

## EDTA CHELATION THERAPY FOR CORONARY ARTERY DISEASE

Release Date: April 30, 2001

RFA: RFA-AT-01-004

National Center for Complementary and Alternative Medicine  
(<http://nccam.nih.gov>)  
National Heart Lung and Blood Institute

Letter of Intent Receipt Date: July 18, 2001  
Application Receipt Date: August 29, 2001

### PURPOSE

The National Center for Complementary and Alternative Medicine (NCCAM) and the National Heart, Lung, and Blood Institute (NHLBI) invite applications for a multi-site, randomized, double-blinded, placebo-controlled trial investigating the efficacy and safety of EDTA (ethylene diamine tetra-acetic acid) chelation therapy in individuals suffering from Coronary Artery Disease (CAD). It is estimated that more than 800,000 visits for chelation therapy were made in the U.S. in 1997. If chelation therapy is safe and effective in treating CAD it would represent a new therapeutic modality that would gain widespread application. However, if chelation therapy is ineffective, these data will provide important information to the U.S. public and allow for informed decision making concerning continued use of EDTA for CAD.

### 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 Request for Applications (RFA), EDTA Chelation Therapy for Coronary Artery Disease, 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/>.

### ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as Principal Investigators.

### MECHANISM OF SUPPORT

This RFA will use the cooperative agreement (U01) mechanism. The cooperative agreement is an assistance mechanism in which NIH will have substantial involvement with the recipient during the performance of the planned activity. The nature of the NIH's involvement is described

under the "Terms and Conditions" of the award. Primary responsibility for the planning, direction, and execution of the proposed project will be that of the applicant/awardee.

The total project period for applications submitted in response to the present RFA may not exceed five years. The anticipated award date is March 1, 2002.

## FUNDS AVAILABLE

Up to \$30,000,000 (total cost) over the entire project period is available to support this initiative. It is expected that one award will be made. The NCCAM and NHLBI intend to commit approximately \$6 million in FY 2001 to fund one new grant in response to this RFA. An applicant may request a project period of up to 5 years and a budget for total costs of up to \$6 million per year. Because the nature and scope of the research proposed may vary, it is anticipated that the size of this award will also vary. Although the financial plans of the NCCAM and NHLBI provide support for this program, awards pursuant to this RFA are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications. At this time, there are no plans to reissue this RFA.

## RESEARCH OBJECTIVES

### Background

CAD is the leading cause of mortality for both men and women in the United States. The prevalence of coronary heart disease is estimated at 12 million, including 7 million suffering from acute myocardial infarction and 6.2 million with angina pectoris (NHLBI 1998 Chartbook). More than 500,000 Americans die of heart attacks each year. Common conventional medical treatments for CAD include percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft (CABG) surgery, procedures that are invasive and costly. Chelation therapy has been used by some physicians for treatment of atherosclerosis, although compelling evidence indicating treatment efficacy is absent.

### Chelation Therapy

Chelation refers to the formation of metal complexes by the bonding of a chelating agent or ligand with a metal to form a heterocyclic ring. Initially, the medical use of chelating agents was to treat heavy metal poisonings, for example, British Anti-Lewisite (2,3-dimercaptopropanol) for arsenical poisoning (1) and citrate for lead intoxication (2). Another chelating agent, ethylene diamine tetraacetic acid (EDTA) was also used to treat lead poisoning in a young child (3) and following its initial approval by the Food and Drug Administration (FDA) in 1953, EDTA was utilized to treat hypercalcemia, other heavy metal poisonings (4-6), and metastatic calcification (7).

Originally, it was a clinical observation that EDTA appeared to reduce symptoms of angina pectoris (8) and it was also noted that it affected cholesterol metabolism (9,10). Subsequently, EDTA was advocated by some physicians to treat symptoms of atherosclerotic disease. In some studies, clinical measures of efficacy such as exercise time, ankle-brachial index, and arteriograms have been reported in addition to subjective data. Chelation has been used most widely in peripheral vascular disease, but also in coronary artery disease, and cerebrovascular

disease. However, few controlled data are available that speak to the usefulness of chelation in the treatment of heart or vascular disease (11-17).

### Pharmacology of EDTA

EDTA is a tetrabasic acid with 4 replaceable hydrogen ions. Importantly, it is poorly soluble in water but it is soluble in alkaline hydroxides. In the US, the commercially available salts are the disodium and the calcium disodium salts of EDTA. In these formulations, EDTA is widely used as an *in vitro* anticoagulant for blood collection and as an antioxidant synergist, stabilizer and preservative for pharmaceutical preparations. For chelation therapy, the most widely used formulation is a protocol recommended by the American College for Advancement in Medicine (ACAM) (18) that includes disodium EDTA and magnesium chloride. This formulation has yet to be tested in rigorous randomized controlled trials.

EDTA chelates various divalent metal ions with differing affinities. It is poorly absorbed from the gastrointestinal tract. Following intravenous administration, EDTA is found primarily in plasma. It is distributed in the extracellular fluid, and it does not appear to penetrate cells. Only about 5% of the plasma concentration is found in spinal fluid. The half life is 20-60 minutes. It is excreted mainly by the kidney, with about 50% excretion in one hour and more than 95% within 24 hours. Almost none of the compound is metabolized. Treatment with EDTA has a low incidence of side effects. The most common side effect reported is a burning sensation experienced at the infusion site. Relatively rare adverse effects include phlebitis at the infusion site, malaise, fever, hypotension, hypocalcemia, headache, nausea, vomiting, diarrhea, insulin shock, bone marrow depression, prolonged prothrombin time and cardiac arrhythmia. Cases of renal toxicity have also been reported.

### Possible Mechanisms of Action of EDTA

Mechanisms involved in the pathogenesis of atherosclerosis include proliferation of smooth muscle cells, abnormalities of lipid metabolism, and endothelial dysfunction. However, historically, calcium deposition was also believed to be important in the development of atheroma. There is an age-associated increase in calcium deposition in the arterial wall. The hypothesis is that EDTA will chelate calcium from atheromatous plaques and thus favorably alter the plaque and the arterial wall, for example by altering endothelial function (19). Other postulated mechanisms of EDTA action include a) inhibition of platelet aggregation (20), b) stimulation of parathormone (PTH) release that in turn mobilizes calcium from plaques and reduces progressive calcification, c) an antioxidant effect by complexing with transitional metals thus interfering with free radical production and lipid peroxidation, d) effects on serum iron (21), and e) transient lowering of serum cholesterol. Some of these hypotheses may be valid, but there are no confirmatory mechanistic studies.

