

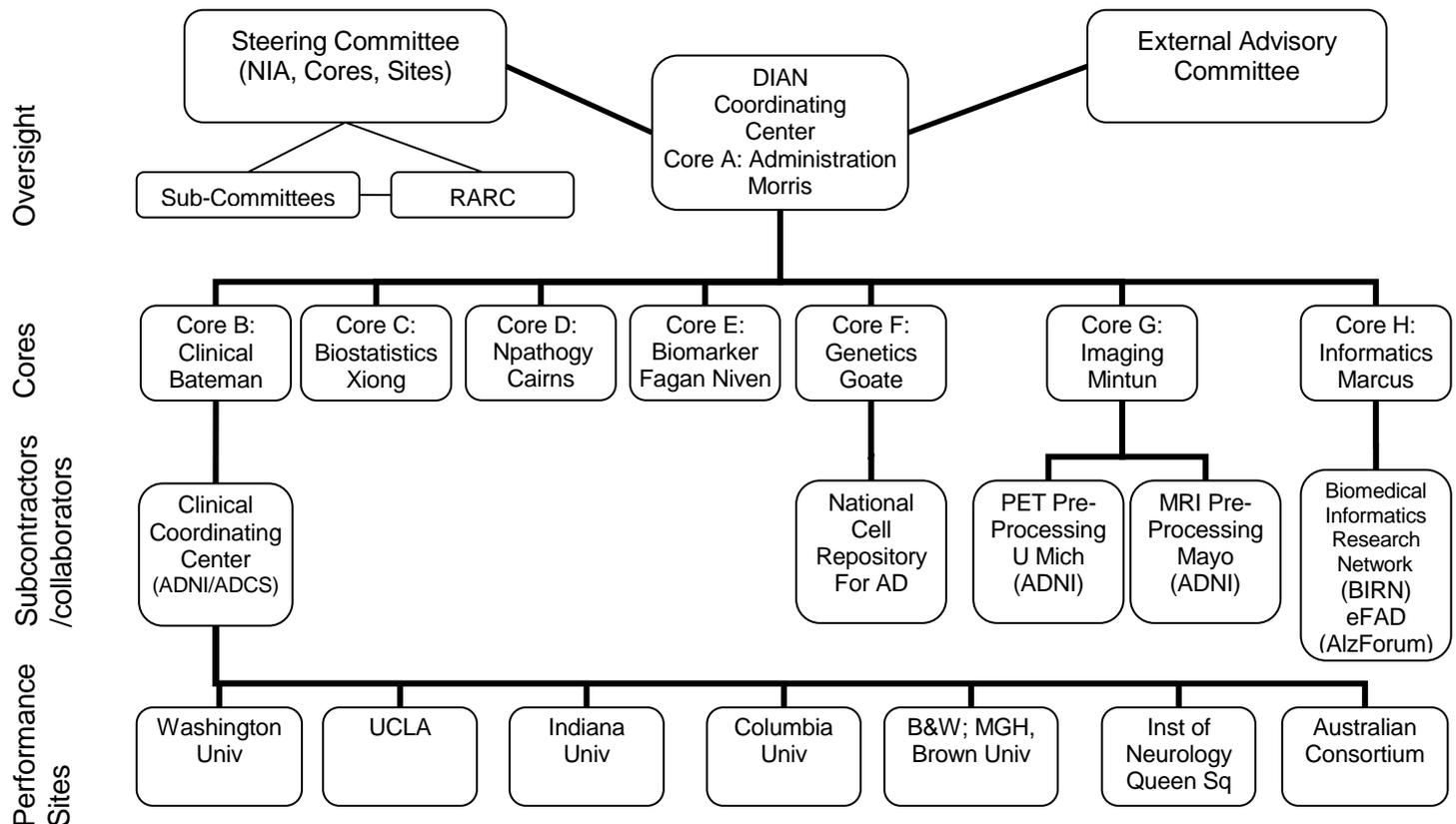
A. SPECIFIC AIMS

The components of DIAN include the DIAN Steering Committee and multiple subcommittees, eight cores (Administration, Clinical, Biostatistics, Neuropathology, Biomarker, Imaging and Informatics), five subcontracts (to ADNI components) and 7 clinical performance sites. The Administration Core will act as the Coordinating Center for Dominantly Inherited Alzheimer Network (DIAN) application. The specific aims of the core are:

