[Note: Commonly used abbreviations in this application are provided here.]

Grants/Performance Sites:

DIAN:	Dominantly Inherited Alzheimer Network, This proposal of an international cooperative of sites to recruit and study ADAD participants for longitudinal study.
ACS:	Adult Children Study, the study of pre-symptomatic changes in individuals of parents with or without Alzheimer disease (P01 AG 026276).
FACS:	Familial Adult Children Study (P01 AG026276-S1): supplement to the ACS, enrolling asymptomatic adult children of parents with Autosomal Dominant Alzheimer Disease
ADRC:	Alzheimer Disease Research Center (P50 AG05681).
MAP:	Memory and Aging Project, the clinical research office for the ADRC, ACS, and FACS that provides clinical and psychometric assessments for all participants.
ADNI:	Alzheimer Disease Neuroimaging Initiative: A national network to determine biomarker changes in late-onset Alzheimer disease (U01 AG24904).
ADCS:	Alzheimer Disease Cooperative Study: A cooperative to advance treatment trials for Alzheimer disease funded by the NIA (U01 AG10483).
NACC:	National Alzheimer's Coordinating Center: Established by the NIA (U01 AG016976) to facilitate collaborative research among the 29 NIA-funded Alzheimer's Disease Centers (ADCs) nationwide.

Definitions:

DAT:	Dementia of the Alzheimer type, the clinically diagnosed syndrome of AD
AD:	Alzheimer disease, histologically verified disorder
ADAD:	Autosomal Dominant Alzheimer Disease, defined by family history and validated by known mutations in *PSEN1*, *PSEN2*, or *APP* genes
Preclinical AD:	Neuropathological changes of AD in asymptomatic individuals (i.e., in the absence of even mild cognitive impairment or MCI).
Aβ:	amyloid-beta protein, a 38 to 43 amino acid product of the amyloid precursor protein (APP)
APOE/ApoE:	The gene and protein, respectively (often used interchangeably); the *APOE* ε4 allele is a polymorphism of APOE that increases AD risk.
CSF:	Cerebrospinal fluid

Procedures:

LP:	Lumbar puncture, procedure to obtain CSF
CDR:	Clinical Dementia Rating, our staging instrument where CDR 0 indicates no dementia and CDR 0.5 and 1 indicate very mild and mild dementia.
MRI:	Magnetic resonance imaging
CAP:	Common anatomic protocol, our standard MRI sequences
PET:	Positron emission tomography
PIB:	Pittsburgh Compound-B, a [^{11}C] benzothiazole amyloid imaging agent

A. SPECIFIC AIMS

The overall goals of the Core B: Clinical (Clinical Core) of the Dominantly Inherited Alzheimer Network (DIAN) are to recruit and retain participants from autosomal dominant inherited Alzheimer disease pedigrees and develop, implement and monitor longitudinal clinical evaluations including: clinical assessments, neuropsychological testing, imaging studies and collection of CSF and blood biomarkers. The overall aim is to collect the clinical and cognitive data necessary to address DIAN's three major hypotheses: 1) Establish an international, multicenter registry of individuals (gene carriers and noncarriers; presymptomatic and symptomatic), 2) In presymptomatic individuals, compare gene carriers and noncarriers to determine the order in which changes in clinical, cognitive, neuroimaging, and biomarker indicators of AD occur prior to the occurrence of dementia, and 3) In symptomatic individuals, compare the clinical, psychometric, neuroimaging, biomarkers and neuropathological phenotypes of early-onset familial AD to those of late-onset "sporadic" AD (using the data sets established by ADNI and by the NACC). As Clinical Core, we will assist and coordinate the participating sites in the evaluation of the research participants as follows:

Clinical Core Aims

1) Establish a Dominantly Inherited Alzheimer Network of international performance sites by developing and

implementing a plan for DIAN longitudinal studies to recruit and retain DIAN participants in longitudinal studies.

2) Coordinate the seven DIAN performance sites in Australia, Boston, Indiana, London, Los Angeles, New York, and St. Louis and direct the ADNI/ADCS Clinical Coordinating Center (CCC) for implementation of protocols including clinical evaluation, psychometrics, LP, MRI, PET, and provisional consent for autopsy.
3) Ensure protection of sensitive and confidential genetic and research data and offer clinical genetic counseling and testing to DIAN participants.

B. Introduction and Background

Alzheimer disease (AD) is the most common cause of dementia and is an increasing public health problem. It is currently estimated to afflict 5 million people in the United States, with an expected increase to 13 million by the year 2050 (Hebert et al. 2003). AD leads to loss of memory, cognitive function, and ultimately independence. AD takes a heavy personal and financial toll on the patient and the family. Because of the severity and increasing prevalence of the disease in the population, it is urgent that better treatments be developed.

Currently, there are some approved medications that temporarily ameliorate symptoms, however, there are no disease modifying treatments. Disease modifying treatments will likely be most effective when given *before* the onset of permanent brain damage. However, by the time clinical diagnosis of AD is made, extensive neuronal loss has already occurred (Price et al. 2001). Identifying the pathophysiologic changes that occur in AD *before* clinical onset is an ideal approach to diagnose those at risk and may provide a measure to study the effect of disease modifying treatments. The study of disease mechanisms that lead to AD in pre-symptomatic humans will likely yield new insights into the pathogenesis, diagnosis, and treatment of AD.

ADAD: The only identified deterministic factor for the development of AD is the presence of a mutation in one of three genes (*APP*, *PSEN1*, *PSEN2*) or duplication of *APP*. The most striking evidence in support of causative genetic factors is the existence of families in which the disease is inherited as fully penetrant autosomal dominant AD - ADAD (Janssen et al. 2003). Fifty-percent of the people from these kindreds (mutation carriers) are destined to develop DAT, most of which are early onset (<60 years). ADAD is similar to the more common, later onset AD in many aspects of clinical presentation, pathologic changes, and biochemical changes. The discovery of ADAD-causing mutations has led to a significant increase of knowledge about AD through molecular biology studies and animal models. Most of the pre-clinical research in AD is based on the mutations that were discovered in ADAD pedigrees. The study of the underlying pathophysiology of ADAD through metabolism studies, biomarkers and imaging techniques will likely lead to further understanding of later onset AD.

While there are presently no proven treatments that delay the onset or prevent the progression of AD, many promising candidates have this potential. During the development and ultimate implementation of these therapies, it will be critically important to have biomarkers which will measure the effects of these treatments on the structure, function and biochemistry of the human brain. In order to establish a baseline and longitudinal dataset which describes the progression of ADAD from a preclinical through moderate stage of DAT, we propose to form the Dominantly Inherited Alzheimer Network (DIAN). DIAN will serve to determine the chronological changes in imaging, biomarkers, and psychometric tests in relation to clinical onset and progression, in a well characterized and uniformly studied group of ADAD individuals.

Patients with ADAD typically present with memory and executive dysfunction similar to late onset AD (LOAD), but at an earlier age (Snider et al. 2005). The age of onset of ADAD also appears to be influenced by ApoE4 (Pastor et al. 2003), as also has been demonstrated in LOAD. There is significant heterogeneity in ADAD, similar to LOAD, in neurologic symptoms and signs including myoclonus, seizures, parkinsonism, dystonias, and behavioral and psychiatric symptoms (Rossor et al. 1996; Ringman 2005; Larner and Doran 2006). The pathology of ADAD and LOAD consists of amyloid-β (Aβ) plaques and neurofibrillary tangles, however, the percent composition of Aβ42 is higher in ADAD (Gomez-Isla et al. 1999). Overall there are many similarities between ADAD and LOAD in clinical presentation, pathology and biochemistry with some specific and quantifiable differences.

