Alcoholic induced mental disorders
	291.1		Alcohol induced persisting amnestic disorder
	291.2		Alcohol induced persisting dementia
	291.5		Alcohol-induced disorder w delusions
Illicit drugs	304.2		Cocaine
	304.3		Cannabis
	304.4		Amphetamines and psychostimulants
	304.5		Hallucinogen dependence
Narcotics	304.0		Opioid dependence
Prescriptions drugs	304.1		Sedative, hypnotic, anxiolytic dependent
Nutritional			
Vitamin B12 deficiency	266		Deficiency of b-complex components
	291.1		Amnestic syndrome
Wernicke/Korsakoff syndrome	291.1		Korsakoff's psychosis
Other disorders			
Sleep disorder	327.23		Obstructive sleep apnea
HIV encephalopathy	323.9+ 42.x		Unspecified causes of encephalitis, myelitis, and encephalomyelitis +HIV disease
Neurosyphilis	94.81		Syphilitic encephalitis
	94.9		Neurosyphilis, unspecified
Cerebral vasculitis	446x		Polyarteritis nodosa an allied conditions
Limbic encephalitis (a para-neoplastic syndromes)	323.81		Other encephalitis or encephalomyelitis (No specific ICD9 code)
Not classified	294.8		Other persistent mental disorders due to conditions classified elsewhere "Organic brain syndrome, NEC"
Secondary codes of interest			
Codes used in combination with conditions classified	294.0		(Persistent) amnestic disorder due to conditions classified elsewhere

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elsewhere			
	294.10 294.11		Dementia classified elsewhere <u>without and with</u> behavioral disturbance
	294.20 294.21		Dementia, <u>unspecified</u> , without and with behavioral disturbance
	437.x		Cerebral atherosclerosis
MCI			
Mild cognitive impairment	331.83		Mild cognitive impairment (may be used in combination 294.9)
Memory Loss	780.93		Amnesia

* Most common coding for typical Alzheimer’s disease (331.0) with dementia classified elsewhere (331.0) without (294.1) or with (294.11) behavioral disturbance. Inpatient DRGs when Alzheimer’s is sequenced as the principal diagnosis, the cases group to DRG 56 and 57 (Degenerative nervous system disorders without and with major complications) while delirium tracks to DRG 889 (mental diseases and disorders).

† Most common coding for vascular (or multi-infarct dementia is 290.4x (vascular dementia) + cerebral atherosclerosis (437.0). The fifth-digit sub-classification with code 290.4x identifies the presence of delirium, delusional features, or depressive features.

Appendix VI: Multidisciplinary Dementia Program

The Multidisciplinary Dementia Program (MDP) is organized around a formal programmatic approach to caring for patients:

- A) **Referral.** Patients are referred to the Clinic through the E consult system. Referral is encouraged for all DSA patients with cognitive complaints and concerns.
- B) **Memory Disorder class.** Patients and their family are initially seen in a two hour educational class where topics covered include:
- Advance directives and end of life planning
 - POLST
 - Legal (financial and medical) issues facing dementia patients
 - Normal age related memory loss vs. mild cognitive impairment vs. dementia
 - Diagnosis of dementia
 - Delirium in dementia
 - Progression of dementia
 - Causes of dementia
 - Treatment of dementia (appropriate medication use)
 - Driving and dementia
 - Treatment of dementia
 - Safety issues
 - Dealing with dementia patients
- C) **Team evaluation.** Following Memory disorder class patients are seen for a 2 hour personalized evaluation. A history form is completed and the medical and dementia history is reviewed in detail. Patient is seen by a multidisciplinary team comprised of a neurologist, a nurse practitioner, a social worker, and a pharmacist. Cognitive testing and neurological exam are performed, social needs are evaluated and addressed, and medication review performed. Diagnosis and treatment plan is developed and communicated to the patient and family. End of life planning discussions are encouraged. Patients and families are instructed to contact the dementia program in the event of dementia related problems
- D) **Dementia class.** Following a diagnosis of dementia patients and family are seen in a 1 hour dementia education class which focuses on prognosis and progression of dementia and medication treatment of dementia. All patients at this point are strongly encouraged to discuss end of life planning and complete a POLST.
- E) **Follow up.** Patients call and email directly to the members of the program for dementia related concerns and problems. Patients with dementia are prone to delirium with relatively minor medical issues and early intervention is a goal of the follow up calls
- F) **Caregiver class.** Patients in mid to later stage dementia frequently develop behavior problems. These issues frequently can lead to ED visits and subsequent hospitalization if not effectively managed. These behaviors are managed through follow up calls and family members are referred to the caregiver class where behavior techniques are taught to deal more effectively with these issues. POLST form is reviewed and if not yet completed families are encouraged to do so.

