THE ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

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Department of Health and Human Services (DHHS)

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PARTICIPATING ORGANIZATIONS:

National Institutes of Health (NIH)
(http://www.nih.gov)

COMPONENTS OF PARTICIPATING ORGANIZATIONS:

National Institute on Aging (NIA)
PURPOSE OF THIS RFA

The National Institute on Aging (NIA) invites applications from qualified institutions for a Cooperative Agreement (U01) to establish a Coordinating Center (CC) together with a Neuroimaging Center (NC) and a consortium of clinical sites for the NIA Neuroimaging Initiative. The purpose of this Initiative, planned as a public-private partnership, is to develop a multi-site, longitudinal, prospective, naturalistic study of normal cognitive aging, mild cognitive impairment (MCI), and early Alzheimer's disease (AD) as a public domain research resource to facilitate the scientific evaluation of neuroimaging (magnetic resonance imaging [MRI], positron emission tomography [PET]), and other biomarkers for the onset and progression of MCI and AD. A primary goal is to identify the biomarkers of disease progression that are most promising for use as surrogate endpoints in phase 2 and 3 clinical trials for the prevention and treatment of AD.

An essential feature of this initiative is that the clinical, neuropsychological, imaging, and biological data and samples will be made available to all qualified scientific investigators at time intervals to be determined by the Steering Committee and estimated to be every 3-6 months, with raw data available more frequently. The period of support for the Neuroimaging Initiative will be five years.
RESEARCH OBJECTIVES

Advances in the understanding of the pathophysiology and genetics of AD are providing opportunities for developing disease-modifying therapies. A number of neuroimaging technologies and biological substances in the blood and cerebrospinal fluid (CSF) now appear to have considerable potential for measuring progression in this disease (Frank, R.A., et al., Neurobiology of Aging 24:521-36, 2003). A number of studies in AD and MCI have demonstrated that imaging parameters are more sensitive and consistent measures of disease progression than cognitive assessment. Some studies have shown that imaging measures correlate with cognitive test performance in MCI and AD— an initial step in the validation of markers that accurately predict the course of disease and that could be used as surrogate endpoints to establish claims for disease-modifying treatment. The technical feasibility of using structural MRI measures as a surrogate endpoint of disease progression in multi-center clinical trials has been demonstrated (Jack, C.R., et al., Neurology 60:253-260, 2003).

A slowed rate of atrophy in a structure known to be affected by AD together with neuropsychological test data indicating that cognitive function was stabilizing or improving, would be strong evidence for a disease-modifying effect. In phase 2 trials, imaging and other markers can help to rapidly identify appropriate doses, assess safety, and compare drugs in early development. Biomarkers decrease the time and cost of phase 2 and 3 clinical trials, increasing the safety and efficiency of drug development.

Collaborating with the Food and Drug Administration (FDA) on projects such as the Initiative helps the NIH bridge the gap between research and the regulatory process, speeding the fruits of research into treatments for disease, a priority for both agencies. The FDA is increasingly accepting of surrogate endpoints based on imaging, which are not yet fully validated, including as primary endpoints in pivotal trials (recent examples include Etanercept, Eloxatin), given the marker is reasonably likely to predict clinical benefit (CFR 314.510), a condition that the Initiative can help demonstrate.

A group of cognitively normal older subjects will be studied in order to document changes in neuropsychological, imaging, and biochemical parameters that occur with normal aging. This will allow comparison with the changes occurring in the MCI and early AD groups. A fraction of the normal group would also be expected to develop MCI and possibly AD over the time period studied, so data may also be collected on very early measurable changes in the course of illness.

Primary objectives:
1. Collect serial clinical, neuropsychological, biological, and imaging data (1.5T structural MRI on all subjects with a bridging study to 3T at a subset of sites, and 18fluoro-deoxyglucose (FDG) PET at a subset of sites) on subjects with MCI (followed for three years), normal controls (followed for three years), and subjects with early AD (followed for 2 years), in order to define the rate and variance of change of neuroimaging and other markers of disease onset and progression for comparison with clinical and neuropsychological measures, using
relatively frequent sampling points. The primary goal of these efforts is to identify useful surrogate markers of disease progression that will decrease the time and sample size needed to document disease-modifying efficacy in clinical trials.