### Studies of EDTA Chelation Therapy in Arteriosclerosis

#### Coronary Artery Disease

The use of chelation therapy in coronary artery disease is limited to 12 descriptive studies and four randomized control trials (RCT) (7, 22-33). Although each of the descriptive studies reported a reduction in angina, they are uncontrolled clinical observations or retrospective data, typically with small numbers of patients. Two of the RCT were underpowered to detect a

difference, a third RCT did not publish a final paper, and the fourth noted exercise improvement but was limited to 10 subjects.

#### Peripheral Vascular Disease

Most of the EDTA chelation studies have focused on peripheral vascular disease and are a combination of RCTs and descriptive studies. These RCT's have not demonstrated significant benefit but they were underpowered to detect a small effect and each trial has been criticized by some for methodological problems. Observational reports of the use of EDTA in peripheral vascular disease suggest that chelation can increase exercise duration but in the absence of a placebo control group, spontaneous symptomatic improvement cannot be excluded (7,8,11-17, 22, 25, 29-32, 34-45).

#### Cerebrovascular Disease

The use of EDTA chelation has been reported in patients with cerebrovascular disease. The claims of efficacy with EDTA therapy are based on subjective clinical improvement and in some studies, improved cerebral perfusion or reduction in degree of carotid stenosis (22,25,26,30,34, 36,39,46-48). Typically, however, the patient populations were small and had a variety of cerebral diseases; most importantly, the studies were without appropriate controls, and in some, there was criticism of methodology. Particularly in the older data, the observations tended to be subjective and descriptive. There are no appropriate randomized trials of EDTA in the treatment of cerebrovascular disease. Altogether, there are no substantial data to support claims of efficacy.

#### Developments in the Assessment of EDTA Chelation Therapy for Arteriosclerosis

A protocol for an RCT of chelation therapy in peripheral vascular disease was developed with FDA approval. The study involved assessment of exercise tolerance in 3 experimental groups that were to receive infusions of magnesium alone, or 1 gram of EDTA and magnesium or 3 grams of EDTA and magnesium. Unfortunately, recruitment was slow and within 3 years the study was terminated with recruitment of only about 25% of the total projected 120 subjects. No useful data were obtained (49-51). A second RCT was planned in Texas by Baylor College of Medicine and the University of Texas Medical School but the study was never conducted and the results of a pilot study in 18 patients only reported the effects of EDTA on the parathyroid gland (52). Currently, there is an ongoing Canadian RCT (PATCH-EDTA) designed to assess exercise time in 80 patients with coronary artery disease randomly allocated to EDTA or placebo.

#### OBJECTIVES

The objective of this initiative is to strengthen the knowledge base regarding efficacy and safety of EDTA chelation therapy for persons with CAD through the use of rigorous trial design and validated outcomes measures.

Areas to be considered by applicants include the following:

- Development of control/comparison groups that are appropriate for this project.
- Determination of the efficacy of EDTA chelation therapy in treating CAD on average and in various sub-populations.
- Determination of the safety of EDTA chelation therapy.

- Use of assays to determine metabolic changes in human subjects that may provide information on the potential mechanisms of action of EDTA chelation therapy.

## Research Plan

### 1. General

Although objectives of the RFA can be met through the initiation of a full-scale, randomized, two-arm, double-blind, placebo-controlled, multi-site trial of EDTA Chelation therapy, other designs, including additional treatment arms, will be considered if sufficiently justified. While it is expected that the trial will investigate the EDTA Chelation treatment protocol recommended by ACAM, other protocols can be proposed if justified and adequately supported by the literature. A detailed description of the proposed intervention must be provided. Adequacy of blinding must be described.

The study should consist of four phases: 1) an initial phase during which the protocol is finalized (e.g., study procedure and Manual of Operations, data collection manuals, data management, training, establishment of the Data and Safety Monitoring Board, etc.) by the trial Steering Committee (see "Special Requirement"); 2) a recruitment period; 3) a period of intervention and follow-up; and 4) data analysis and dissemination.

### 2. Outcomes

Plans for patient follow-up and choices of outcome measures should be well defined and clearly justified. Justification and definition of endpoints for the proposal should be provided. Appropriate objective endpoints include mortality, myocardial infarction, stroke, and hospitalization for unstable angina or revascularization. Other outcome measures could include, but are not limited to:

- 1) general health status/quality-of-life indicators;
- 2) mechanistic studies, including but not limited to, plasma markers of oxidative stress, endothelial activation/inflammation and intermediate endpoints such as platelet aggregation, serum concentrations of iron, cholesterol and free calcium; and
- 3) health care utilization (e.g., increased or decreased use of other medications or office visits; cost-effectiveness data).

### 3. Inclusion/Exclusion Criteria

Inclusion and exclusion criteria (including preexisting medical conditions and the use of counter-indicated drugs) should be identified and justified by the applicant; in general, these criteria should address exclusion of individuals who might be harmed by participation in the trial, or who are likely to be poor compilers. A database should be maintained on all potentially eligible subjects who were identified but not enrolled, including the reasons for their exclusion or refusal to participate. Based on the patient profile for CAD, children are excluded from this study.

### 4. Compliance

Research designs that maximize patient compliance should be described and justified in the application.

## 5. Recruitment

For all proposed trial sites, applicants must demonstrate the ability to recruit and randomize the required number of study participants, be able to implement the various study procedures, and provide evidence of the ability to maintain high rates of follow-up during the course of the trial.