1. Organize and coordinate activities and communication of the Cores, subcontractors and clinical performance sites toward achieving the stated goals of DIAN, to include administrative, and budgetary support and monitoring, and problem solving on a continuous basis.
2. Organize and support the DIAN Steering Committee, its subcommittees, the Resource Allocation Review Committee to include arranging meetings, communication and execution of their decisions and recommendations to DIAN components. Core A will also organize and coordinate the clinical training meeting.
3. Following Steering Committee direction, and with all DIAN Cores and Clinical Coordinating Center, delineate protocols; coordinate and monitor participant recruitment and retention; organize and monitor data and tissue collection and storage.
4. With the Steering Committee and subcommittees, establish policies and procedures regarding: protection of research participants; resource (data, images and tissue) sharing and dissemination; publications; future expansion of DIAN to include other sites and languages; and potential new research directions.
5. Arrange for annual external review and advice concerning DIAN goals and progress
6. Generate payments to clinical performance sites for DIAN evaluations and arrange for and finance genetic counseling and testing services when desired, and participant travel when necessary.

The Administrative structure of DIAN is shown in Figure 1. The project **timeline** follows this plan.

Figure 1.



B. BACKGROUND and SIGNIFICANCE

The Dominantly Inherited Alzheimer Network (DIAN) represents the next stage in biomarker discovery for Alzheimer's disease. Historically and currently, Washington University has focused on the interrelationships and predictive value of clinical, cognitive, imaging, and biomedical correlates of the earliest symptomatic stages of Alzheimer's disease (AD) in comparison with healthy aging. This focus is supported by three grants: Alzheimer's Disease Research Center (ADRC), P50 AG05681 (JC Morris, PI), Healthy Aging and Senile Dementia (HASD), P01 AG03991 (JC Morris, PI), and Antecedent Biomarkers: The Adult Children Study (ACS), P01026276 (JC Morris, PI). The first two grants are in their 24th year of continuous funding from the National Institute on Aging (NIA). The ACS grant is its 3rd year of funding. Together they provide the scientific foundation for this application and will contribute valuable resources, infrastructure, and other support to ensure the successful accomplishment of our aims. HASD has emphasized the comparison of healthy aging with late onset Alzheimer's disease. The ACS shifted the focus to middle-aged, cognitively normal individuals where the risk factor of family history distinguished two comparison groups in search of antecedent AD biomarkers. DIAN will narrow this focus on antecedent biomarkers to members of families with a known causative mutation for dominantly inherited AD.

Submission and execution of these successful grants have been coordinated by the same individuals who comprise the DIAN Coordinating Center, also called Core A: Administration. This team has an excellent track record in submitting and obtaining research grants and more importantly accomplishing the research goals of these initiatives.

C. PRELIMINARY STUDIES/PROGRESS REPORT

In preparation for the DIAN application Dr. Morris solicited interested investigators to reply to a survey addressing available research participants and institutional resources to carry out DIAN assessments. Responses were received from many interested institutions and after further discussion and review 7 clinical performance sites (see Table 1) were selected to participate in DIAN.

Table 1. Clinical Performance Sites	Site Leader
Columbia University	Richard Mayeux
Indiana University	Bernardino Ghetti
Univ. of California, Los Angeles	John Ringman
Washington University	Randall Bateman/ John C. Morris
Brigham & Women's Hospital/ Massachusetts General Hospital/Brown University Consortium	Reisa Sperling
Institute of Neurology, Queen Square, University College London	Martin Rossor
Australian Consortium (Prince of Wales Medical Research Institute & University of New South Wales, Sydney; Mental Health Research Institute of Victoria & University of Melbourne, Melbourne, and Edith Cowan University, Perth)	Peter Schofield

Because close adherence to ADNI protocols and methods are recommended, dialog and collaborative interaction with the ADNI principal investigator, Dr. Michael Weiner, was established during the planning of this application as well as with other ADNI key personnel from its Clinical and Imaging components. Subcontracts were established with the ADNI/ADCS Clinical Coordinating Center (Paul Aisen), and the MRI (Clifford Jack), FDG PET (Robert Koeppe), and PET PIB (Chester Mathis) Imaging components of ADNI to assure alignment with ADNI protocols and methods in the performance of DIAN assessments.