2. Collect, process, and store serial blood, CSF, and urine samples in the three groups of subjects for analyses for potential biomarkers of disease progression, including genomic, proteomic, and metabolomic markers that can be correlated with clinical, neuropsychological, and imaging data. Immortalized cell lines will also be established.

3. Establish methodologies for the multi-site collection, quality assurance/quality control, and distribution/sharing of neuroimaging and other biological data, in conjunction with clinical and neuropsychological data.

4. Place the longitudinal databases in the public domain and make the data available to all qualified investigators at time intervals to be determined by the Steering Committee (estimated to be every 3-6 months, with raw data available more frequently) for a variety of analyses that will provide insight into the natural history of MCI and AD, evaluate the ability of biomarkers to predict the onset and rates of progression of MCI and AD, including conversion from MCI to AD, and evaluate which methods provide the greatest statistical power for distinguishing pathological changes from normal aging.

Initial MRI images will need to be evaluated as per inclusion/exclusion criteria, for example, ruling out potential participants with multiple lacunes in a critical memory structure. Calculation of measures such as hippocampal, entorhinal cortex, and temporal horn volumes for incorporation into the database is anticipated as being fundable through this Initiative. As such, applicants to the Initiative should use the anticipated rates of change in these or other potential biomarkers to generate primary hypotheses on how these measures relate to cognitive decline and conversion to AD. Using estimates of sources of variance and magnitude of treatment benefit, applicants are encouraged to generate hypothetical power calculations for clinical trial design. Minimal data analyses are included as part of this RFA, but funding for more extensive analyses will be encouraged through other mechanisms such as RO1, RO3, and R21 grants.

Applicants for the Neuroimaging Initiative will need to establish three components for the Initiative: (1) a CC for delineating protocols, organizing and monitoring data and sample collection, storage, and distribution, and other administrative functions such as organizing Steering Committee meetings; (2) a strong NC or Core for delineating imaging protocols, establishing and monitoring quality assurance (QA) and quality control (QC) procedures for the collection of imaging data among the sites, storage and distribution of imaging data, and image processing; and (3) clinical sites, each providing a core team of researchers skilled in the recruitment and clinical evaluation of subjects with normal cognition, MCI, and AD, and the implementation of assessment tools for MCI and AD. All sites must also have MRI (1.5T) capability and access to adequate time on an MRI scanner; a subset of sites must have capability and access to adequate time on a PET scanner; and a subset of sites, on a 3T MRI scanner.

Individual potential clinical sites may be included in more than one
A Steering Committee, comprised of the principal investigator (PI) of the cooperative agreement, the leaders of the CC, NC, and each of the clinical sites, the NIA Program Administrator, representatives from partnering pharmaceutical and/or medical imaging companies, and the FDA, will have primary responsibility for finalizing standard definitions, procedures, and laboratory measures common to the protocols of the study sites. The Steering Committee will also encourage and consider proposals for ancillary studies. These studies will most likely require funding from sources outside of this cooperative agreement.

The criteria for MCI should follow those discussed as amnestic and multiple-domain MCI in Petersen (2003), so may include subjects who have mild cognitive deficits outside of the domain of memory in addition to memory impairment (Petersen RC, Nature Reviews 2:646-653, 2003). Inclusion of subjects with symptoms of depression or who are being treated with anti-depressant medications that do not have strong anti-cholinergic actions is encouraged, as many studies establish depression as a risk factor for AD. Applicants should include inclusion/exclusion criteria that will be uniform across all sites for each of the subject groups, although final details will be determined by the Steering Committee.