## 6. Sample Size and Power Calculations

To ensure acceptable statistical power, the clinical trial design should include an adequate number of participants and should be of sufficient duration to address the study questions of efficacy, safety, tolerability and acceptability, as well as any other secondary research questions. To this end, expertise in biostatistics and clinical trial design are essential during the planning phase of the study. Study size and duration will vary according to specific study hypotheses, target population and endpoints; as such, the study size and duration should reflect both the choice of outcome measures and the predicted effect sizes. Sample size calculations should include the possibility of interim analyses of the data. Given these parameters, it is understood that the calculated sample size may underpower (or overpower) the study. The applicants should discuss ways they might directly assess the adequacy of their sample size calculations (e.g., through internal or external pilot studies) and make appropriate adjustments in recruitment and/or follow-up as necessary.

## SPECIAL REQUIREMENTS

### Study Organization

#### Steering Committee

A Steering Committee will be established to serve as the main governing body of the trial. Trial sites will be required to accept and implement the protocol and procedures approved by the Steering Committee. Descriptions of Committee membership, scheduling, responsibilities and authority are listed under "TERMS AND CONDITIONS OF THE AWARD."

#### Executive Committee

The Executive Committee, composed of the Steering Committee Chair, Coordinating Center Principal Investigator, the NCCAM Program Officer, an NHLBI Scientific Adviser and the Awardee will make recommendations to the Steering Committee regarding study conduct. The Awardee will serve as chair of the Executive Committee. The Executive Committee will meet to monitor study progress and to review non-endpoint data. Executive Committee meetings will be scheduled for the day prior to Steering Committee meetings. The recruitment progress of each center and of the whole trial will be updated bimonthly by the Awardee for the Executive Committee. Other reports for the Executive Committee may be requested of the Steering Committee as needed. In any votes of the Executive Committee, each member will have a single vote.

#### Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board will be appointed by the Director of NCCAM with input from the Awardee. Descriptions of Board membership, scheduling, responsibilities, and authority are listed under "TERMS AND CONDITIONS OF THE AWARD."

#### Minimum Requirements for Application

Each application must include the following elements; applications that fail to meet these requirements will be considered unresponsive to the RFA and will not be reviewed:

##### 1. Investigators

The application must name a single Principal Investigator (PI) who will have scientific responsibility for the application as a whole, including all consortium-related research activities. The PI is required to commit a minimum of 10% effort to these administrative duties. In addition, the PI is the Senior Investigator (see below) from his or her Institution and will be expected to commit 10% effort to these scientific activities, bringing her or his total commitment to 20% effort (10% administrative and 10% scientific). The PI must have substantial experience in the treatment and management of CAD and in the design, implementation and evaluation of clinical trials. Such experience must be documented in full. Biographical sketches for all key investigators must be provided. In addition, applications must name a Senior Investigator for each trial site in the consortium that will be responsible for on-site clinical and scientific implementation, direction and management of the trial protocol, as well as the coordination of requirements for any adjunct studies of underlying mechanisms and surrogate markers. Senior Investigators are required to commit at least 10% effort to this trial. Senior Investigators must have substantial experience in the treatment and management of CAD and in the design, implementation and evaluation of clinical trials. The application should also name a Trial Manager (or Coordinator) who is an individual with substantial technical/administrative experience in managing patient enrollment, patient follow-up, and multi-source data collection for clinical studies, such as an experienced nurse manager. Each trial site associated with the trial may also name a Trial Site Manager (or Coordinator) if adequately justified. The application can also include an Administrative Manager to handle budgetary, IRB and sub-contract issues as appropriate and justified.

##### 2. Trial Organization and Administration

The trial group will be an identifiable organizational unit formed by a consortium of cooperating institutions. Such a unit will involve the interaction of broad and diverse elements. Therefore, lines of authority and sanction by the appropriate institutional officials must be clearly specified. Specifically, the applicant must provide: a clear, concise plan, in narrative and diagrammatic form, that depicts the interrelationships among the members of the consortium, their relevant experience/expertise, and the contribution of each to fulfillment of the objectives of this RFA; an organizational chart of the consortium showing the name, organization, and scientific discipline of the PI and of all key scientific, technical and administrative personnel; and a mechanism for selecting and replacing key professional or technical personnel. Include a description of the role, responsibility and authority of the PI, Senior Investigators and Trial Manager. The application must include a written commitment to accept the participation and assistance of NCCAM staff in accordance with the guidelines outlined under "Terms and Conditions of Award: NCCAM Staff Responsibilities." The application must also include a signed letter from the PI and all Senior Investigators that states: a) their commitment to this cooperative trial; b) their willingness to serve on the Steering Committee and to adhere to the decisions reached by that Committee,

including following the finalized protocol and adjunct studies; and c) their commitment that recruitment of patients for the EDTA chelation trial will take precedence over any subsequent clinical trials started after the EDTA chelation trial is awarded.

#### 4. Preliminary Studies

Data that show the feasibility of the trial should be presented; this should include prior examples of patient recruitment, retention and follow-up. Additional supporting data from other research should be included so that the approach chosen is clearly justified. Conceptualization and planning must have progressed to a stage sufficient to allow for an overall assessment of the likelihood of the trial's success.

#### 5. Patient Availability and Recruitment

The applicant institution and each institution participating in the trial must: document their experience and capacity to recruit and retain study participants; provide a description of the population currently available for the proposed protocol; describe the procedures for screening this population to identify eligible individuals, for recruiting these individuals into the trial; and describe proposed mechanisms for monitoring accrual performance and criteria for continued participation by each participating institution.

#### 6. Data Coordination, Management and Quality Control

Applicants should document their previous experience and must present:

- a) a plan for randomization, data coordination, data collection and management across trial sites;
- b) a rationale for the need for a Data Coordinating Center to interact with, and coordinate among, multiple trial sites and a description of the responsibilities of the Data Coordinating Center;
- c) a plan describing development of appropriate placebo control group(s);
- d) a description of the proposed intervention(s) and outcome measures;
- e) methods for monitoring the quality and consistency of the intervention and outcome measures;
- f) protocols for data collection, formatting and transmission to and from individual trial sites; prototypes of data collection forms should be included in an appendix;
- g) a comprehensive set of procedures to assure data quality and also procedures to assure confidentiality of subjects;
- h) a plan for training programs to educate staff at trial sites about operating procedures with the goal of maximizing efficiency of data operations;
- i) data quality control systems;

In addition, the applicants should provide evidence of their prior management capability to:

- a) estimate appropriate and reasonable resources needed for the EDTA chelation trial;
- b) manage resources efficiently during the research;
- c) adjust assigned resources to changing demands as the research work progresses;
- d) keep NCCAM informed of changes of resource allocations; and
- e) subcontract with affiliated trial sites or other outside organizations.