The average age of onset of ADAD has a wide range (29-60 years for *PSEN1* mutations) (Lleo et al. 2004) and generally is consistent within kindreds of ADAD (Kumar-Singh 2006). However, not all ADAD has an early onset, with rare *PSEN1* mutations being reported as segregating with disease into the eighth decade. The age of onset correlates with increased Aβ42 and decreased Aβ40 deposition in ADAD kindreds (Samir Kumar-Singh 2006). In addition, other factors including Apolipoprotein E4 and less education have been shown to be associated with an earlier onset in the same kindred (Pastor et al. 2003). Because of a younger, well-defined

age at onset, and near 100% penetrance, these kindreds will likely provide important information about the time course and relationship between genetics, pathogenesis, pathophysiology, biomarker, imaging, and clinical changes (**Table 1**, below).

Table 1.

Query	Pathogenesis	Pathophysiology	Pathology	Biomarkers	Clinical Changes
Assay	Genetic testing	CSF Aβ metabolism	PET PIB and MRI	CSF ELISA	CDR and psychometrics
Result	Genetic mutation of *PSEN1*, *PSEN2*, or *APP*	Possible Aβ42 overproduction	Amyloid deposition, and atrophy	Decreased Aβ42, increased Tau, others	Memory, attention, and executive dysfunction

Genes: The pathogenesis of ADAD has been well studied from the first identified causative mutation in *APP* (Goate et al. 1991), to the identification of causative mutations in more than 50% of ADAD kindreds in 1 of 3 genes: *APP*, *PSEN1*, *PSEN2* (Lopera et al. 1997; Lleo et al. 2002; Raux et al. 2005; Behrens et al. 2007). These 3 genes and duplication of *APP* (Rovelet-Lecrux et al. 2006) (including trisomy 21) are the only identified pathogenic causes of ADAD, being necessary and sufficient to cause DAT. Since these discoveries, significant advances in the pathophysiology of AD have been made.

The first mutation to be identified was the amyloid protein precursor (*APP*) gene on chromosome 21. As its name suggests, *APP* encodes the precursor of the Aβ peptide deposited in the AD brain (Haass et al. 1993; Johnson-Wood et al. 1997). Proteolytic processing studies have demonstrated that Aβ is a normal product of APP metabolism, and is generated at high levels in neurons. Aβ is a heterogeneous group of peptides varying in length from 38-43 amino acids. Mutations in *APP* that cause familial early onset Alzheimer disease all modify APP processing so that ratio of Aβ42 to Aβ40 is increased in plasma of affected patients or when these mutations are over-expressed in cell culture (Scheuner et al. 1996; Hecimovic et al. 2004) . Over 160 mutations have been reported in presenilin 1 (*PSEN1*) on chromosome 14 and presenilin 2 (*PSEN2*) on chromosome 1. (Levy-Lahad et al. 1995; Sherrington et al. 1995) (http://www.alzforum.org; http://www.molgen.ua.ac.be/ADMutations). It is well documented that ADAD mutations in the presenilins result in increased Aβ42/40 ratios and this ratio predicts the mean age of onset of dementia (Samir Kumar-Singh 2006). The absence of *PSEN1* results in a dramatic decrease in Aβ levels secreted by cells and in mice (De Strooper et al. 1998; Nyabi et al. 2002). The increase in Aβ42/40 ratio can be detected in the culture supernatants of cells transfected with mutant *APP* or *PSEN1* constructs and in vivo in mouse models (Scheuner et al. 1996; Jankowsky et al. 2004). In addition, the biochemistry of Aβ deposits in 30 ADAD kindreds indicates that all have increased Aβ42 deposition compared to Aβ40 (Borchelt et al. 1996). Perhaps most relevant, the plasma of subjects carrying these mutations demonstrates increased Aβ42/40 (Gomez-Isla et al. 1999). While autosomal dominant early onset AD is uncommon, the fact that mutations within three different genes (accounting for more than 50% of ADAD) lead to similar changes in the levels of Aβ products suggests that there is a final common pathway in AD pathogenesis, at least in these genetic forms of the disease. These observations support the hypothesis that Aβ (particularly Aβ42 and Aβ40 production) is central to the Alzheimer disease process.

The timing of Aβ deposition in a well characterized ADAD kindred will lead to important information about Aβ deposition in relation to clinical onset of AD in these families. Because the age of onset of DAT is similar in the same kindred, estimates of the order of changes in biomarkers and clinical testing will be determined initially in a cross-sectional fashion, which will be further validated in longitudinal studies of DIAN participants. In addition, the distribution of deposition as determined by PET PIB is likely to be an important parameter in comparing ADAD with late-onset AD.

ACS and FACS – longitudinal antecedent biomarker studies: The Washington University Antecedent Biomarkers for AD: The Adult Children Study (ACS) program project was funded to determine changes in antecedent biomarkers in populations of adult children (45-74 years) at increased or decreased risk of future DAT based on their parents' AD status. In a supplement to the ACS, the Washington University Familial Adult Children Study (FACS) has focused on adult children from parents with ADAD in an effort to identify the earliest changes that can be detected by clinical, psychometric, CSF, blood, or imaging biomarkers. DIAN will be an international collaboration of sites to implement uniform longitudinal studies similar to the FACS. DIAN will coordinate studies at multiple sites in order to coordinate research efforts and maximize numbers of participants to address critical scientific questions. As the ACS and FACS are well-developed research projects, DIAN will benefit from having much of the development, infrastructure and start-up already completed.

The Washington University ADRC is based administratively in the Department of Neurology at Washington University School of Medicine (WUSM), where Dr. Morris is the PI of the ADRC and HASD. Dr. Morris is the architect and PI of the ACS PPG to evaluate antecedent biomarkers. In addition, Dr. Morris has led successful efforts to build a uniform assessment for AD through the Uniform Data Set (UDS) and the NACC. Dr. Morris will serve as associate director of the Clinical Core and will assist Dr. Bateman in directing and coordinating DIAN clinical operations.

Dr. Bateman is currently an Assistant Professor of Neurology at WUSM. Dr. Bateman's research focus is on the pathophysiology of AD. In addition to measuring a range of candidate biomarker proteins, Dr. Bateman developed a novel technique at Washington University that measures the production and clearance rates of human CNS proteins. The technique is being utilized to address a basic hypothesis in AD research, namely whether over-production or under-clearance of Aβ is associated with AD. Dr. Bateman is the Program Director of the Familial Adult Children Study (FACS), which he developed with mentorship from Dr. Morris. The FACS is designed to specifically recruit and test early onset ADAD participants including full clinical evaluations for CDR and psychometrics, 36 hour CSF collections, PET PIB, and MRI. Under Dr. Bateman's leadership, the FACS is ahead of schedule in enrollment and completion of all studies with very high rates of participation (see Washington University Performance Site).