NIA staff, in conjunction with four working groups of experts, discussed how to achieve the goals of the Initiative. Reports on the findings of these groups are posted on the NIA web site ([http://www.nia.nih.gov](http://www.nia.nih.gov)). Suggested time points for assessment were as follows:

- **Healthy Controls**: Baseline, 12, 24, & 36 months;
- **MCI**: Baseline, 3, 6, 12, 18, 24, 30, & 36 months;
- **Mild AD Group**: Baseline, 3, 6, 12, 18, & 24 months.

All subjects would complete clinical, neuropsychological, 3D volumetric MRI (1.5T) evaluations, and blood sampling at each time point. At less frequent time points, in a sub-set of subjects, CSF samples would be collected and at those sites with the capability, PET scanning and 3T MRI.

Blood samples will be collected, processed and stored for the establishment of immortalized cell lines. The findings of a working group on promising biomarkers in blood, CSF, and urine, which are feasible to collect in a multi-center study are published in Frank, R.A., et al., Neurobiology of Aging 24:521-36, 2003. Applicants may propose other measures as well, and should also plan for the collection, shipment, and storage of aliquots of samples for analyses of substances to be determined by future research including proteomic and metabolomic studies. The results of all analyses will need to be submitted for inclusion in the centralized dataset, consistent with the data-sharing plans of the Initiative.

Funding for the analysis of substances in the specimens collected is not anticipated to be available from the funds for this Initiative, with the exception of Apolipoprotein E alleles and standard clinical laboratory assessments. Funding for the establishment of cell lines is anticipated.
To advise the Steering Committee, applicants should also plan to recruit an external advisory committee, consisting of scientists from outside the institutions awarded funding for the Initiative. External advisory committee members should not be recruited until the NIH review is complete. This committee will be used to evaluate the progress of the Initiative, ensure that data monitoring procedures are sufficient and that quality data are being collected to the highest standards possible, evaluate the effectiveness of communications among the CC, NC, and clinical sites, and any other activities for which outside expertise is required or desirable. The NIA project coordinator, who will also serve as the program administrator, will attend each meeting of this committee as an observer.

The CC is expected to work in collaboration with its NC, the clinical sites, and the NIA project coordinator to assist in protocol development and planning, subject recruitment, project administration, and close-out.

MECHANISM OF SUPPORT

This RFA will use the NIH cooperative agreement (U01) award mechanism. As an applicant you will be solely responsible for planning, directing, and executing the proposed project. This RFA is a one-time solicitation. Future unsolicited, competing-continuation applications based on this project will compete with all investigator-initiated applications and will be reviewed according to the customary peer review procedures. The anticipated award date is not later than September 30, 2004.

The NIH U01 is a cooperative agreement award mechanism. In the cooperative agreement mechanism, the Principal Investigator retains the primary responsibility and dominant role for planning, directing, and executing the proposed project, with NIH staff being substantially involved as a partner with the Principal Investigator, as described under the section "Cooperative Agreement Terms and Conditions of Award." The total project period for an application submitted in response to the present RFA may not exceed 5 years.

FUNDS AVAILABLE

The NIA intends to commit up to $12 million in FY 2004 for the initial year of funding for the Neuroimaging Initiative. An applicant may request a project period of up to 5 years and a budget for total costs of up to $12 million per year. The size of the proposed budget for each year should be appropriate for the phase being conducted in that year. No more than one award will be made as a result of this RFA and funding of this award is contingent upon availability of funds.

ELIGIBLE INSTITUTIONS

You may submit an application if your institution has any of the
following characteristics:

- For-profit or non-profit organizations
- Public or private institutions, such as universities, colleges, hospitals, and laboratories
- Units of State and local governments
- Eligible agencies of the Federal government
- Domestic institutions
- Foreign institutions are eligible to serve as clinical sites but not as the CC or NC.