D. RESEARCH DESIGN AND METHODS

Specific Aim 1: Organize and coordinate activities and communication of the Cores, subcontractors and clinical performance sites toward achieving the stated goals of DIAN, to include administrative, and budgetary support, monitoring, and problem solving on a continuous basis.

Dr. Morris's experience at leading large, multi-component research initiatives has been detailed in the Overview of this application. He meets formally weekly with the Associate Directors (Goate and Holtzman) and the Executive Director, Dr. Buckles, to maintain efficient administrative operations. In practice, Morris and Buckles interact on a daily basis (their offices are adjoining) to maintain optimal communication and operations. Morris and Buckles also communicate as appropriate with NIA staff and will be responsible for all administrative aspects of DIAN. Buckles has worked with Morris since 1992 in conducting research and in administering and implementing multiple-component grants. Dr. Buckles is highly experienced in the administrative and budgetary operations of program projects. Currently, she serves on the NIA Biospecimen Task Force to establish 'Best Practice' guidelines for the acquisition, processing, storage, and dissemination of biospecimens for Alzheimer's disease research. She also is the current Chair of the Alzheimer's Disease Center Administrators' Steering Committee.

Core Communication

All Core Leaders meet bimonthly at the Executive Committee meetings shared with the ADRC Executive Committee. Core A: Administration, Core B: Clinical, and Core C: Biostatistics meet twice a week at the Clinical Conference, chaired by Morris and at the Biostatistics Operations meeting. Every 6 months these three Cores meet with each of the other Cores: Imaging, Genetics, Neuropathology and Informatics to solve problems and monitor progress in subject participation, data collection and management, and other administrative issues.

Steering Committee

The PI, Associate Directors, Executive Director, Core Leaders, Dr. Weiner (ADNI), and all performance site leaders (n=7) will be joined by a bioethicist, an ADAD family representative, a representative from the Food and Drug Administration, and appropriate staff from the NIA to form the Steering Committee for DIAN. The bioethicist and family representative will be chosen from nominees suggested by the other members of the Steering Committee and with the approval of NIA staff. The Steering Committee has the responsibilities of governing DIAN, including finalizing the definitions, procedures, and measures proposed in this application. Once these are finalized, the Steering Committee will coordinate the development by the Cores and the Clinical Coordinating Center of the DIAN Manual of Operations to guide all DIAN functions and performance sites

Clinical Performance Sites

Although the Clinical Coordinating Center (Paul Aisen, UC San Diego Subcontract) will be responsible for coordinating and monitoring the clinical performance sites, Core A: Administration will be responsible for primary communication with and between sites and also for generating payment to the sites for their clinical activity as reported by the Clinical Coordinating Center.

Specific Aim #2: Organize and support the DIAN Steering Committee, its subcommittees, the Resource Allocation Review Committee to include arranging meetings, communication and execution of their decisions and recommendations to DIAN components. Core A will also organize and coordinate the clinical training meeting.

The Steering Committee will meet every 2 months (6 times a year, see Timeline at end of section). One meeting each year will be "face-to-face". To minimize costs and inconvenience, whenever possible the face-to-face meeting will be held in conjunction with another meeting that normally is attended by many DIAN personnel (e.g., International Conference on Alzheimer's Disease, annual meeting of the American Academy of Neurology). The other 5 meetings each year will be held by teleconference. Given the 15 hour difference in time zones between London and Sydney, we may need to alternate the inclusion of each site in the teleconferences. However, the site (London or Sydney) not included in a particular teleconference will be asked to comment and contribute to the agenda in advance of the meeting and will of course review the minutes. Dr. Aisen (ADCS) or another representative from the CCC will participate in the Steering Committee meetings. Matters requiring attention prior to a scheduled Steering Committee meeting will be addressed by electronic mail, telephone, or FAX.