Dr. Bateman's experience with supervising clinical trials is further demonstrated by the successful completion of two industry sponsored studies. As the PI, Dr. Bateman directed the trials and completed goals and study completion ahead of schedule. Dr. Bateman is also the PI of a Beeson award in aging (for which Dr. Morris is a mentor), and the PI of several research studies on the metabolism of Aβ. To date, Dr. Bateman has enrolled a in the past 6 months a total of 60 participants for CSF metabolism studies, 6 of whom have been in families with early onset AD. Dr. Bateman has experience with coordinating diverse research programs and in the recruitment of ADAD participants.

One aim of DIAN is to detect differences between carriers vs. non-carriers of Alzheimer disease (AD) causing mutations. Biomarker testing (CSF, blood, and imaging) is compared to a highly sensitive clinical evaluation, the Clinical Dementia Rating (CDR) scale (Morris 1993), which can detect the earliest clinical changes of dementia of the Alzheimer type (DAT). Five projects of ACS are currently testing different techniques of pre-symptomatic detection of AD, and include clinical assessment using CDR, positron emission tomography with Pittsburgh Compound-B (PET PIB) imaging of amyloid in the brain, MRI imaging of the structure of the brain, psychometric testing of attention and personality, and cerebrospinal fluid (CSF) analysis of potential biomarkers. Adult children of parents with an ADAD will provide greatly increased power to determine changes in biomarkers of AD because of the deterministic nature of the disease and lower variability in age of onset. Perhaps most importantly, ADAD participants will provide uniquely informative insights into the pathophysiology of AD through the study of these biomarkers in relationship to the presence of a causative mutation of ADAD.

Conclusion: There is substantial evidence that ADAD shares a final common pathway with later onset AD. ADAD research will allow for better understanding of the pathophysiology of AD through CSF biomarkers, Aβ deposition (PET PIB), structural (MRI) and functional changes (clinical and psychometrics) of the brain in ADAD. Longitudinal studies of clinical, psychometric, imaging, and CSF biomarkers will determine the earliest preclinical changes and the order of changes. Comparison of ADAD with late onset AD will provide valuable insight into the applicability of ADAD as a model form of the common late onset AD, and how to interpret data from animal and cell culture models based on ADAD mutations. Biomarker changes in ADAD can be used as a basis to measure pharmaco-dynamic effects of proposed disease modifying therapies to assist in development. This information will likely lead to improved diagnostic testing and more precise pharmacodynamic testing of disease modifying treatments.

C. PRELIMINARY STUDIES

The ACS PPG and its parent ADRC and PPG HASD at Washington University have provided the infrastructure and resources for the development of the FACS, in which the ACS aims, assessments, and protocols are applied to members of ADAD families. The FACS recently was further supported with a supplemental award to the ACS PPG (P01-AG026272-S1), enabling preliminary data to be obtained to demonstrate the feasibility of the research design for DIAN. Dr. Bateman developed the scientific rationale for the FACS and has directed the study, including recruitment of ADAD participants for research studies. FACS is on schedule for enrollment and completion of research studies, including clinical assessment, psychometric testing, MRI, PET PIB, CSF and blood biomarker studies. In addition, Dr. Bateman serves as an active advisor on the Alzheimer Research Forum early-onset AD series (http://www.alzforum.org/eFAD/default.asp).

The Clinical and Genetics Cores of the ADRC have extensive experience recruiting and arranging for studies in participants from outside the greater St. Louis area (Morris et al. 1984). Autosomal dominant AD studies including clinical assessment, psychometric testing and genetics studies have been arranged for 39 participants from outside the greater St. Louis area, most being from out of state. A *PSEN-1* kindred was invited to participate in an ADRC supported study that includes clinical assessments, MRI and LP for CSF, with 28 members invited and 27 participating (96%). From four kindreds in the Washington University Genetics Core, there are 80 potential DIAN participants. Initially, six were invited to become the initial participants in the FACS. All six agreed (100%), traveled to St. Louis, signed consent forms and entered the study. All participated in clinical and psychometric testing, LP, MRI, and PET PIB, except one participant was excluded from LP due to a history of mild spina bifada (a contraindication to LP).

Based on our experience, ADAD participants are highly motivated to further research in AD. Using these rates of participation, we have identified 406 immediately eligible participants at the 7 DIAN performance sites who have demonstrated ~ 95% participation rate for clinical evaluations, PET PIB, MRI and LP studies. We will use methods that have been developed at the Washington University ADRC to facilitate high rates of participation with LP and brain autopsy, as well as successful methods for recruitment and retention at other DIAN performance sites. In addition, other participants may be recruited through local initiatives at the individual performance sites and through broader efforts (e.g., eFAD of the AlzForum). This pool of participants will fulfill the 240 needed participants for analysis.

Of note, most eligible DIAN participants have not been clinically tested for ADAD mutations. To avoid indirect notification of mutation status, it is important to invite all potential DIAN participants to the research program, regardless of mutation status. The participants without mutations will contribute to the study as sibling controls. Our preliminary data indicate both mutation positive and mutation negative participants are highly motivated to participate. Similar successful experiences have been realized at the other DIAN performance sites (see Clinical Performance Site Descriptions that follow this Core).

DIAN eligibility and sample population: Over 400 participants are presently being followed at seven performance sites and are eligible for participation in DIAN. Additional individuals from ADAD families will be recruited to DIAN if needed to complete the sample size or if DIAN eventually expands. Identification of these additional individuals will be facilitated through DIAN's interaction with NCRAD, Alzforum (see Core H: Informatics), Alzheimer's Association, NIA/ADEAR, and other means as necessary. Preliminary data on the age of 406 prospective participants that are followed by the seven performance sites have reported ages of 86 participants compared to the age of onset of their affected parent for each pedigree (Table 2).

Table 2.

Age range categories relative to Parental Age at Onset (PAAO)	Number	Percent
+4 to 5 years after	7	8
-3 to +3 years	31	36
-4 to 10 years before	25	29
-10 years before	23	26
Total	86	100

A summary of the seven performance sites current participants, identified mutations and infrastructure support is listed in the **table 3** below:

Table 3.	B&W-MGH Brown (Sperling)	Indiana (Ghetti)	UCLA (Ringman)	ION-UCL (Rossor)	Australia (Schofield)	Columbia (Mayeux)	Wash U (Bateman)	Total
# Families								
APP	1	2	2	6	3	0	0	14
PSEN1	9	9	17	16	18	24	4	97
PSEN2	0	1	1	0	0	0	0	2
								113
# Asymptomatic Ss currently enrolled								
APP	2	7	4	5	4	0	0	22
PSEN1	57	5	22	12	26	20	19	161
PSEN2	0	2	0	0	0	0	0	2
								185

# symptomatic Ss currently enrolled								
APP	1	3	0	6	0	0	0	10
PSEN1	22	8	5	5	8	45	2	95
PSEN2	0	0	0	0	0	0	0	0
								105

THE ALZHEIMER'S DISEASE COOPERATIVE STUDY

The ADCS was established in 1991 as a response to a request for applications to develop the organizational infrastructure to carry out trials for new and promising drugs in AD, and to further develop new instrumentation for the evaluation of patients enrolled in clinical drug trials. Beginning with 30 centers, the ADCS has gradually expanded its utilized centers over the past 12 years so that at the present time it has 82 sites in the US and Canada to conduct its clinical trial activity. This demonstrates the infrastructure to implement protocols across multiple sites. The ADNI was established to develop and implement uniform imaging and biomarker studies in late onset AD and is well suited to implement DIAN's imaging studies (see Core G: Imaging).