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

SPECIAL REQUIREMENTS

The CC and the clinical sites should obtain IRB approvals consistent with the guidance on repositories from the NIH Office of Human Research Protections (OHRP): [http://ohrp.osophs.dhhs.gov/humansubjects/guidance/reposit.htm](http://ohrp.osophs.dhhs.gov/humansubjects/guidance/reposit.htm). The NIH brochure on research on human specimens may also be useful and can be found at: [http://www.cdp.ims.nci.nih.gov/policy.html](http://www.cdp.ims.nci.nih.gov/policy.html)

1. (A) Special requirements for the Neuroimaging Initiative CC are as follows:

   - The applicant should state the willingness and ability to cooperate with the Neuroimaging Initiative clinical sites and NC and NIA staff in all design, data collection, management and distribution functions. The applicant should provide a plan for developing a cooperative relationship among the clinical sites and between the various organizational components.

   - A formal data-sharing plan must be included in the application, including a plan for a system that allows databases to be queried, in conjunction with CC staff, by investigators not directly associated with the Initiative.

(B) Special requirements for the NC or Core are as follows:

   - Images should be centrally archived for centralized analysis for those comparisons that address the primary aims of the study. Applicants should describe procedures that will allow investigators from different organizations to analyze data using other methods (e.g., different image reconstruction, image deformation, or normalization techniques) in order to optimize the study of imaging measures as putative surrogate markers of AD. Data should be stored in the original and in any modified formats.
The NC applicant should state the willingness and ability to cooperate with the Neuroimaging Initiative CC and clinical sites and NIA staff in all design, data collection, management and distribution functions.

(C) Special requirements for clinical sites are as follows:

- Site applicants should state the willingness and ability to cooperate with the Neuroimaging Initiative CC and Neuroimaging Center and NIA staff in all design, data collection, management and distribution functions.

2. Cooperative Agreement Terms and Conditions of Award

The following special terms of award are in addition to, and not in lieu of, otherwise applicable OMB administrative guidelines, HHS Grant Administration Regulations at 45 CFR Parts 74 and 92 and other HHS, PHS, and NIH Grant Administration policy statements.

The administrative and funding instrument used for this program is a cooperative agreement (UO1), an assistance mechanism (rather than an acquisition mechanism) in which substantial NIH scientific and/or programmatic involvement with the awardees is anticipated during performance of the activity. Under the cooperative agreement, the NIH purpose is to support and/or stimulate the recipient's activity by working jointly with the award recipient in a partner role, but it is not to assume direction, prime responsibility or a dominant role in the activity. Consistent with this concept, the dominant role and prime responsibility for the activity resides with the awardees for the project as a whole, although specific tasks and activities in carrying out the collaborative aspects will be shared among the awardees and the designated NIA project administrator.

A. Awardee Responsibilities

The Coordinating Center (CC) awardee agrees to work cooperatively with the Neuroimaging Initiative Neuroimaging Center (NC) and clinical sites and will have the primary responsibility for developing and implementing systems necessary for communications among the various Neuroimaging Initiative organizational components. The CC will facilitate the design and refinement of all protocols, manuals of operation, and forms.

The awardee institution will retain custody of, and primary rights to, the data developed under this award, subject to Government rights of access consistent with current HHS, PHS, and NIH policies, with the added stipulation that all primary data shall be shared within time periods to be specified, as a fundamental purpose of this Initiative is the establishment of an unrestricted public database.

The primary governing body of the study will be the Steering Committee, which will have responsibility for the final details of study design and policy decisions and will define the rules regarding access to common data.

B. Staff Responsibilities
The designated NIA Project Administrator will serve as a member of the Steering Committee and have substantial scientific/programmatic involvement during conduct of this cooperative agreement, through technical assistance, advice and coordination above and beyond normal program stewardship of grants. The awardee agrees to accept assistance from the designated NIA Project Administrator, as described below:

- Participation, through the Steering Committee, in the monitoring of issues relating to recruitment, follow-up, QA/QC, and adherence to protocols.

- Assistance in the development and/or adjustment of study protocols.

An NIA Program Director will be responsible for the normal program stewardship on this award. The Program Director may also be designated as the NIA Project Administrator described above.