DIAN will train and standardize all performance sites on the assessment and data collection protocols and their uniform administration (see DIAN Timeline at end of section). Should DIAN be awarded, the inaugural Steering Committee meeting will plan the Training and Standardization meeting for all performance sites to occur within the first 3 months of the funding period. Clinicians, neuropsychologists, and study coordinators from each performance site, in addition to the site leader, will attend this meeting.

Dr. Morris developed and implemented training and standardization meetings for clinicians and neuropsychologists at all ADCs in regard to the UDS, and will coordinate the same training for DIAN sites (Institute of Neurology, London; Australian Collaboration) who have not yet been standardized on the UDS. Similar training and standardization protocols have been developed and implemented by ADNI for its imaging and biomarker studies. The process by which non-ADNI DIAN sites will be qualified by the ADNI imaging subcontractors is discussed in **Core G: Imaging**. The non-ADNI sites also will be trained with the ADNI Biofluid Protocol for the collection, processing, and storage of biological fluids (**Core E: Biomarkers**). Procedures for quality control for DIAN data collection will be developed by the Steering Committee unless they already are in place (e.g., the CCC for clinical and cognitive data; image data through ADNI subcontractors).

Specific Aim #3: Following Steering Committee direction, and with all DIAN Cores and Clinical Coordinating Center, delineate protocols; establish, coordinate and monitor participant recruitment and retention organize and monitor data and tissue collection, and storage.

Core A: Administration will facilitate the implementation of the protocols proposed in the various Cores of this application following review and possible modification by the Steering Committee.

Following standardization, the sites will recruit, enroll, and follow individuals from ADAD kindreds to reach a total sample size of 240 individuals. Surveys of the 7 DIAN performance sites indicate that over 400 DIAN-eligible participants presently are enrolled in site-specific research studies, and this pool will be targeted for recruitment to DIAN. As noted in **Core B: Clinical**, our experience is that ADAD individuals already participating in research are highly motivated and committed to completing even the comprehensive assessments, including LP, proposed for DIAN. We will also be able to identify and recruit ADAD individuals who learn of DIAN through its website and through our listing with eFAD on the Alz Forum (www.alzforum.org) (see Letter of Support from J Kinoshita). Other potential organizations that can be used to aid recruitment include the NIA's Alzheimer Disease Education and Referral Center, the Alzheimer's Association, and Alzheimer-based research programs that are not current DIAN performance sites (see Letter of Support from T Bird).

Specific Aim #4: With the Steering Committee and subcommittees, establish policies and procedures regarding: protection of research participants; resource (data, images and tissue) sharing, dissemination, publications; future expansion of DIAN to include other sites and languages, and potential new research directions.

The Steering Committee will designate Subcommittees to address specific topics and operations; a proposed initial roster of Subcommittees is shown in Table 2.

Table 2	Datasharing & Publications	Expansion (sites & languages)	Participant Liaison & Protection	Tissue-Biospecimen	Imaging
Chair	R. Mayeux	B. Ghetti	M. Rossor	D. Holtzman	M. Mintun
Members	V. Buckles	J. Ringman	R. Bateman	A. Fagan	N. Fox
	M. Rossor	R. Bateman	R. Sperling	N. Cairns	J. Ringman
	S. Salloway	R. Mayeux	R. Martins	C. Masters	R. Sperling
	C. Xiong	W. Brooks	Family Rep	B. Ghetti	D. Marcus
	P. Schofield	M. Rossor	Bioethicist	A. Goate	M. Weiner
	TBN	Family Rep	TBN	J. Hardy	C. Rowe

The Subcommittees will perform essential duties. For example, the proposed Tissue and Biospecimen Subcommittee will oversee the allocation and distribution of biological specimens generated by DIAN. This Subcommittee will establish procedures by which investigators can request access to the biospecimens and, with the PI and NIA staff, nominate members to form the Resource Allocation Review Committee (RARC). The RARC will be composed of individuals who are not directly involved with DIAN and have no relevant conflicts of interest. It will review applications for use of the DIAN biospecimens and provide their recommendation for approval or disapproval to the Steering Committee. We anticipate that DIAN will have a large impact. Many more institutions that could be accommodated budgetarily expressed interest in becoming as a DIAN performance site. Once DIAN is established and fully operational, the Expansion Subcommittee and the Steering Committee will consider how additional qualified sites worldwide may be included. Three major factors will need to be

addressed: 1) the ability and willingness of the candidate site to adopt DIAN's standardized protocols for uniform administration to DIAN participants; 2) translation issues for languages other than English and Spanish; and 3) costs.