#### 7. Adverse Events



All studies must have a structured adverse event determination, monitoring and reporting system, including standardized forms and protocols for referring and/or treating subjects experiencing adverse events. The proposed schedule for reporting adverse events to the DSMB, the NCCAM Program Officer and/or the FDA should be described.

#### 8. Reporting and Publications

The PI will be required to submit quarterly progress reports to the NCCAM and the DSMB. These reports should include recruitment data, indices of quality control, reports of significant side effects or morbidity (previously reported to the DSMB, the NCCAM Program Officer and the FDA), and deviations from the protocol. Such reports are in addition to the annual awardee noncompeting continuation progress report. The DSMB (see Terms and Conditions of Award) may require additional information. The PI also will be requested to present both a mid-term and final report to the NCCAM Advisory Council.

#### TERMS AND CONDITIONS OF THE AWARD

The following terms and conditions will be incorporated into the award statement and provided to the Principal Investigator as well as to the institutional officials at the time of the award. These special Terms and Conditions of Award are in addition to and not in lieu of otherwise applicable OMB administrative guidelines, HHS grant administration regulations in 45 CFR part 74 and 92, and other HHS, and NIH grant administration policy statements.

The administrative and funding instrument used shall be a cooperative agreement (U01), an "assistance" mechanism (rather than an "acquisition" mechanism) in which substantial NCCAM scientific and/or programmatic involvement with the Awardee is anticipated during performance of the activity. Under the cooperative agreement, the purpose of the NCCAM is to support and/or stimulate the recipient's activity by involvement in and otherwise 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 the above concept, the dominant role and prime responsibility for the activity reside with the Awardee for the project as a whole, although specific tasks and activities in carrying out the studies will be shared among the Awardee, other study investigators and the NCCAM Program Officer.

Under the cooperative agreement, a relationship will exist between the recipient of this award and the NCCAM, in which the performers of the activities are responsible for the requirements and conditions described below, and agree to accept program assistance from the NCCAM Program Officer.

A. Awardee(s) Rights and Responsibilities. The Awardee(s) will retain custody of and have primary rights to the data developed under these awards, subject to Government rights of access consistent with current DHHS, and NIH policies. The Awardee will have substantial and lead responsibilities in all tasks and activities. These include protocol development, data collection, quality control, final data analysis, and assistance with preparation of publications. The Awardee agrees to work cooperatively with the NCCAM, and agrees to accept guidance from the trial Executive and Steering Committees, and to follow the Manual of Operations approved by the Steering Committee, DSMB and NCCAM. At the time of award, the Awardee will be requested

to nominate prospective DSMB members to the Director of NCCAM, who will select the DSMB members; other specific Awardee responsibilities are described below:

### 1. Data Coordination and Management

The Awardee will be responsible for ensuring the provision of centralized data management and coordination assistance for this trial. Under the direction of the Steering Committee, the Awardee (or its designee) will provide technical assistance and data management services to the trial sites with respect to quality control, uniformity of data collection, management of the collective database, and data analysis.

Each trial site will be responsible for providing the Awardee with all primary study data for management, quality control and analysis, using procedures and standards determined by the Steering Committee. Specific analyses to be performed by the Awardee will be directed by the Steering Committee.

### 2. Quality Control and Data Assurance

The Awardee must follow procedures developed by the Steering Committee for the prevention and/or identification of false or otherwise unreliable data and for quality assurance of data collected by the trial sites. The Awardee must follow Steering Committee procedures for the assurance of data quality and quality control in accordance with Steering Committee FDA and NCCAM guidelines.

The Awardee is responsible for ensuring that all trial sites have routine independent audits. These audits should, at a minimum, include the auditing of primary subject records over the course of the trial to verify conformance with eligibility criteria, recruitment and outcome data, and adverse events, as well as to monitor for non-compliance with protocol or regulatory requirements, or possible alteration of data and other discrepancies that become apparent. In the event that the NCCAM determines that the Awardee failed to comply with these guidelines, the accrual of new patients at the sites shall be suspended immediately upon notice of the NCCAM determination. The suspension will remain in effect until the Awardee conducts the required audit and the audit report or remedial action is accepted by the NCCAM. In the event that the audit identifies discrepancies or misconduct, these findings must be reported the NCCAM Project Officer, the Awardee and the DSMB within two weeks. All accrual at the non-complying trial site(s) will be suspended until remedial action is taken and accepted by the NCCAM. The Awardee will be responsible for notifying any affected trial sites of the suspension. During the suspension period, no funds from this award may be provided to the trial site(s) for new accruals, and no charges to the award for new accruals will be permitted. The NCCAM will also notify the PI's institution that is the direct recipient of a cooperative agreement from the NCCAM if it is necessary to suspend accrual at that institution or at a third party institution supported under that institution's cooperative agreement.

### 3. Protocol Closure

The Awardee, in consultation with the DSMB, shall establish and implement mechanisms for interim monitoring of results and monitoring protocol progress. If the DSMB wishes to close accrual to a study prior to meeting the initially established accrual goal, the interim results and other documentation should be made available to NCCAM staff for review and concurrence prior to implementation of the recommendation by the DSMB. It is recommended that

statistical guidelines for early closure be presented as explicitly as possible in the protocol in order to facilitate these decisions.

#### 4. Procedures in the Event of Scientific Misconduct

If a duly authorized governmental or institutional body issues a final determination that scientific misconduct has occurred or if the Awardee determines that other events have occurred which have significantly affected the quality or integrity of the trial data or patient safety, the Awardee is responsible for notifying the DSMB, the NCCAM, the collaborating investigators, the appropriate Institutional Review Boards (IRBs), the FDA and other sponsors of the affected work.