Accurate diagnosis, telling patients and family what to expect, encouraging early calls for delirium with early intervention, effective home management of behavior problems, and proactively promoting early end of life planning discussions are hallmarks of the program.

Appendix VII: Prevention Quality Indicators Technical Specifications

Agency for Healthcare Research and Quality (AHRQ), Version 4.4, March 2012

<u>PQI 01 Diabetes Short-term Complications Admissions Rate</u>
<u>PQI 02 Perforated Appendix Admission Rate</u>
<u>PQI 03 Diabetes Long-term Complications Admission Rate</u>
<u>PQI 05 Chronic Obstructive Pulmonary Disease or Asthma in Older Adults Admission Rate</u>
<u>PQI 07 Hypertension Admission Rate</u>
<u>PQI 08 Congestive Heart Failure (CHF) Admission Rate</u>
<u>PQI 09 Low Birth Weight Rate</u>
<u>PQI 10 Dehydration Admission Rate</u>
<u>PQI 11 Bacterial Pneumonia Admission Rate</u>
<u>PQI 12 Urinary Tract Infection Admission Rate</u>
<u>PQI 13 Angina without Procedure Admission Rate</u>
<u>PQI 14 Uncontrolled Diabetes Admission Rate</u>
<u>PQI 15 Asthma in Younger Adults Admission Rate</u>
<u>PQI 16 Rate of Lower-Extremity Amputation Among Patients With Diabetes</u>

Available online at: www.qualityindicators.ahrq.gov/Archive/PQI_TechSpec_V44.aspx.

Accessed February 16, 2015.

Appendix VIII: IDEAS Organization Structure

The IDEAS-Study organization structure has been modeled after other successful studies of this type, and attempts to provide the optimal balance between tight control and broad engagement. The combination of a Steering Committee (with associated subcommittees), Operations Center, and Stakeholder Group create an effective structure which will promote rapid completion of the study while ensuring maximum data integrity.

Upon learning of the CMS non-coverage decision for amyloid imaging, and the opportunity to pursue coverage under a CED, Dr. Maria Carillo and the Alzheimer's Association formed the Amyloid Imaging CED Stakeholder Group, which has grown over time to represent a comprehensive group of constituents. The Stakeholders Group has provided a forum for community engagement to develop the registry proposal and has stimulated participation by various leaders in Alzheimer's disease and imaging, to include: Alzheimer's Association, Society of Nuclear Medicine and Molecular Imaging (SNMMI), World Molecular Imaging Society (WMIS), radiopharmaceutical vendors, imaging vendors, Alzheimer's disease specialists, ethicists, and others. Early in the process, this group invited National Oncologic PET Registry (NOPR) investigators and ACR to participate in the dialogue and then to serve as part of the project team to develop the IDEAS Study, leveraging the knowledge and experience of the NOPR research team. As this relationship has evolved, ACR has been positioned to serve as the operations center for the IDEAS Study. Industry interest and support for this initiative has been evident since the formation of the Stakeholders Group. Three vendors have received FDA approval for amyloid PET tracers (Eli Lilly and Company [Avid Radiopharmaceuticals, Inc.], GE Healthcare, and Piramal Life Sciences) and have been in discussion with three national distributors (PETNET Solutions, IBA RadioPharma Solutions, and Cardinal Health) to arrange for distribution of each agent nationally under the IDEAS Study. The vendors have disparate capabilities to produce and disseminate agent and likely will have unequal demand from IDEAS Study sites. As a result of these common and potentially competing interests, the vendors have agreed to work through the Medical Imaging and Technology Alliance (MITA) as a voice of consensus.