Although not a goal of the RFA, the DIAN cohort may be very attractive for the evaluation of potential therapies for AD. Clinical trials in DIAN with agents now in development already have been explored preliminarily with the PI by several pharmaceutical companies. The Steering Committee, working with the participant Liaison and Protection Subcommittee, will develop a process wherein formal proposals to conduct clinical trials in the DIAN cohort are evaluated and approved. Such proposals will need to be funded outside of the DIAN grant.

Specific Aim #5: Arrange for periodic external review and advice concerning DIAN goals and progress

If DIAN is awarded, with the advice of the Steering Committee and NIA staff an External Advisory Committee (EAC) will be recruited by the PI. EAC members will be from outside the participating DIAN institutions and will be selected based on expertise relevant to the various Cores and functions of DIAN. The responsibilities of the EAC include visiting the DIAN Coordinating Center (Washington University) annually to evaluate progress, assess the effectiveness of communications among the DIAN components, and ensure that the conduct of the studies is of the highest possible quality. NIA staff will be invited to attend the EAC meetings, and DIAN investigators outside of Washington University will have the opportunity to participate by teleconference. The EAC will generate a report of its findings each year.

Specific Aim #6: Generate payments to clinical performance sites for DIAN evaluations and arrange for and finance genetic counseling and testing services when desired, and participant travel when necessary for participation.

Three additional administrative duties will be performed by Core A: Administration. Although the Clinical Coordinating Center (UC San Diego Subcontract) will monitor clinical performance site activity, it will generate and provide to Core A invoices specifying the payments to the sites. The funds for these payments are contained in the budget for Core A: Administration and will be dispersed by Core A personnel.

The RFA requires genetic counseling services be offered to all DIAN participants because of their family status. Each of the performance sites was queried as to the availability of clinical genetic counseling services and also CLIA-approved genetic testing (independent of DIAN); all 7 sites have these services available. Based on our own and published experiences¹ with such counseling, the number of participants who will elect to undergo testing is predicted to be low (<10%). CLIA-approved genetic testing can only be undertaken following completed genetic counseling.

Finally, DIAN participants may be required to travel and remain overnight at the closest clinical performance site. Rather than attempt to estimate what these costs might be per site, participant travel costs will be reimbursed by Core A.

E. Human Subjects

Core B: Clinical details the specific protections, policies and procedures in dealing with DIAN research participants. Although Core A: Administration does not interact directly with human subjects, it is ultimately responsible for their DIAN experience. The Administration and Clinical Cores are active in efforts to improve the conduct of research with cognitively impaired individuals and to ensure the protections afforded our research participants. Morris co-authored the Washington University IRB policy on conducting research with cognitively impaired subjects (see <https://hrpo.wustl.edu/HRPO/Doc/0/J5HHS6QQ3TRK3FJJ7N9OFCGV17/Cognitive.rtf> for complete text of this policy). The Administration Core will verify that all components using human subjects are reviewed by the Washington University Human Research Protection Office (HRPO) as well as their local institutional review boards. A federal Certificate of Confidentiality will be requested to protect DIAN research data from involuntary disclosure. Any investigator seeking access to ADRC research resources such as human subjects, tissue, and data must also demonstrate HRPO approval or waiver. Some DIAN investigators (Bateman, Buckles, Xiong) serve on the Washington University Human Research Protection Office (HRPO) committees to facilitate dementia research at the University and provide expertise to the HRPO committees reviewing dementia-related protocols. As mentioned above, Core A: Administration will work with Core B: Clinical and the Clinical Coordinating Center to help all clinical performance sites obtain IRB approval for DIAN evaluations.

DIAN participants will be informed in their consent documents (an example consent form can be found in the Clinical Core Appendix) that data and biological samples collected will be coded to prevent disclosure of

protected health information (PHI) and any research health information, in compliance with HIPAA regulations; and these data and biological samples may be shared with other institutions or companies as approved by DIAN's Steering Committee. Subjects also relinquish any proprietary interest in the data or specimens they provide in the course of this research.