The Awardee is also responsible, if the events described above have occurred, for ensuring that submitted but unpublished abstracts and manuscripts are corrected, if possible. If publication deadlines have passed or if abstracts and/or manuscripts containing the affected data have already been published, the Awardee is responsible, within 90 days after learning of the event(s) significantly affecting the quality of the trial data or patient safety, for submitting to NCCAM a re-analysis of the results deleting the false or otherwise unreliable data, and disclosing within the text the reason(s) for the reanalysis. The Awardee must submit the reanalysis for publication. In addition, true copies of data files and other supporting documentation from studies affected by scientific misconduct or other findings affecting the quality or integrity of data or patient safety shall be made available to the NCCAM in a timely manner upon request by the NCCAM Program Officer. The NCCAM reserves the right to reanalyze, to publish, or to distribute its analyses of these data when it is in the interest of public health. Prior to release, publication or distribution of such analyses, the NCCAM will provide such analyses to the awardee. The Awardee must use its best efforts to notify all scientists, research laboratories, and other organizations to which the awardee has sent research materials affected by false or otherwise unreliable data.

#### 5. Reporting Requirements

Interim reports of the trial and adjunct studies shall appear in the minutes of each Steering Committee meeting and shall include specific data on patient accrual. Quarterly accrual information must be provided by the Steering Committee to NCCAM and the DSMB. A system for providing such information in a timely manner should be in place. Participants must provide accrual data to the Steering Committee in accordance with Steering Committee procedures. All recipients of NCCAM support for clinical trials, including trial sites responsible for coordinating and monitoring such trials, must promptly notify the NCCAM, the FDA and any other sponsors of the trial of adverse events (i.e., adverse drug reactions) according to directions provided in the adverse event reporting section of the protocol. The Awardee will notify all institutions/investigators participating in this project, about the above requirement and about the institutions'/investigators' responsibility to report adverse events as specified in the protocol.

#### 6. Federally Mandated Regulatory Requirements

Each trial site participating in a consortium arrangement is required to meet the DHHS and NIH regulations for the protection of human subjects and FDA requirements for the conduct of research using investigational agents. At a minimum, these include:

- a. methods for assuring that each institution at which site investigators are conducting clinical studies has a current, approved assurance on file with the Office for Human Research Protections (OHRP); that study protocols are reviewed and approved by the responsible registered IRB prior to patient entry; that active protocols are reviewed at least annually by the IRB; and that all protocol amendments are approved by the IRB.
- b. methods for assuring or documenting that each patient, or patient's parent/legal guardian, gives fully informed consent to participation in a research protocol prior to the initiation of the experimental intervention. All informed consent documents must be available for review upon request by the NCCAM or Steering Committee, or FDA or Industry sponsor, if applicable.

## B. NIH Staff Responsibilities

### 1. Normal Stewardship

- a) The NCCAM will name a Program Officer whose function will be to assist the Principal Investigator, the Executive Committee and the Steering Committee in oversight of the trial. In addition, the NCCAM Program Officer will retain overall administrative responsibility for the award and will be the contact point for all facets of interactions with the Awardee concerning such issues. In addition, ad hoc advisory committees may be formed as needed to assist/advise the NCCAM Program Officer.
- b) A change in the PI, or in any key personnel identified on the Notice of Award, must have the prior written approval of the NCCAM Grants Management Specialist in consultation with the NCCAM Program Officer.
- c) The NCCAM Program Officer will assist with the review and approval of adjunct protocols to ensure they are within the scope of the grant and also for safety considerations, as required by Federal regulations.
- d) The NCCAM Program Officer will review the progress of each trial site through consideration of the annual reports, site visits, patient logs, etc. As required for these activities, the Program Officer will be assisted by other NCCAM staff and contractors. This review may include, but is not limited to, safety issues, compliance with protocol, specifications, patient accrual, adherence to uniform data collection procedures, data management and quality control, and the timeliness of data reporting. The NCCAM Program Officer is able to request additional data from investigators as needed on these issues. Based on this review, the NCCAM reserves the right to close the study (or any individual trial site(s)) to accrual, or to terminate the study (or any individual trial site(s)) for reasons including:
  - 1) failure to implement the final collaborative protocol in a timely fashion;
  - 2) substantive changes in the agreed-upon protocol to which the NCCAM does not agree;
  - 3) substantial shortfall in participant recruitment, follow-up, data reporting, quality control, or other major breach of the protocol;
  - 4) emergence of new information that diminishes the scientific importance of the study question;
  - 5) patient safety and regulatory concerns;
  - 6) accrual goals met early and;
  - 7) study results that are already conclusive.
- e) The NCCAM Program Officer will review all DSMB reports. As necessary, the NCCAM Program Officer will request advice of the DSMB on study protocol and safety issues, data management, data quality, data analysis, recruitment, retention and protocol adherence issues arising over the course of study, and advisability of terminating the study.

f) The NCCAM will have access to and may periodically review all data generated under this award. The NCCAM Program Officer reserves the option, at any point in the trial, to obtain an independent audit of a sample of primary subject records for comparison with the trial's regular audit reports. Auditors so engaged will report directly to NCCAM and be reimbursed directly by NCCAM, i.e., reimbursement will not be drawn from the award for the trial, and costs of such audits will not be borne by the awardee institution(s). The NCCAM Program Officer has the authority to adjust funds provided to the trial sites as appropriate for the level of participation in trial sites activities, including (but not limited to) accrual. This procedure can be either prospective (i.e., reimbursement by the case) or retrospective (financial adjustment at the time a non-competing continuation [Type 5] award is made).

## 2. Substantial Additional Involvement

a) The Program Officer will have substantial scientific-programmatic involvement including participation in database development, budget monitoring, modification and finalization of the trial and any adjunct protocols, quality control, data analysis and interpretation, preparation of publications, and coordination and performance monitoring. The prime responsibility for these activities resides with the Awardee although specific tasks and activities in overseeing the studies will be shared between the awardee and the NCCAM Program Officer.

b) Certain organizational changes require the prior written approval of the NCCAM Program Officer. These changes include the addition or replacement of a trial site that is associated with this study.

c) The NCCAM Program Officer may contribute, through review, comment, analysis, and/or co-authorship, to reporting results of the study to interested scientific and lay organizations. Co-authorship by the NCCAM staff will be subject to approval in accordance with NIH policies regarding staff authorship of publications resulting from extramural awards.