Summary of Preliminary Studies:

1. The Clinical Core has the experience and expertise in coordinating multi-site initiatives to achieve the aim of uniform clinical evaluations, imaging and biomarker collections for an international collaboration.
2. Longitudinal studies of FACS participants are on schedule and the infrastructure for obtaining and analyzing clinical, PET PIB, psychometrics, and MRI is an effective model for DIAN, an international registry and collaboration of ADAD participants.
3. International sites that focus on ADAD research have sufficient numbers of ADAD participants and active research programs to meet the primary aims of this proposal. The current performance sites have capacity and commitment for the longitudinal assessment of 240 DIAN participants. Recruitment and enrollment of ADAD participants are high and there is a large active pool of potential participants (n=406) to meet the aims of this proposal.
4. The ADNI and ADCS infrastructure are effective and have capacity for DIAN participants to manage the imaging, biological fluid collection, and clinical assessments.

D. Research design and methods:

Clinical Core Aim 1: Establish a Dominantly Inherited Alzheimer Network of international performance sites by developing and implementing a plan for DIAN longitudinal studies to recruit and retain DIAN participants in longitudinal studies.

DIAN Overview: Over years 01 – 06, 240 participants age 21 or older will complete longitudinal clinical assessment, psychometrics, LP, 3T MRI, FDG PET and PET PIB imaging. Participants will be adult children of known ADAD as defined by mutation identification in consanguineous relatives and clinical or pathologic DAT in a related parent consistent with ADAD. Fifty percent of the participants will be mutation carriers (due to autosomal dominant inheritance) and the other fifty percent will serve as sibling controls. Results of DIAN's genetic studies and other research findings will not be disclosed, however, independent clinical genetic counseling and testing will be offered and funded as part of this study. Because in vitro and in vivo evidence suggests ADAD mutations act through a common pathway (increased levels of Aβ42 or the ratio of Aβ42 to Aβ40) and because for many specific mutations the number of eligible individuals is small, mutation carriers will be grouped together. Fifty baseline DIAN participant evaluations will be completed in year one, followed by increasing evaluations in years 2 through 6.

During the preparatory phase, the protocol in the grant will be converted into a clinical protocol suitable for use at DIAN performance sites. Methods of clinical evaluation (Core B: Clinical), genetic analysis (Core F: Genetics), blood and CSF biomarker analysis (Core E: Biomarker), MRI, PET PIB, and FDG PET analysis (Core G: Imaging), data entry and data flow (Core H: Informatics) and statistical analysis protocols (Core C: Biostatistics) will be completed in consultation with participating DIAN sites and the DIAN cores. The sample IRB Protocol and Consent Form (see Appendix) will be modified and sent to all sites that they may complete appropriate submissions to their respective institutional review boards. All DIAN performance sites have English as the primary language; however, some have Spanish speaking ADAD participants. The Uniform Data Set (UDS) is the standard clinical assessment that incorporates CDR assessment and is utilized at all NIA Alzheimer Disease Centers. The UDS assessment has been translated into a Spanish version that has

been used at Alzheimer Disease Centers since April 2007. Future revisions will consider translation into other languages (e.g. Italian or French) for use in other ADAD populations at future potential DIAN sites.

The Clinical Core will be responsible for training the performance sites on the standard uniform assessment of the UDS. Dr. Morris trained all US Alzheimer Disease Centers on the UDS and will ensure proper training of DIAN participating sites. Should DIAN be funded, the initial training will commence with the Clinical Core hosting a training meeting for all performance sites before or after the International Conference of Alzheimer's Disease (ICAD) in Chicago in 2008. This training meeting will utilize current UDS training programs and also specific training regarding DIAN protocols and studies. Training for implementation of DIAN studies will be performed by the appropriate DIAN cores (Biomarker, Genetics, Imaging and Informatics Cores) and their subcontractors. For example, clinical training in the UDS will utilize programs developed by Dr. Morris for training US ADCs. LP training will include recruitment materials such as brochures and videos, educational sessions on the safety and tolerability of LPs and procedural training on proper techniques. Training for imaging protocols will include protocol reviews, and ADNI coordination. Neuropsychometric training will include review and practice of the modified UDS psychometric tests and psychometrician orientation. Training in discussion of brain donations for neuropathology to obtain high rates of consent (~75%) using ADNI methods and forms. Performance site quality assurance will be implemented through ADNI and ADCS. Using the methods that will be implemented through this

The DIAN registry will be created with assistance from the Informatics and Genetics Cores. Current DIAN participants that meet eligibility requirements will be reviewed by the Genetics Core and pedigree, and family relationships will be determined as participants from multiple sites may be related in the same pedigree. This information will be recorded by the Informatics Core as the initial registry for DIAN.

Participants: 240 DIAN participants will be enrolled into the registry with genetics analysis, longitudinal clinical assessment, and psychometrics, with a goal of near 100% completion of LP, 3T MRI, FDG PET and PET PIB imaging based on our experience of highly motivated and dedicated participants for AD research and effective methods of recruitment and retention. DIAN participants will be recruited from ADAD kindreds identified by each performance site, NCRAD, the Alzheimer Association, internet based web pages (see Core H: Informatics), the NIA Office of Communications and Public Liaison (OCPL) and referral from family members. We have had discussions with the NIA OCPL and the Alzheimer's Disease Education and Referral (ADEAR) Center. There is a history of cooperation and shared goals with ADEAR in recruiting for studies with Washington University. The Clinical Core will work with the Informatics Core and multiple public and private organizations to recruit ADAD families into DIAN. The Informatics Core will host an internet web site for DIAN (similar to the current FACS page, http://facs.wustl.edu), and the Clinical Core will post information at appropriate publicly accessible sites including the Alzheimer Association centers, the Alzheimer Forum (www.alzforum.org), and NCRAD newsletters. In coordination with the Informatics Core, Alzforum will organize and implement an outreach campaign directing ADAD families to DIAN (see Core H: Informatics).

DIAN recruitment will target current research participants from kindreds with established research relationships with our collaborating performance sites to enroll a total of 240 participants. DIAN participants have inclusion criteria of being an adult (>21 y) child of a parent with ADAD as proven by family history and genetic confirmation of a disease causing mutation (currently in one of three genes: *APP, PSEN1, PSEN2*) in a family member. Potential DIAN participants will be screened with telephone administered screening forms for inclusion and exclusion criteria, including advanced dementia, contra-indication for imaging studies or LP. This screen identifies depression and other psychiatric conditions to ensure proper attention and referral to medical care. Two informants (usually family members) will be identified by the participant to serve as collateral sources of information. One informant will be available during clinical assessment to serve as collateral source, either by telephone (if the participant is able to independently travel) or in person at the performance site. Written information regarding the DIAN research studies will be sent to the participant and informant before the initial visit. At the initial visit, further information regarding the DIAN studies including MRI, FDG PET, PET PIB, LP, and brain autopsy consent will be discussed with the participant and informant.

Participants will undergo the same clinical, psychometric, imaging and biomarker assessments at every visit with the exception of drawing blood for genetic analyses which will only be performed at baseline. The type of assessments done will not vary depending on the affected status of the participant. Follow-up visit dates will be determined based on the risk of clinical conversion of the participant, as estimated from the age of onset of DAT of the affected parent minus the age of the participant. The age of onset of the parent will be obtained by history obtained from the collateral source during the baseline visit. In order to capture the earliest changes in biomarkers, detect changes near the time of clinical onset, accommodate for finite resources, and minimize burden to the participants, DIAN participants will be evaluated on a schedule optimized for ADAD

participants (below). For example, preliminary results obtained by the FACS indicate that PET PIB imaging changes may occur between 10 to 15 years (but not before) the parents age of onset (see Core G: Imaging). The criteria for frequency of longitudinal follow-up are below in **Table 4**.