Responsible Conduct of Research Training. In response to the NIH mandate that all key personnel have received or will receive training in the responsible conduct of human research. The Administration Core will ensure that all DIAN investigators and staff have completed their respective institution's equivalent of the "Responsible Conduct of Research" training.

Health Insurance Portability and Accountability Act (HIPAA). The Administration Core has been diligent in achieving compliance with HIPAA privacy and security regulations and has met all local and federal deadlines for existing Center and PPG mechanisms. Buckles served on the Washington University Department of Neurology HIPAA Stakeholders committee and wrote the departmental HIPAA policy and procedures.

F. VERTEBRATE ANIMALS – None

G. SELECT AGENT RESEARCH - None

H. LITERATURE CITED

1. Steinbart EJ, Smith CO, Poorkaj P, Bird TD. Impact of DNA testing for early-onset familial Alzheimer disease and frontotemporal dementia. Arch Neurol 2001; 58:1828-1831.

I. MULTIPLE PI LEADERSHIP PLAN – Not applicable

J. CONSORTIUM/CONTRACTURAL ARRANGEMENTS – Core A: Administration will establish a contractual relationship with the Northern California Institute for Research and Education (NCIRE) will be established to support the effort of Dr. Michael W. Weiner (ADNI PI) in coordinating DIAN procedures and activity with those of ADNI.

K. RESOURCE SHARING

Intellectual Property and Data Sharing. The DIAN project is committed to the sharing of intellectual property and research resources (e.g. tissue and data) with minimum restriction. Intellectual property and data generated from DIAN will be administered in accordance with the policies of Washington University, the Washington University ADRC, and NIH, including the Bayh-Dole Act of 1980, the NIH Data Sharing Policy and Implementation Guidance of March 5, 2003, the RFA-AG-04-011, and the Health Insurance Portability and Accountability Act (HIPAA).

Inventions: Ownership of sole or joint inventions developed from DIAN will be owned by the institution(s) employing the inventor(s). Inventorship shall be determined by U.S. Patent Law, Title 35, United States Code. University and participating investigators/institutions will disclose any inventions developed under the project and such inventions will be reported and managed as provided by NIH policies. Sole inventions will be administered by the institution employing the inventor. Joint inventions shall be administered based on mutual consultation between the parties. Similar procedures will be followed for copyrights.

Materials: Materials generated from DIAN will be disseminated in accordance with Washington University ADRC/participating institutional (see "Requesting Resources" below) and NIH policies. Depending on such policies, materials will be transferred to others under the terms of a material transfer agreement or simple letter of agreement using the least restrictive language possible. The Administration Core will follow the NIA Biospecimen Task Force guidelines related to material transfer agreements.

Resource Sharing Plan:

1. **Data Sharing Upon Publication:** Data generated by DIAN that is published will be made publicly available at the time of the acceptance of manuscripts for publication, consistent with NIH policies on data sharing (http://grants.nih.gov/grants/policy/nihgps_2003/index.htm and http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part7.htm#_Toc54600131). Research data which documents, supports and validates research findings will be made available after the main findings from the final research data set have been accepted for publication. Such research data will be de-

identified to prevent the disclosure of personal identifiers. The only exception to this policy would be if research participant confidentiality could not be guaranteed.

2. **AD Genetics Data Sharing:** The DIAN Genetics Core will follow NIH guidelines on the sharing of genetic material and associated data as stated in the "POLICY FOR SHARING RESOURCES AND DATA FROM STUDIES ON THE GENETICS OF ALZHEIMER'S DISEASE." Please see Core F: Genetics for specific genetic data sharing policies under this policy. The only exception to this policy would be if research participant confidentiality could not be guaranteed.
3. **Resource Sharing with Qualified Investigators:** An essential feature of DIAN is that the clinical, neuropsychological, imaging, and biological data and samples will be made available to all qualified scientific investigators. Data and tissue samples generated by DIAN for the DIAN Central Archive and respective tissue repositories will be shared with qualified investigators per NIH guidelines and specific policies and timeline to be developed by the DIAN Steering Committee. However, we approach this plan with caution due to the extreme sensitivity of the data and the limited sample size (i.e. a relatively small amount of data could eliminate all uncertainty about the identity of a participant). We look forward to developing a sharing plan that can guarantee research participant confidentiality.