## C. Collaborative Responsibilities

### 1. Steering Committee

A Steering Committee will be established to serve as the main governing body of the trial. The Steering Committee will be composed of the NCCAM Program Officer, the NHLBI Scientific Adviser, the cooperative agreement Principal Investigator, the Trial Manager and up to five trial site Senior Investigators (see below). At the first Steering Committee meeting, the Chairperson will be selected by the Steering Committee from members other than the PI or NIH staff, or alternatively, from among experts in the field who are not participating directly in the trial. A plan should be provided for selecting Senior Investigators to the Steering Committee; this should include their length of term and plans for rotation among Senior Investigators, if appropriate. Outside ad hoc consultants will be added as appropriate and needed. All major scientific decisions will be determined by the Steering Committee, with the PI, Steering Committee Chair and Senior Investigators, the NCCAM Program Officer, the NHLBI Scientific Adviser and the Trial Manager having one vote each. The first meeting will be convened by the NCCAM within two months of the award. The Committee will meet at least once more during the first 12 months of the study and annually thereafter. This Committee will have primary responsibility for finalizing the trial protocol, and approving the design and implementation of all adjunct studies, facilitating the conduct and monitoring of the clinical trial and adjunct studies, analyzing and interpreting study data, reporting study results, and setting guidelines for authorships. Each Steering Committee member (or their surrogate) will be expected to participate in all other

Steering Committee activities, e.g., conference calls, special subcommittees as may be necessary, etc.

The Steering Committee will be responsible for ensuring the provision of centralized data collection, management and quality assurance. Under the direction of the Steering Committee, the NCCAM will provide technical assistance, as available, to the trial sites with respect to quality control, uniformity of data collection, management of the collective database, and data analysis. Specific data analyses to be carried out will be determined by the Steering Committee. The results of those analyses will be delivered to the Steering Committee as the group responsible for determining if further analyses should be performed, how the results are interpreted, and how the findings should be disseminated. Applicants should include in their budget requests support for on-site data collection and transmittal, as well as for centralized data collection and management.

Each trial site will follow the procedures required by the final protocol generated by the Steering Committee regarding study conduct and monitoring, patient management, data collection, data management, data analysis and quality control. Trial sites will be required to accept and implement the common protocol and procedures approved by the Steering Committee. The Steering Committee will establish mechanisms for assessing performance of the trial sites, including institutions participating in consortia arrangements, with particular attention to accrual of adequate numbers of eligible patients, timely submission and quality of required data and conscientious observance of protocol requirements. At a minimum, this will include:

- 1) assessment of protocol adherence, treatment administration, and measurement of outcomes;
- 2) tracking and reporting of patient accrual and adherence to defined accrual goals;
- 3) ongoing assessment of case eligibility and availability;
- 4) timely medical review and assessment of patient data;
- 5) rapid reporting of morbidity, and measures to ensure communication of this information to all interested parties;
- 6) interim evaluation and consideration of measures of outcome as consistent with patient safety and good clinical trials practice;
- 7) timely communication of study results to NCCAM, the scientific community and the U.S. Public; and
- 8) an on-site quality control and safety monitoring program.

The Steering Committee shall establish and follow policies and procedures for, and conducting periodic review of, the performance and membership status of each trial site. This review should examine scientific contributions, patient accrual, data accuracy and timeliness, protocol compliance, long-term patient follow-up and audit results. These procedures should be as simple as appropriate in order to encourage maximum participation of physicians entering patients and to avoid unnecessary expense. This information will be made available to the NCCAM in a timely fashion.

#### Publication and Presentation of Study Findings

Timely publication of major findings is encouraged. Publications and oral presentations of work performed under this agreement will require appropriate acknowledgment of both the trial sites

and NCCAM support. Analyses to be performed using the collective data from all trial sites will be determined and directed by the Steering Committee, as will policies for authorship on any subsequent publications. Trial sites wishing to perform analyses of local data will inform the Steering Committee of any such analyses prior to initiation in order to avoid duplication. Review and approval by the Steering Committee will be required for all analyses, including that of local data by individual trial sites, prior to publication or presentation according to criteria that will be developed by the Steering Committee. The Steering Committee may establish a Publications Subcommittee to serve this function. The NCCAM Project Officer will have access to data generated under this Cooperative Agreement and may periodically review the data and progress reports. NCCAM Staff may use information obtained from the data for the preparation of internal reports on the activities of the study. However, the Awardee will retain custody of and have primary rights to all data developed under these awards.

### 3. Investigational Drug Management

It is the sole responsibility of the applicant to obtain all necessary clearances from the Food and Drug Administration as required, including completion of an Investigational New Drug (IND) application. Applicants are strongly encouraged to consult their local Institutional Review Boards (IRB) concerning IND status and the IRB approval process. It is important to note that neither IND or IRB approval is required prior to submission of an application. IRB approval, is required at the time of award. Provisional IRB approval contingent on a successful IND application is acceptable. In addition, all trial sites are expected, in cooperation with the NCCAM, to comply with all FDA monitoring and reporting requirements for investigational agents.

### 4. Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board will be appointed by the Director of NCCAM, with input from the Awardee, and meet at least twice a year. DSMB meetings will be open only to designated NCCAM staff and other individuals who have been approved to have access to unmasked data. The DSMB will be composed of experts in relevant medical, botanical, statistical and bioethical fields who are not otherwise involved in the trial. An NCCAM staff member other than the designated trial Program Officer will serve as the Executive Secretary of this Board. The Board will oversee participant safety, evaluate results, monitor data quality, adverse events and patient accrual, and provide operational and policy advice to the Steering Committee and the Director of NCCAM regarding the status of the study. The DSMB will document progress in written reports at least twice annually to the Director of NCCAM through the NCCAM Program Officer, and will provide periodic supplementary reports to designated NIH staff upon request.