Table 4.	
Index: Parent's age at onset of dementia	Follow up interval
≥ 10y younger	follow-up every 5 y
10y – 3y younger	follow-up every 3 y
3y – 0y younger	annual
0 – 3y older	annual
> 3y older	once, at 5 y older than parent's AAO

The Clinical Core will coordinate with Core A: Administration to ensure proper recruitment and enrollment of DIAN participants are made to meet the scientific goals of detecting pre-clinical changes in imaging and biomarkers. The Clinical Core will monitor enrollment to ensure that no more than twenty percent of DIAN participants are symptomatic. Of those potential recruits who are asymptomatic, our goal will be to enroll fifty percent within 3 years of parental age at onset, and 30 percent within 3 to 10 years before parental age at onset (current estimate 29%). Recruitment of participants from multiple sources will supplement the numbers of participants already being followed at DIAN performance sites.

Telephone follow-up with the participant and collateral source will be performed annually to inquire about any cognitive changes. If cognitive changes are reported by telephone follow-up, the participant will be evaluated at the performance site. In this way, sensitivity for detecting clinical changes will be increased while minimizing burden on participants and resources.

Participants will be screened to be cognitively normal (CDR 0) or only very mildly to mildly demented (CDR 0.5-1) at enrollment. Arrangements for transportation, housing, and food will be made for each participant and one collateral source, as most participants will be traveling to the closest participating performance site. The clinical assessment, MRI, PET PIB, psychometric testing, and CSF studies may be completed concurrently over three days or in several visits. **Table 5** summarizes the assessments at baseline and follow up. The participant and collateral source may stay at accommodations arranged by the performance site if traveling from outside the local area. Reasonable accommodation and travel costs will be paid for by DIAN.

Table 5			
Procedure		**Baseline**	**Follow-up**
Study explanation		**X**	
Consent		**X**	
Blood for Genetic Analysis		**X**	
Demographics, Family History, Inclusion and Exclusion Criteria		**X**	
Medical History, Physical Exam, Neurological Exam, Hachinski, Vital signs, Medications (From the UDS)		**X**	**X**
Clinical Evaluation – CDR, GDS, NPI (NEO, Lifestyle)		**X**	**X**
Psychometric Battery*	UDS Measures	**X**	**X**
	Web-based psychometrics (Wash U to provide)	**X**	**X**
3T MRI		**X**	**X**
FDG-PET		**X**	**X**
PET PIB		**X**	**X**
LP		**X**	**X**

The entire study will be discussed with the participant, including all associated risks and benefits before travel for the study. Written information and consent forms will be mailed to the participant for review before the studies. At no cost to the participant, genetic counseling will be encouraged for each participant, given the sensitive and complex nature of having a 50% risk of early onset AD. All performance sites have resources to deliver independent clinical genetic counseling and testing (paid for by DIAN). Clinical genetic testing will be provided for those interested participants as part of genetic counseling. Genetic care, counseling, and testing will be paid for as part of this study. **DIAN investigators involved in all clinical, cognitive, and other assessments will be without knowledge of the mutation status of the participant.**

Clinical Core Aim 2: Coordinate the seven DIAN performance sites and interact with Clinical Coordinating Center for implementation of protocols including clinical evaluation, psychometrics, LP, MRI, PET, and provisional autopsy.

Clinical evaluation:

The UDS will be used for clinical evaluations. The clinical evaluation is tailored for the unique characteristics of the ADAD participants, including younger age, various clinical presentations of DAT, and psychometric performance.

Five of the DIAN performance sites are already evaluating AD with the UDS, the uniform standard evaluation used by all Alzheimer Disease Centers in the United States. Training protocols are available for all DIAN sites, which will be used at the training meeting. The UDS offers the unique advantage of being able to compare clinical presentations of ADAD with the more common late-onset AD already being collected by the NACC. The UDS also has Spanish translations for future enrollment of Spanish speaking DIAN participants. The UDS is face valid in that it measures intra-individual change and is informant based. It is highly sensitive in detecting **change** from prior levels of function and **interference** with everyday activities and thus is critical for the goals of the Clinical Core in characterizing truly non-demented people and individuals in the earliest symptomatic stages of DAT. This approach permits Core clinicians to diagnose AD with high accuracy (93% as confirmed at autopsy), even in the earliest symptomatic stages of the illness (Berg et al., 1998). The participant and a collateral source (usually a family member or close friend) are interviewed by trained clinicians. The participant also receives a full neurologic exam. Based on changes in memory, judgment/problem solving, orientation, community activities, home/hobbies, and personal care, the participant is rated as no dementia (Clinical Dementia Rating (CDR) = 0), very mild dementia (CDR = 0.5), mild dementia (CDR = 1), moderate dementia (CDR = 2), or severe dementia (CDR = 3). In addition, a clinical diagnosis is given for any detected dementia or cause of cognitive change.

The UDS has been supplemented with several clinical evaluations that will provide increased sensitivity and avoid ceiling effects in this younger population. These supplements include measures of personality (NEO), social position, and physical activity (see Appendix). The UDS also will be supplemented with additional cognitive measures described below in Psychometrics. The Washington University ACS has implemented and administered the UDS and supplements described to over 208 ACS and FACS participants to allow sensitive and accurate assessment of the clinical and psychometric changes that occur in DAT in this younger population. The UDS intake clinical form is attached (see Appendix) and will be modified for follow-up visits.

The Clinical Core will monitor and review all CDR >0 diagnoses and changes in CDR level. The Clinical Core will adjudicate all CDR changes and review with DIAN performance sites any discrepancies in classification with data provided on the UDS.

Psychometrics:

We will use two approaches to cognitive assessment. All participants will receive the ADC UDS neuropsychological battery when they visit the sites. The five United States centers already administer this 30-minute battery, which is a subset of the measures administered by ADNI.

This standardized battery was designed for older adults, including those who are demented. Ceiling effects can be expected for some of the measures in non-demented young and middle-aged individuals. More sensitive measures are required to detect the very earliest indications of cognitive dysfunction. Further, many of these individuals are employed and live some distance from the centers, making it difficult and burdensome to obtain longitudinal assessments frequently. More than half of the participants will not be at an age for high risk of clinical conversion and will receive on-site evaluations only every 3 or 5 years. Therefore our second approach will be to take advantage of modern developments in psychometric test theory, such as Item Response Theory (Embretson, 1996) and in technology. We will develop web-based assessments that will assure standardization of administration and allow annual longitudinal evaluation and monitoring of participants even when they are not being evaluated at the performance sites. This approach facilities use of alternate forms, a major advantage in longitudinal research, and eventual expansion of assessment to non-English speakers.

Although web-based assessment has been used since the 1980s, it is a new approach for test developers and many challenges remain. In addition to the determination of the basic psychometric properties of these new instruments, attention must be paid to issues of security and confidentiality.

A working group at Washington University will develop the web based battery which will then be vetted by the Steering Committee and clinical performance sites before adoption and implementation. Professors Martha Storandt, Carol Woods, and David Balota from the Washington University ADRC have developed

protocols to measure cognitive function in the younger ACS population and will jointly chair the panel to develop appropriate measures for DIAN participants.