The RFA recommends that a potential resource review procedure be proposed.

Resource Sharing Plan Example: When investigators wish to access data or tissue, they will follow the procedures and policies established by the DIAN Resource Allocation Review Committee (RARC). All policies and procedures, forms, etc will be on the DIAN Informatics Core website for easy access. Qualified investigators initiate requests for resources by providing basic information about their research project (e.g. PHS398 Form, Sections A-D), an NIH biosketch, and some basic information about their own resource to carry out their project (information required for NIA progress reports). Prospective investigators are encouraged to consult with appropriate Core leaders prior to submission. The RARC will solicit expert reviews of the request, discuss, and issue decisions. The criteria to be used by reviewers are: scientific merit, feasibility and IRB issues, appropriateness of principal investigator qualifications, burden on sample(s) (e.g., straining tissue resources), burden on staff, and appropriateness to DIAN goals/themes. The RARC would operate under standard rules of parliamentary procedure when considering requests for resources. After discussion, a request may be approved by a simple majority of the members present and voting. Core C: Biostatistics will consult with investigators to generate a analysis dataset (See Core C) and will work with investigators if statistical consultation is needed.

L. CONSULTANTS – The Steering Committee will identify the areas of expertise to be represented on the DIAN External Advisory Committee (EAC). We will recruit senior scientists to form our (EAC). The Committee will visit the DIAN Coordinating Center (Core A: Administration) each year to review our operations and advancement toward the goals of DIAN.

DIAN Timeline

Year 1												
Month	1	2	3	4	5	6	7	8	9	10	11	12
Steering Committee (SC) Meeting – Select bioethicist, family representative, FDA representative, – Nominate candidates for the External Advisory Committee – Review, discuss, modify, and finalize the standard definition, procedures, and measures for all protocols – Develop plans for Training and Standardization Meeting for finalized protocols – Refine recruitment methods for DIAN participants – Formalize data sharing plans and process												
Training and Standardization Meeting for Clinical, Cognitive, and Biofluid Protocols (to be attended by all Core leaders, representatives from the CCC, site leaders, and site clinicians, neuropsychologists, and study coordinators)												
Initiation and Qualification of nonADNI sites by ADNI subcontractors												
Working Group for Development of Web-based Neuropsychological Measures Convened by Core B: Clinical												
Core H: Informatics develops data services to capture, archive data, & support data sharing plan once established												
Regulatory approvals (IRB, Radiation Safety, etc) completed at performance site												
SC Meetings (teleconferences) every 2 months												
Recruitment, Enrollment, and Baseline Evaluation of Participants (n=50)												
Hold initial EAC meeting												
Year 2												
Month	13	14	15	16	17	18	19	20	21	22	23	24
SC Meetings (or teleconferences) every 2 months												
Recruit, Enroll, and Evaluate 60 new Participants												
Complete Follow-up Evaluations on 25 DIAN Participants												
2nd EAC meeting												
Year 3												
Month	25	26	27	28	29	30	31	32	33	34	35	36
SC Meetings (or teleconferences) every 2 months												
Recruit, Enroll, and Evaluate 60 new Participants												
Complete Follow-up Evaluations on 30 DIAN Participants												
3rd EAC meeting												

Year 4												
Month	37	38	39	40	41	42	43	44	45	46	47	48
SC Meetings (or teleconferences) every 2 months												
Recruit, Enroll, and Evaluate 70 new Participants												
Complete Follow-up Evaluations on 35 DIAN Participants												
4th EAC meeting												
Year 5												
Month	49	50	51	52	53	54	55	56	57	58	59	60
SC Meetings (or teleconferences) every 2 months												
Complete Follow-up Evaluations on 115 DIAN Participants												
5th EAC meeting												
Year 6												
Month	49	50	51	52	53	54	55	56	57	58	59	60
SC Meetings (or teleconferences) every 2 months												
Complete Follow-up Evaluations on 120 DIAN Participants												
6th EAC meeting												