The initial tasks of the DSMB are to review the entire protocol and informed consent forms with regard to subject safety; identify needs for protocol modification; review the Manual of Operations; and, after receipt of a satisfactory protocol, recommend to the NCCAM initiation of expenditure of project funds. The DSMB will also identify the relevant data parameters to be reported by the Awardee and the Steering Committee to the DSMB, and the format of these data. Subsequently, it must meet on a regular schedule (not less than twice a year) over the course of study (with additional meetings as needed) to:

1. Review data (including masked data) relating to recruitment, randomization, compliance, retention, protocol adherence, trial operating procedures, form completion, intervention effects, auditing of primary subject records, data management, quality control, and subject safety;
2. Identify problems relating to safety over the course of the study;
3. Identify needs for additional data relevant to safety issues and request these data from the study investigators;
4. Review unmasked outcome data as needed and appropriate over the course of the trial;
5. Propose appropriate analyses and periodically review developing data on safety and endpoints;
6. At each meeting, consider the rationale for continuation of the study, with respect to progress of randomization, retention, protocol adherence, data management, safety issues, and outcome data, if relevant, and make recommendation to the Director of NCCAM for or against continuation of the trial.
7. Provide advice on issues regarding data discrepancies found by the data auditing system or other sources. If the NCCAM Program Officer requests this advice, it should be provided in writing within two weeks of the date of this request.
8. Send the NCCAM Program Officer written reports following each DSMB meeting, and additionally as needed, on all issues reviewed by the DSMB

At the time of award, the Awardee will be requested to nominate prospective DSMB members to the Director of NCCAM. The NCCAM reserves the right to appoint additional members to the DSMB to include scientific expertise in topic areas relevant to the trial such as biostatistics, ethics, or patient advocacy. The NCCAM Program Officer is charged with facilitating implementation of DSMB recommendations by the NCCAM and with conveying DSMB recommendations and requests to the Awardee. The trial sites must comply with the approved policies and procedures of the DSMB.

#### D. Arbitration

Any disagreement that may arise in scientific-programmatic matters between award recipients and NCCAM may be brought to arbitration. An arbitration panel will be composed of three members--one selected by the Steering Committee (with NIH members not voting) or by the individual awardees in the event of an individual disagreement, a second member selected by NCCAM and the third member selected by the two prior members. This special arbitration procedure in no way affects the awardee's right to appeal an adverse action that is otherwise appealable in accordance with the PHS regulations at 42 CFR part 50, Subpart D.

#### INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

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 biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification are 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 research involving human subjects should read the UPDATED "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research," published in the NIH Guide for Grants and Contracts on August 2, 2000

(<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-048.html>); a complete copy of the updated Guidelines are available at

[http://grants.nih.gov/grants/funding/women\\_min/guidelines\\_update.htm](http://grants.nih.gov/grants/funding/women_min/guidelines_update.htm): The revisions relate to NIH defined Phase III clinical trials and require: a) all applications or proposals and/or protocols to 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) all investigators to report accrual, and to conduct and report analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

## 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. Reviewers are cautioned that their anonymity may be compromised when they directly access an Internet site.

## LETTER OF INTENT

Prospective applicants are asked to submit a letter of intent that includes a descriptive title of the proposed research, the name, address, and telephone number of the Principal Investigator, the identities of other key personnel and participating institutions, and the number and title of the RFA in response to which the application may be submitted. 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 on or before July 18, 2001 to:

Christine Goertz, D.C., Ph.D.  
National Center for Complementary  
and Alternative Medicine (NCCAM)  
National Institutes of Health  
6707 Democracy Blvd. Suite 106  
Bethesda, MD 20892-5475  
(FedEx, UPS or other courier use zip code 20817)  
Office (301) 402-1030  
Fax (301)480-3621  
Goertzc@mail.nih.gov

## APPLICATION PROCEDURES

The research grant application form PHS 398 (rev. 4/98) is to be used in applying for these grants. These forms are available at most institutional offices of sponsored research and from the

Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, email: GrantsInfo@nih.gov.

The RFA label available in the PHS 398 (rev. 4/98) 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 sample RFA label available at: <http://grants.nih.gov/grants/funding/phs398/label-bk.pdf> has been modified to allow for this change. Please note this is in pdf format.

Submit a signed, typewritten 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  
BETHESDA, MD 20892-7710  
BETHESDA, MD 20817 (for express/courier service)

At the time of submission, two additional copies of the application must be sent to:

Christine Goertz, D.C., Ph.D.  
National Center for Complementary  
and Alternative Medicine (NCCAM)  
National Institutes of Health  
6707 Democracy Blvd. Suite 106  
Bethesda, MD 20892-5475  
(FedEx, UPS or other courier use zip code 20817)  
Office (301) 402-1030  
Fax (301)480-3621  
Goertzc@mail.nih.gov

Applications must be received on or before 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. 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. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of substantial revisions of applications already reviewed but such applications must include an introduction addressing the previous critique.

#### Preparation of the Application

The general instructions provided in PHS-398 must be used for the preparation of applications except as modified under "Special Requirements" and as listed below. Because the "Terms and

Conditions of Award" will be included in all awards issued as a result of this RFA, it is critical that each applicant provides specific plans for responding to the terms and conditions of award and requirements stated in the RFA. Plans must take into account NIH staff involvement, as well as how all the responsibilities of Awardee will be fulfilled. The following items apply to all applications:

### 1. General

All applicants should demonstrate their ability to manage a complex trial, and provide a detailed patient recruitment plan, a detailed data management plan, and sample size and power calculations. In addition, it is important to evaluate any side effects or complications of treatment.

### 2. Trial Organization

The application should describe the organization of the study and how the trial will be managed. The application should identify the single applicant organization that will be legally and financially responsible and accountable for the use and disposition of funds awarded on the basis of this RFA to other trial sites and institutions participating in the consortium, and show availability of personnel and facilities capable of performing and supporting the administrative functions necessary. The application should provide a plan to assure the maintenance of close cooperation and effective communication among members of the consortium. The application should discuss the capability of the applicant organization and each institution in an applicant consortium to participate and interact effectively in cooperative, multi-center clinical trials. The application should discuss the coordination of participating trial sites, including proposed methods of blinding, communication, data transfer, and trial oversight (e.g., how will recruitment goals of trial sites be monitored). A timetable for completion of the various stages of the trial should be included.