C. Collaborative Responsibilities

The Steering Committee, comprised of the PI of the cooperative agreement, the leaders of the CC, NC, and each of the clinical sites, the NIA project administrator, representatives from partnering pharmaceutical and/or medical imaging companies, and the FDA, will have primary responsibility for finalizing standard definitions, procedures, and laboratory measures common to the protocols of the study sites. The SC will meet every three to six months, or as dictated by the needs of the Neuroimaging Initiative. Each member of the Steering Committee will have one vote, and all major scientific decisions will be determined by majority vote of the Steering Committee. Subcommittees appointed by the Steering Committee, comprised of appropriate staff from the CC, NC, and clinical sites, will be involved in the design of protocols and manuals of operations, and in ongoing functions of the Neuroimaging Initiative, such as consideration of potential ancillary studies and preparation of publications.

To oversee the allocation and distribution of biological specimens generated from the Neuroimaging Initiative, the Steering Committee will select a Resource Allocation Review Committee (RARC). This group will review applications for use of the biological specimens. The format of the application and criteria for the use of repository biological specimens will be developed by the RARC with advice and approval from the Steering Committee and made available to all potential users. The RARC will be made up of individuals not directly involved in the Neuroimaging Initiative and without conflicts of interest. Membership on this committee will rotate periodically according to a procedure developed by the RARC.

D. Arbitration

Any disagreement that may arise on scientific/programmatic matters (within the scope of the U01 award) between U01 awardees and the NIA may be brought to arbitration. An arbitration panel will be composed of three members: one selected by the Steering Committee (without NIH representatives voting) or by the individual U01 awardee in the event of an individual disagreement; a second member selected by the NIA; and, the third member selected by the two prior selected members. For
U01 awardees, this special arbitration procedure will in no way affect the awardee's right to appeal an adverse action in accordance with PHS regulations at 42 CFR Part 50, Subpart D, and HHS regulations at 45 CFR Part 16, nor will it affect the government's rights with regards to grants enforcement.

WHERE TO SEND INQUIRIES

We encourage inquiries concerning this RFA and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues.

- Direct inquiries regarding programmatic issues to:
  Susan Molchan, M.D.
  Program Director, Alzheimer's Disease Clinical Trials
  Neuroscience and Neuropsychology of Aging Program
  National Institute on Aging
  Gateway Bldg., Suite 350
  7201 Wisconsin Ave.
  Bethesda, MD 20892-9205
  Telephone: (301) 496-9350; FAX: (301) 496-1494
  E-mail: molchans@mail.nih.gov

- Direct inquiries regarding peer review issues to:
  Mary Nekola, Ph.D.
  Chief, Scientific Review Office
  National Institute on Aging
  7201 Wisconsin Avenue, Suite 2C-212
  Bethesda, Maryland 20892-9205
  Express Mail Zip Code: 20814
  Telephone: 301/496-9666; FAX: 301/402-0066
  E-mail: nekolam@nia.nih.gov

- Direct inquiries regarding financial or grants management matters to:
  Linda Whipp
  Grants Management Officer
  National Institute on Aging
  7201 Wisconsin Avenue, Suite 2N-212
  Bethesda, Maryland 20892-9205
  Express Mail Zip Code: 20814
  Telephone: 301/496-1472; FAX: 301/402-3672
  E-mail: whipp1@nia.nih.gov

LETTER OF INTENT

Prospective applicants are asked to submit, by December 16, 2003, a letter of intent that includes the following information:

- Descriptive title of the proposed research
Although a letter of intent is not required, is not binding, and does not enter into the review of a subsequent application, the information that it contains allows IC staff to estimate the potential review workload and plan the review.