We anticipate initially focusing on measurement of visuospatial ability, executive function, and attention for several reasons. These functions are often affected very early in the course of sporadic AD (Storandt et al. 2006). The visuospatial measures in the existing test battery are confounded with speed and the battery includes little in the way of assessment of executive function and attention. Balota has extensive experience administering computerized measures of attention to young and middle-aged adults through Project 3 of our current ACS PPG and to demented individuals through another program project. Some of these can be adapted for use in this project. We will also add web-based measures of memory to supplement those included in the UDS and ADNI battery.

Imaging:

ADNI has completed 428 3T MRI, 1064 PET FDG and 42 PET PIB scans including quality controls and corrections. The ADRC Imaging Core supplements this experience with more than 350 PET PIB scans performed at Washington University. The cumulative experience of ADNI and the Imaging Core ensure expert acquisition of images.

The MRI and PET will be collected on the same day or on adjacent days. The PET imaging will include FDG and PIB to measure metabolism and Aβ deposition respectively. The Clinical Core will work with Core G: Imaging to ensure the safety of the participant, including radiation exposure, and reduce burden of participation in protocol development and inclusion and exclusion criteria as specified by ADNI protocols.

The performance site technician or coordinator will upload the image files to the DIAN Central Archive (DCA) over a secure computer connection immediately after acquisition and then enter scan information into the DCA's web-based data entry system. See Core G: Imaging for quality control, inspection and pre-processing and Core H: Informatics for image database management.

PET Imaging: Per the RFA, we have contracted with the imaging components of ADNI (Drs. Koeppe, Jack and Mathis) to initiate non-ADNI sites with ADNI protocols.

PET – PIB: PET – PIB imaging will be performed per ADNI standard protocols and quality controls (see Core G: Imaging).

FDG-PET: FDG-PET will be obtained according to ADNI standard protocol which has already been implemented at the majority of participating sites.

MRI: *MR Scanning and Preprocessing of Images.* MR scans will be performed on a 3T MRI that has been validated by ADNI. Prior to the scan, the procedure will be explained in detail to each participant, and techniques to tolerate small spaces and avoid claustrophobia will be discussed. In a recent survey of DAT and nondemented elderly participants that had participated in neuroimaging studies at Washington University (n = 186), we found that only 5.4% of these participants described the procedures as unpleasant. Moreover, 88.7% of these participants stated that they would be willing to repeat the scanning procedure in the future. These results suggest that the MR scanning required for this project will be well tolerated by the participants.

Genetics Studies:

At the baseline visit, four samples of blood for genetic analysis will be drawn by the DIAN performance site. Two tubes will be sent to NCRAD for the generation of lymphoblastoid cells lines so there will be a renewable source of genetic material from each participant. Two tubes will be sent to the DIAN Core F: Genetics for mutation and *APOE* allele testing (see Core F: Genetics).

Blood and CSF collection:

Blood and CSF will be obtained in coordination with the Core E: Biomarker Core, ADCS and DIAN performance sites. Adopting protocols used by ADNI (with slight modification as outlined below), the Clinical Core will oversee the standardized collection and processing of biological fluids (CSF, plasma, and serum). All collection protocols are compliant with HIPAA regulations and will be approved by the institutional review board at each performance site. CSF and blood (for serum and plasma) will be obtained in a uniform manner at 8:00 AM following overnight fast after the MRI is obtained to avoid affecting the images. Following fluid collection, subjects will recline for 60-90 minutes during which time they will eat breakfast and return home. A follow-up phone call to the subject will be made the following day to document their health status (see Core E: Biomarker).

After written and oral consent is obtained, 40 mL of blood will be collected via venipuncture of the arm. Following blood draw, CSF will be obtained by standard LP at the L3/L4 level using sterile technique. Vital signs will be taken prior to, immediately following, and one hour following the procedure. All subjects will

remain lying flat for one hour after the LP. If a post-LP headache develops that is severe or does not resolve within 48 hours, subjects may be treated with a blood patch at no cost to them. In order to minimize the risk of post-LP headache, the LP will be performed using a small caliber atraumatic spinal needle (22, 24 or 25 gauge Sprotte needle). CSF (20-25 mL) will be collected from the participant and aliquoted into tubes. LPs will be performed Monday-Thursday only (not Friday) so as to avoid weekend sample shipment and allow for weekday scheduling of blood patches in rare cases of post-LP headache.

Summary of DIAN studies:

Table 6: A summary of the DIAN studies, including duration of time for each study. DIAN studies may be performed consecutively or at separate times, and may be performed in any order. Some studies must be fasting and so are scheduled for the morning. As most participants in DIAN will be visiting the DIAN performance site from outside the area, accommodations can be arranged.

<table>
<tr><th>Table 6</th><th>Day 1</th><th>Day 2</th><th>Day 3</th></tr>
<tr><td>07:00</td><td></td><td></td><td rowspan="3">CSF and blood collection (Fasting)
2.5 hours</td></tr>
<tr><td>08:00</td><td>DIAN Performance Site
Meet with Coordinator
1 hour</td><td rowspan="2">PET PIB
PET FDG (Fasting)
2.5 hours</td></tr>
<tr><td>09:00</td><td rowspan="2">Intake, Genetics collection, and Clinical Assessment
2 hours</td></tr>
<tr><td>10:00</td><td></td><td></td></tr>
<tr><td>11:00</td><td>Physical and Neurological Exams
1 hour</td><td>Lunch and travel to DIAN Performance Site</td><td>Rest in Hotel</td></tr>
<tr><td>12:00</td><td>Lunch</td><td rowspan="2">DIAN Psychometrics #2
2 hours</td><td>Lunch</td></tr>
<tr><td>13:00</td><td rowspan="3">DIAN Psychometrics #1
2 hours</td><td>Review of Participation Subject Questions and Feedback</td></tr>
<tr><td>14:00</td><td rowspan="2">3T MRI
1.5 hours</td><td rowspan="3">Return Home</td></tr>
<tr><td>15:00</td></tr>
<tr><td></td><td>Accommodations</td><td>Accommodations</td></tr>
</table>

Ancillary Studies:

Additional research studies will be encouraged from DIAN performance sites. The Clinical Core will assist in notification and recruitment of DIAN participants for additional research studies which may include imaging, biological fluid collection, psychometric testing, clinical testing, computer or telephone interviews, or treatment trials. These ancillary studies will be directly funded by the initiating site(s), however, the Clinical Core will assist in participant identification and notification.

All procedures will be approved by the Human Studies Review Board at the performance site. Informed consent will be obtained. Numbers of participants recruited, enrolled, and completed will be recorded. Statistical analysis and support will be provided by the DIAN Core C: Biostatistics. Protection of DIAN participants for confidentiality, safety, and time demands will be reviewed by the DIAN Participant Liaison and Protection Committee.

Future Studies: Future studies will analyze the data obtained grouped by gene mutation (*APP*, *PSEN1*, and *PSEN2*) and possibly by specific mutation. For example, recent discussions of presenilin mutation pathogenesis (loss of function or gain of toxicity) may be addressed by comparing certain biomarkers of *PSEN1* mutations with *APP* mutations or duplications.

Clinical Core Aim 3: Ensure protection of sensitive and confidential genetic and research data and offer clinical genetic counseling and testing to DIAN participants.