### 3. Research Design and Data Analysis

The applicant should describe the procedure for assignment of patients to experimental conditions, as well as the procedures used to assure compliance with, and standardized implementation of, the proposed protocol. Applicants should also discuss potential biases in the proposed research protocol and how they will be addressed. A detailed description, including a rationale, for of the placebo control selected must be provided. Clinical (including behavioral), laboratory and physiological tests and protocols should be described briefly, with additional detail provided in the appendix if needed. Methods of randomization and standardization across trial sites should be described and endpoints clearly defined. The specific criteria and procedures for unblinding should be specified and justified in the application. Applicants should discuss patient availability and recruitment. Discuss the characteristics of the population and the approaches proposed for recruitment, retention and follow-up. Discuss plans for maintaining the cooperation of the study population over the length of the trial, including compliance with the assigned treatment, as well as plans for addressing any anticipated changes in the composition of the study population over the course of the trial (e.g., different mortality rates in men versus women). Data should be presented supporting recruitment and retention estimates.

Describe the methods of data analysis, linking the analyses to the hypotheses to be tested. Include methods of data preparation and presentation, analytic methods, and approaches to data synthesis. Discuss how interim analyses will be handled, as well as comparisons across

subgroups. Data analyses should consider stratification by risk and protective factors when appropriate. Choice of these factors should be specified and justified in the application, and incorporated into sample size calculations. Applications should demonstrate the scientific expertise required to design, conduct and analyze all proposed adjunct studies. Such expertise may be provided by a single scientist serving the entire consortium or more than one such scientist depending upon the proposed adjunct studies.

#### 4. Women and Minority Subjects

Women and minority individuals should be included in the study population in accordance with NIH requirements. Specific recruitment targets for women and minority subjects and plans for achieving these goals must be explicitly stated in a separate section of the application.

Approximate percentages of women and minority groups expected in the study sample and the basis for these estimates must be provided. Generally, representation of women and minorities should occur in the study population in the same proportions as in the U.S. population having the disease being studied. It is recognized that this may require oversampling.

#### 5. Budget

All costs required for the proposed trial and adjunct studies should be included in the application and fully justified. If the trial is designed for more than a five-year period, complete, justified budgets for the future years also must be included. The review of the application will evaluate the entire project. Budgeted costs should include the costs of clinical research associated with the proposed protocol costs for patient recruitment and follow-up, adjunct studies, data collection, management and quality control, and independent on-site quality assurance audits. Costs at participating trial sites, exclusive of salary, should be calculated on a per patient-visit. Requested budgets should also include travel to the Bethesda, Maryland area for two 1-2 day Steering Committee meetings during the first 12 months, and annually thereafter for the Principal Investigator, the Trial Manager and up to five trial site Senior Investigators.

### REVIEW CONSIDERATIONS

Upon receipt, applications will be reviewed for completeness by the CSR and responsiveness by the NCCAM. Incomplete and/or non-responsive applications will be returned to the applicant without further consideration. 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 NCCAM in accordance with the review criteria stated below. As part of the initial merit review, all applications will receive a written critique and 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, assigned a priority score, and receive a second level review by the NCCAM and NHLBI National Advisory Councils.

#### 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 discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these

criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

(1) Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

(2) Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

- Overall feasibility and the likelihood of achieving the clinical trial goals and the potential for a successful trial.
- Pilot phase experience including evidence of patient recruitment and retention.
- Adequacy of the statistical features of the study including sample size projections and power estimates, methods of analysis, and the use of sequential analyses of data.
- Logistical aspects of the project including plans for patient recruitment, quality control of data, proper randomization and masking procedures, data collection, data management and reporting, and plans for defining access and restriction to data. If preliminary data are not available, the proposal should include a pilot phase to validate these procedures.
- Availability of suitable subjects for the clinical trial and the likelihood of participation through to completion of the study.
- Adequacy of methods for data collection and reporting from each consortium institution.

(3) Innovation: Does the project employ novel concepts, approaches or method? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

(4) Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

(5) Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

- Commitment of the consortium institutions and staff to a collaborative protocol and to the success of the study. The inclusion of letters of agreement from collaborating investigators, countersigned by the appropriate institutional official, is necessary. These letters should state the willingness of the investigators to work with the Steering Committee and NCCAM staff, and to comply with the policies and procedures developed by the Steering Committee concerning this trial.
- Adequacy of the facilities including technical resources and space.

- Appropriateness of both the consortium organization and administration at each trial site.

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

- The adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.
- A reasonable proposal for study budget and duration in relation to the research plan.
- The adequacy of the proposed protection for humans, animals or the environment, to the extent they may be adversely affected by the project proposed in the application.

Schedule:

Letter of Intent Receipt Date: July 18, 2001  
Application Receipt Date: August 29, 2001  
Peer Review Date: Oct/Nov, 2001  
Council Review: January 2002  
Earliest Anticipated Start Date: March 1, 2002

#### AWARD CRITERIA

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

- scientific merit (as determined by peer review)
- availability of funds
- programmatic priorities.

#### INQUIRIES

Inquiries concerning this RFA are encouraged. The opportunity to clarify any issues or answer questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

Christine Goertz, D.C., Ph.D.  
National Center for Complementary  
and Alternative Medicine (NCCAM)  
National Institutes of Health  
6707 Democracy Blvd. Suite 106  
Bethesda, MD 20892-5475  
(FedEx, UPS or other courier use zip code 20817)  
Office: (301) 402-1030  
Fax: (301)480-3621  
Goertzc@mail.nih.gov

Direct inquiries regarding review issues to:

Chief Review Branch  
National Center for Complementary  
and Alternative Medicine (NCCAM)  
National Institutes of Health  
6707 Democracy Blvd. Suite 106  
Bethesda, MD 20892-5475  
(FedEx, UPS or other courier use zip code 20817)  
Office: (301) 496-4792  
Fax: (301)480-3621

Direct inquiries regarding fiscal matters to:

Victoria Carper  
National Center for Complementary  
and Alternative Medicine (NCCAM)  
National Institutes of Health  
6707 Democracy Blvd. Suite 106  
Bethesda, MD 20892-5475  
(FedEx, UPS or other courier use zip code 20817)  
Office: (301) 594-9102  
Fax: (301)480-3621

#### AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.213. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies and Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and promote the non-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.

References cited in this RFA can be obtained at <http://nccam.nih.gov>

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