The letter of intent is to be sent by the date listed at the beginning of this document. The letter of intent should be sent to:

Susan Molchan, M.D.
Program Director, Alzheimer's Disease Clinical Trials
Neuroscience and Neuropsychology of Aging Program
National Institute on Aging
Gateway Bldg., Suite 350
7201 Wisconsin Ave.
Bethesda, MD 20892-9205
Telephone: (301) 496-9350; FAX: (301) 496-1494
E-mail: molchans@mail.nih.gov

**SUBMITTING AN APPLICATION**

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). Applications must have a Dun and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the Universal Identifier when applying for Federal grants or cooperative agreements. The DUNS number can be obtained by calling (866) 705-5711 or through the web site at http://www.dunandbradstreet.com/. The DUNS number should be entered on line 11 of the face page of the PHS 398 form. The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

**SUPPLEMENTARY INSTRUCTIONS**

Introduction and Background sections should be provided for the application as a whole. Following those sections three separate sections should be prepared, one for the CC (up to 25 pages), one for the NC or Core (up to 25 pages), and one for the clinical sites (3-4 pages/site). In addition, please include a chart of the clinical sites summarizing patient (MCI and early AD) recruiting experience and potential, neuropsychological and clinical experience with MCI and AD patients, experience as part of multi-site studies, MRI (1.5T) experience, MRI scanner availability and access, and if applicable, PET experience and PET scanner availability and access, and/or 3T MRI experience, availability, and access.

Individual potential clinical sites may be included in more than one application.
Provide a flow chart or time line of the evaluations and procedures planned for subjects. Plans for ensuring compliance with HIPAA, data integrity, quality control, and data sharing should be discussed.

Personnel: For each of the three components of the Initiative, the application must describe the expertise of key scientific, technical and administrative personnel and include a mechanism for replacing key professional or technical personnel should the need arise.

Budget: The budgets should be based on the applicant's best judgment of activities likely to be involved during the different phases of the Initiative as delineated under the section on Research Objectives. Budgets should include costs of organizing at least two Steering Committee meetings annually and for attendance of necessary CC, NC, and clinical site staff to these meetings. Budgets should include costs of at least two external scientific advisory committee meetings annually. Budgets should include projected data handling costs, reporting functions, meetings, and other communications costs. Funding for extensive analyses will be encouraged through other mechanisms such as research grants but budgets for evaluation of scans for exclusion criteria, for example, ruling out potential participants who have multiple lacunes in a critical memory structure, and determination of measures such as hippocampal, entorhinal cortex, and temporal horn volumes for incorporation into the database will be needed. Clinical sites will be reimbursed for costs on a per visit/per protocol basis.

Attempts should be made by the applicant institution to utilize existing clinical facilities, such as General Clinical Research Centers and AD Centers. Costs relating to the clinical efforts for the Neuroimaging Initiative may be funded through the Initiative, provided there is no overlap of funding. Only those research patient costs directly related to Initiative activities may be charged to the Initiative.

Include an explanation of the programmatic, fiscal, and administrative arrangements made between the grantee administration and the collaborating institutions.

USING THE RFA LABEL: The RFA label available in the PHS 398 (rev. 5/2001) application form must be affixed to the bottom of the face page of the application. Type the RFA number on the label. Failure to use this label could result in delayed processing of the application such that it may not reach the review committee in time for review. In addition, the RFA title and number must be typed on line 2 of the face page of the application form and the YES box must be marked. The RFA label is also available at: 

SENDING AN APPLICATION TO THE NIH: Submit a signed original of the application, including the Checklist, and three signed, photocopies, in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
APPLICATION PROCESSING: Applications must be received by the application receipt date listed in the heading of this RFA. If an application is received after that date, it will be returned to the applicant without review.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within 8 weeks.

The Center for Scientific Review (CSR) will not accept any application in response to this RFA that is essentially the same as one currently pending initial review, unless the applicant withdraws the pending application. However, when a previously unfunded application, originally submitted as an investigator-initiated application, is to be submitted in response to an RFA, it is to be prepared as a NEW application. That is, the application for the RFA must not include an Introduction describing the changes and improvements made, and the text must not be marked to indicate the changes from the previous unfunded version of the application.

PEER REVIEW PROCESS

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by Aging. Incomplete applications will not be reviewed.