A special meeting was held by the Clinical Core to plan for the sensitive genetic information and special ethical considerations involved in a study of autosomal dominant inherited AD. The meeting included clinical genetics counselors, physicians and nurses who are familiar with ADAD, AD patient representatives, human studies committee representatives, genetics researchers, and social workers as well as members from the Washington University ADRC. After consultation with outside experts in genetics testing and ADAD, a consensus was reached regarding best practices for managing sensitive genetic information, informed consent, genetic counseling and testing. The outcomes of this consensus are listed below.

As a clinical service (benefit for participating in research) we will offer but not require genetic counseling and subsequent testing. The research grant will pay for both counseling and testing if the participant wishes to obtain it. The Genetics Core can track use of counseling, testing and participation. Participants may contact the research team directly, or after another family member (proband) gives them information. They may also be sent information from existing research teams which have a relationship with them (other ADRC centers, NCRAD, etc.) Informed consent (written) will include the following information:

1) Research tests results (except clinically important information) will not be released to participant.

2) The purpose of study and why participant is being invited will be explained to the participant. (e.g. the study of early onset autosomal dominant AD that invites participants at 50% risk of AD).

3) An option for clinical genetic testing will be described and offered in the consent. An option to be contacted for future clinical trials will be described and offered in the consent. An option if research results become meaningful clinically to re-contact the participant to inform them they may wish to obtain clinical testing.

4) Medically relevant information may be disclosed to the participant's primary care physician (via dictated note) and will be offered to the participant after explanation of risk of information sent to primary physician can cause discrimination from insurers, employers or others. In addition, explanation of third-party risks to parents, siblings or children regarding confidentiality, loss of insurance/employment will be explained to the participant. Life threatening information must be managed by the research physician regardless of normal feedback mechanisms (i.e. tumor in the brain, hypertensive emergency, etc.) and includes proper medical care will be arranged (but not necessarily paid for).

5) Clinical feedback (verbal and written note) will be given to the participant/collateral source by the evaluating physician. Each DIAN evaluating clinician will be trained in feedback session to have well-informed discussion (e.g. clinical exam is not 100% predictive of outcome), implications of changes that have not been noticed by family, but are detected on clinical evaluation. Training of physicians giving feedback will occur at the training meeting and will be monitored by the Clinical Core. The participating sites will monitor for depression or psychiatric reactions at each visit and telephone follow-up and arrange for medical care if indicated.

Confidentiality and de-identification: Confidentiality and de-identification will be performed to HIPAA standards or applicable standards in Australia or England. Only qualified members of the DIAN research team will have access on a need-to-know basis. No identifying information will be associated with genetic tests. Double blind numbers (i.e. subject number linked to genetic test number which is linked to genetic test results) will be used to prevent accidental disclosure of results. Participants will be instructed not to tell clinical evaluator their genetic status (if known) in order to avoid bias of clinical evaluation and only clinicians that do not know genetic status may evaluate the participant.

Data Transfer: Clinical assessments including UDS, supplements and neuropsychiatric testing will be directly sent to Informatics Core for coordinating data and studies. See Core A: Administration for the DIAN resource sharing plan.

Core Interactions:

DIAN Performance sites: (see Clinical Performance Site descriptions that follow this Core.

A close working relationship has been developed with other performance site leaders in a collaborative fashion. For example, Dr. John Ringman (Los Angeles) refers his participants for studies only available at Washington University. Drs. Bateman, Fox, Johnson, Klunk, and Sperling worked closely with Gabrielle Strobel and June Kinoshita to develop the eFAD series on the Alzheimer Forum website. In addition to the ongoing working relationship, a consensus for the need to share resources and advance research in ADAD has been established at recent AD and biomarkers meetings by the participating sites of DIAN.

Core A: Administration:

Dr. Bateman will serve on the DIAN steering committee as Clinical Core Director and is also a member of the Liaison and Protection subcommittee and the Expansion (sites & languages) subcommittee.

Core C: Biostatistics:

The Clinical Core will consult with the Biostatistics Core to review statistical power analysis including enrollment of participants by years to predicted age of onset, clinical status, and completion of studies to ensure enrollment and completion of studies is sufficiently powered to address DIAN hypotheses.

Core D: Neuropathology:

The Clinical Core will coordinate and train performance sites in obtaining voluntary consent for autopsy (current rates of autopsy at Washington University are 75%) using brain autopsy forms (see Appendix). The brain autopsy consent rate will be reviewed with performance sites and training and assistance will be offered as needed. A target of 50% participants consented is expected.

Core E: Biomarker:

The Clinical Core will coordinate the sample collection procedure, percent of Lumbar Punctures completed (Goal of 80%) and any participant discomfort and side effects.

Core F: Genetics:

The Genetics Core will review statistics on genetic samples received, percent of mutation carriers, QA/QC of sample identification to meet goals of recruitment and specific aims.

Core G: Imaging:

The Clinical Core will review the number of scans and percentage of successful participants that will ensure numbers are reached for valid comparison. The Clinical Core will also review any clinical issues to enrollment (e.g. claustrophobia in MRI).

Core H: Informatics:

The Clinical Core will review data from the Informatics Core regarding registration of clinical assessments including UDS and neuropsychometric assessments, CDR status, number of enrolling and completing DIAN research studies and number of enrolling and completed ancillary studies to monitor the completion of goals and evaluation of attrition and participant burden.

Summary of Research design and methods:

DIAN will generate a wealth of information on the pathophysiology, pathology, biomarkers, and clinical changes of autosomal dominant Alzheimer disease. This study will provide for a comprehensive analysis of multiple aspects of Alzheimer disease in a uniquely informative population.

Future Aims:

The DIAN Clinical Core will assist DIAN investigators to test specific hypotheses based on the clinical, imaging and biomarker data collected. The overall goal is to determine the relationship between clinical, imaging and biomarker results, which will be addressed with the following future specific aims:

1) Determine the rate of clinical conversion from cognitively normal to dementia in a carefully studied population of DIAN participants including average age of onset and CDR and psychometric rate of progression.
2) Determine the effect of ApoE4 status on the age of onset and progression in mutation carriers.
3) Determine the chronological order and rate of change of biomarker, imaging, psychometric and clinical changes in mutation carriers vs. non-carriers.
4) Determine similarities and differences between ADAD and sporadic AD in clinical presentation, psychometric testing and biomarkers.

E. Human Subjects: Protection of Human Subjects

1. RISKS TO THE SUBJECT

a. Human Subjects Involvement and Characteristics: All procedures will be approved by the Human Studies Review Board at each DIAN performance site. Informed consent will be obtained after all risks and the purpose and procedures involved in these studies are described to the volunteer and a signed consent form obtained. The DIAN participants are at 50% risk of early onset AD, and represent a special population in terms of sensitivity of research results and genetic information. Approximately 20% of subjects will have very mild or mild dementia.

b. Sources of Materials: Blood and CSF samples will be obtained per protocol and will be used for research purposes only. Clinical and psychometric testing will be obtained from interviews and examinations of participants and collateral sources.

c. Potential Risks: The likely risks to the subject include local discomfort from intravenous catheter placement and LP. In addition to the initial discomfort, there is a low risk (<3%) of post-LP headache. In the majority, the headache resolves after treatment with a patch, which is provided free of charge at the end of the study. There is a very rare risk of infection or blood clot at the needle insertion site.