The IDEAS Project Team is described fully in the protocol and is ideally suited for the ongoing development and conduct of the IDEAS Study. Project Team members include the Study PI, Dr. Gil Rabinovici, Associate Professor of Neurology at the University of California, San Francisco, a behavioral neurologist with research expertise in amyloid PET, Dr. Bruce Hillner from Virginia Commonwealth University and Dr. Barry Siegel from Washington University, the chair and co-chair, respectively, of the National Oncologic PET Registry (NOPR), Dr. Constantine Gatsonis, Chair of the Department of Biostatistics at Brown University and Chief Statistician of the NOPR and world-renowned expert in diagnostic imaging statistical methods and analysis, Dr. Rachel Whitmer, a Senior Scientist and Epidemiologist at Kaiser Permanente Division of Research and an expert on population-based studies of dementia risk factors and outcomes, and Dr. Maria Carrillo, Chief Science Officer of Medical & Scientific Relations for the Alzheimer's Association. A Scientific Advisory Group will be convened on an ad hoc basis to provide additional expertise to the Project Team.

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The Operations Center for the IDEAS Study will be based in the ACR Clinical Research Center in Philadelphia, PA. As the Operations Center, the ACR has complete oversight and responsibility for conducting the research initiative under an Agreement with CMS to develop and manage the study under the CMS CED provision.

In very general terms, these responsibilities include:

- Oversight and management of study documentation and regulatory compliance
- Recruiting and contracting with participating sites (dementia experts and PET facilities)
- Creation and management of the IDEAS Study database; collection, transfer and archival of data
- Management of all funds, to include collection, accounting, and distribution of funds

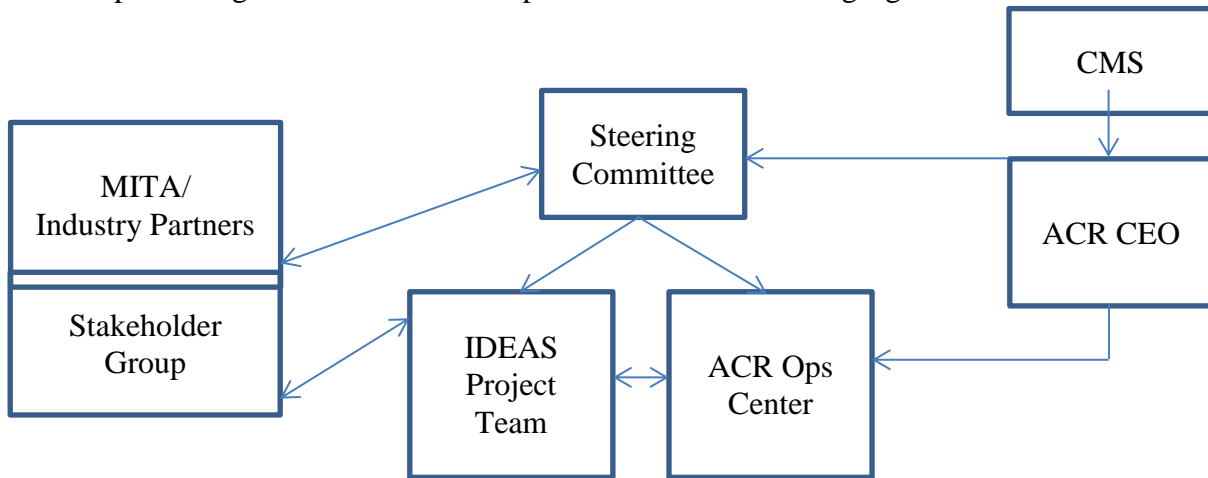
The daily activities undertaken within the Operations Center are guided by regulations and formal research guidelines, the clinical study protocol, and the leadership of the IDEAS Study Project Team. The IDEAS-Study Project will be governed by a Steering Committee. The IDEAS Steering Committee will convene at least quarterly and will support the contract between CMS and ACR by monitoring study progress against established timelines, evaluating scientific program initiatives, ensuring publication and dissemination of data, and approving budgets while monitoring financial compliance thereof. The proposed Steering Committee membership will consist of:

The proposed membership will consist of:

- Chair - ACR CEO or Designee
- ACR Representative
- Alzheimer's Association Representative
- CMS Representative
- Industry Representative (3)
- IDEAS Project Team PI
- IDEAS Project Team Statistician
- IDEAS Project Team Imaging Co-chairs (2)
- IDEAS Outcomes Co-Chair
- IDEAS Operations Center Director (non-voting)
- MITA Representative (non-voting)

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A simplified organization structure is presented in the following figure:



Subcommittees will be created under the Steering Committee as needed to perform additional functional roles. It is expected that initial subcommittees should include a Publications and Data Access Committee and a Communications Committee.