If the application is not responsive to the RFA, NIH staff may contact the applicant to determine whether to return the application to the applicant or submit it for review in competition with unsolicited applications at the next appropriate NIH review cycle.

Applications that are complete and responsive to the RFA will be evaluated for scientific and technical merit by an appropriate peer review group convened by the NIA in accordance with the review criteria stated below. As part of the initial merit review, all applications will:

Material included in appendices must follow the instructions in PHS 398.
Undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of the applications under review, will be discussed and assigned a priority score

- Receive a written critique
- Receive a second level review by the National Advisory Council on Aging

**REVIEW CRITERIA**

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to evaluate the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. The scientific review group will address and consider each of the following criteria in assigning the application's overall score, weighting them as appropriate for each application.

- **Approach**
- **Investigator**
- **Environment**

**APPROACH:** Are the conceptual framework, hypotheses, design, and methods adequately developed, well-integrated, and appropriate to the aims of the project? Are potential problem areas acknowledged and alternative tactics considered? Does the proposed approach in managing the logistical and data coordination have scientific and technical merit? Are the proposed plans and experience relating to subject recruitment and retention, staff training, data collection, monitoring, management, editing, processing, and reporting adequate? Has justification for specific acquisition parameters been provided? Are plans for the collection, shipment, and storage of biological samples adequate? Are the plans for coordination with the study site investigators adequate? Is the approach to developing a cooperative relationship among the study sites and between the various Neuroimaging Initiative organizational components adequate? Are the plans for exercising appropriate leadership in matters of study design, data acquisition, data management, and data distribution demonstrated?

**INVESTIGATOR:** Are the applicant and his/her staff appropriately trained and well-suited to carry out this work? Is the work proposed appropriate to the applicant's experience level as the PI? Does the application provide evidence of specific competence and relevant experience of professional, technical, and administrative staff pertinent to the operation of a CC and NC for multi-site studies? Prior experience collecting data and patient specimens from multiple clinical sites and monitoring data quality should be demonstrated. Do NC applicants have experience with quality-controlled collecting, cleaning, processing, and analysis of MRI and FDG-PET scans of the brain, including studies of AD? Is there evidence of experience in and willingness to participate appropriately in a collaborative study as described in this RFA? Are there adequate assurances that the CC personnel have experience in utilizing procedures that insure the safety and confidentiality of medical records? These questions should
also be addressed with reference to the lead investigator and staff of the NC. Investigators and staff at the clinical sites should document experience and capabilities as noted above under Special Requirements, and document experience recruiting and evaluating normal elderly, MCI, and early AD subjects, MRI (and if applicable PET) experience/access, and collecting blood and CSF for scientific protocols.

ENVIRONMENT: For the CC, the NC, and the clinical sites, does the scientific environment in which the work will be done contribute to the probability of success? Is there evidence of institutional support? Has the application documented the adequacy of the proposed facility, technical hardware, and space for the CC/NC/clinical sites? Is there an appropriate organizational and administrative structure to the proposed CC/NC? Evidence of institutional support and commitment should be provided.

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, the application will also be reviewed with respect to the following:

o The capability of recruiting an appropriate number of subjects during an approximately 18 month recruitment period. For clinical sites, a documented record of past success of recruiting efforts for MCI, normal control, and AD subjects.

o All sites must also have 1.5T MRI capability and access to adequate time on an MRI scanner. Subsets of sites must have capability and access to adequate time on a PET scanner and 3T MRI. For clinical sites, a documented record of previous MRI (and PET if applicable) research experience.

PROTECTION OF HUMAN SUBJECTS FROM RESEARCH RISK: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed. (See criteria included in the section on Federal Citations, below).

The Neuroimaging Initiative CC will be setting up a repository of samples from human subjects. Therefore, the CC must comply with current human subjects protection policies regarding potential patient identifier information that are associated with these stored samples.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH: The adequacy of plans to include subjects from both genders and all racial and ethnic groups (and subgroups). Plans for recruitment and retention of subjects will also be evaluated. (See Inclusion Criteria in the sections on Federal Citations, below).