There is a potential risk of genetic or other research information becoming known by participants or others. This information will be held strictly confidential due to the especially sensitive nature of these participants. There will be disclosure to the participants about this risk.

This study involves the risk of claustrophobia from lying in enclosed spaces during imaging studies, the risk from metallic implants or devices during exposure to a magnetic field, and the risk of radiation exposure (see 2c below). Although all data are held in strict confidentiality there is always a very small risk of breaching these safeguards, with the potential for deleterious effects for the subject and his/her family for insurance and employment. This information will be held strictly confidential due to the especially sensitive nature of these participants. There will be disclosure to the participants about this risk.

2. ADEQUACY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent: Full informed consent will be obtained from the participant before they arrive for the study. Recruitment will occur by contact via the proband of the pedigree, who will provide contact information to the potential participant, who would then need to contact the study coordinator. Once contacted by the interested participant, informed consent will be given before any study is performed.

b. Protection Against Risk:

Approximately 20% of subjects will have very mild or mild dementia. Although mildly demented subjects may retain competency for informed consent, our policy is to obtain informed consent from the subject and the next-of-kin or responsible caregiver who serves as the informant. We obtain a copy of the durable power of attorney (DPOA) for health document when available. For subjects who do not have a DPOA for health we given information to assist the subject to obtain one or to designate a research proxy. We are very sensitive to issues related to the subject's ability to understand the elements of consent and their capacity to make decisions. We follow the Washington University School of Medicine "Guidelines for Research Proposals involving Adults Subjects with Cognitive Impairment" which was authored by Drs. Morris and Berg (the former ADRC program project PI). Informed consent will be obtained by the DIAN performance site (after training by the DIAN Clinical Core); the purposes of the study, its assessment procedures, and risks and benefits are explained. The original signed consent forms are kept with the subjects' confidential file and a copy is given to the subject/responsible caregiver.

Protection of the participants for management of their genetic risk will be managed by a genetic counselor. Participants will be encouraged to receive genetic counseling from the local genetic counselor. This counseling will be paid for by the study, as it may not be covered by insurance or be affordable to those without insurance. After full counseling about options are given, the participant will also be offered clinical genetic testing for ADAD mutations. If the participant chooses to be tested, the clinical test will also be paid for by this study. Full counseling and post-test support will be provided.

Privacy protection of participants' research results will be maintained at all times. Participants are assigned a non-identifying code number upon enrollment, which is used on all data and samples. A master list is kept secured in HIPAA compliant fashion(with two separate locks, one to the door and the other to a cabinet). The investigators will not know research results of individual participants. Data will be analyzed in group fashion, and no individual results will be published, unless it is completely non-identifying. Our certificate of confidentiality offers further protection of research records. Data collected for this project will be covered by the ADRC's Certificate of Confidentiality(#AG 99-02A) from the Department of Health and Human Services to protect the research data and medical information from subpoena.

The potential risks related to imaging in this study will be minimized in the following manner:
1) Claustrophobia from MRI or PET imaging will be reduced by explaining the nature of the magnetic resonance scanner and positron emission tomography in detail to all participants prior to their enrollment. If severe claustrophobia occurs, the study will be terminated upon the subject's request. 2) Except for the effect on metallic implants such as pacemakers (which is specifically discussed with the subjects), there are no known risks from brain MRI. A possible history of any intraoccular, intracranial, or intrathoracic metal will exclude the subject from the study. 3) In PET studies the risk of radiation exposure will be minimized by using smallest dose possible of radioactive tracers. The amount of radiation exposure to the subject will be approved by the local Radioactive Drug Research Committee acting under the authority of the FDA or the appropriate local regulatory committee outside the US. The maximum dose in any year cannot exceed the

limit for occupational exposure set by the FDA or local regulatory committee. In this study the injected dose of the PET PIB will not exceed 30 mCi of [11C]PIB yielding a radiation dose equivalent of 465 mrems. For a single FDG PET study (5mCi) that will be used in this project, the bladder wall will receive a dose of 1.6 rad which is below the dose guidelines of 5 rad published in the Code of Federal Regulations (21CFR §361.1). well below the dose guidelines of 5 rad published in the Code of Federal Regulations (21CFR §361.1). We have decided to limit the total radiation exposure for each subject to a maximum of 40 mCi (or 8 PET studies), which will keep the dosage for target organs below acceptable limits (at 13 rads) and follows standard ADNI protocol. The risk from the radiation exposure in these studies is small when compared with other everyday risks. 4) Embarrassment is minimized by the efficient, empathetic, and professional manner of the staff.

c. Data Monitoring Plan

Each DIAN Performance Site PI will monitor the study for adverse events, adherence to the protocol, inclusion/exclusion criteria, and accrual/withdrawal rates and report this information to the Clinical Core. All serious adverse events (SAE) will be reported to all associated IRBs: a) death – immediately; b) life-threatening with 7 calendar days; c) all other SAEs within 15 calendar days using a SAE report. Should there be an adverse event that occurs that increases the risks to the participants, the following steps will be taken: suspension of the study until risks are re-evaluated and discussed with the IRB. Other reports that will be generated are yearly summary reports. These will be sent to the IRB annually.

All identifying information will be kept on a master list with the non-identifying numbers in a locked file drawer in a locked office. No identifying information will be used on samples, data, or analysis.

d. POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO THE SUBJECTS AND OTHERS

There is a potential benefit of genetic counseling and testing that is offered to the subject and will be paid for by this research proposal. This research has a potential benefit to others in that it may lead to an early diagnostic test or help in the development of new therapies for Alzheimer disease.

e. Women and Minority Inclusion in Clinical Research

1. Inclusion of Women—Women will be recruited and enrolled in all studies described.

2. Inclusion of Minorities—All minority groups are encouraged to participate in this research, however, most known kindreds with ADAD are Caucasian. Races or ethnic categories of minorities will be encouraged to participate.

3. Inclusion of Children—Due to the age-related nature of Alzheimer disease, persons under the age of 21 will not be studied.

f. IMPORTANCE OF THE KNOWLEDGE TO BE GAINED

The formation of DIAN will provide the power to determine the processes of AD in a uniquely informative group of individuals that would not be possible at a single site. It will likely lead to discoveries that will direct the field in the understanding AD in humans, and may lead to advancements for sensitive tests and opportunities for treatment mechanisms. Perhaps most importantly, DIAN would allow for new disease modifying therapies that target Aβ processing to be used in a patient population where there is clear evidence as to Aβ causative role in AD. This proof of concept treatment trial may accelerate advancements of treatments for the more common late-onset AD. The risk of serious or permanent adverse effects is very low and the likely risks of discomfort are very mild. Therefore, a large potential benefit to society for advancing knowledge of Alzheimer disease and developing new tests and treatments outweigh the low risks to participants.

F. Vertebrate Animals Not Applicable
G. Select Agent Research Not Applicable

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I. MULTIPLE PI LEADERSHIP PLAN not applicable

J. CONSORTIUM/CONTRACTUAL—A subcontract will be established with the University of Califronia at San Diego to contract for the services of the Alzheimer's Disease Cooperative Study, Paul Aisen, PI to be the Clinical Coordinating Center for DIAN.

K. RESOURCE SHARING: All data collected will be managed and stored by the DIAN bioinformatics core and by the administrative core. See Core C: Biostatistics and Core A: Administration.

L. CONSULTANTS/COLLABORATORS-