ADDITIONAL REVIEW CONSIDERATIONS

SHARING RESEARCH DATA: Applicants requesting more than $500,000 in direct costs in any year of the proposed research must include a data sharing plan in their application. The reasonableness of the data sharing plan or the rationale for not sharing research data will be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or priority score.
BUDGET: The reasonableness of the proposed budget in relation to the proposed research.

RECEIPT AND REVIEW SCHEDULE

Letter of Intent Receipt Date: December 16, 2003
Application Receipt Date: January 16, 2004
Peer Review Date: April-May, 2004
Council Review: August, 2004
Earliest Anticipated Start Date: September 1, 2004

AWARD CRITERIA

Award criteria that will be used to make award decisions include:

- Scientific/technical merit (as determined by peer review)
- Availability of funds
- Programmatic priorities

REQUIRED FEDERAL CITATIONS

HUMAN SUBJECTS PROTECTION: Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained. http://ohrp.osophs.dhhs.gov/humansubjects/guidance/45cfr46.htm

SHARING RESEARCH DATA: Starting with the October 1, 2003 receipt date, investigators submitting an NIH application seeking more than $500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why this is not possible. http://grants.nih.gov/grants/policy/data_sharing Investigators should seek guidance from their institutions, on issues related to institutional policies, local IRB rules, as well as local, state and Federal laws and regulations, including the Privacy Rule. Reviewers will consider the data sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH: It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in
(http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html); a complete copy of the updated Guidelines are available at

The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in
compliance with the new OMB standards; clarification of language
governing NIH-defined Phase III clinical trials consistent with the new
PHS Form 398; and updated roles and responsibilities of NIH staff and
the extramural community. The policy continues to require for all NIH-
defined Phase III clinical trials that: a) all applications or
proposals and/or protocols must provide a description of plans to
conduct analyses, as appropriate, to address differences by sex/gender
and/or racial/ethnic groups, including subgroups if applicable; and b)
investigators must report annual accrual and progress in conducting
analyses, as appropriate, by sex/gender and/or racial/ethnic group
differences.

REQUIRED EDUCATION ON THE PROTECTION OF HUMAN SUBJECT PARTICIPANTS:
NIH policy requires education on the protection of human subject
participants for all investigators submitting NIH proposals for
research involving human subjects. You will find this policy
announcement in the NIH Guide for Grants and Contracts Announcement,
dated June 5, 2000, at

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT:
The Office of Management and Budget (OMB) Circular A-110 has been
revised to provide public access to research data through the Freedom
of Information Act (FOIA) under some circumstances. Data that are (1)
first produced in a project that is supported in whole or in part with
Federal funds and (2) cited publicly and officially by a Federal agency
in support of an action that has the force and effect of law (i.e., a
regulation) may be accessed through FOIA. It is important for
applicants to understand the basic scope of this amendment. NIH has
provided guidance at

Applicants will be placing data collected under this RFA in a public
archive, which must provide protections for the data. The application
should include a description of the archiving plan in the study design
and include information about this in the budget justification section
of the application. In addition, applicants should think about how to
structure informed consent statements and other human subjects
procedures given the potential for wider use of data collected under
this award.

STANDARDS FOR PRIVACY OF INDIVIDUALLY IDENTIFIABLE HEALTH INFORMATION:
The Department of Health and Human Services (DHHS) issued final
modification to the "Standards for Privacy of Individually Identifiable
Health Information", the "Privacy Rule," on August 14, 2002. The
Privacy Rule is a federal regulation under the Health Insurance
Portability and Accountability Act (HIPAA) of 1996 that governs the
protection of individually identifiable health information, and is
administered and enforced by the DHHS Office for Civil Rights (OCR).
Those who must comply with the Privacy Rule (classified under the Rule as "covered entities") must do so by April 14, 2003 (with the exception of small health plans which have an extra year to comply).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This RFA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople/.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and to discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.