Statement of Work – Clinical Studies Monitoring Service (CSMS) National Center for Complementary and Alternative Medicine

List of Acronyms and Definitions

AE: Adverse event

Communication: a communication is a verbal or written interaction between two or more parties. Verbal communication that involves an action item will be confirmed in writing.

CO: Contracting Officer

COTR: Contracting Officer's Technical Representative

CRA: Clinical Research Associate

CRF: Case Report Form

CRO: Contract Research Organization- Organization that assumes, as an independent contractor of the sponsor, one or more obligations of the sponsor.

CTCAE: Common Terminology Criteria for Adverse Events- a standardized vocabulary for defining and grading adverse events.

CSMS: Clinical Studies Monitoring Service

DER: Division of Extramural Research

DHHS: Department of Health and Human Services

DSMB: Data and Safety Monitoring Board- a DSMB is an independent group of experts that advises NCCAM/OCRA and the study investigators. The primary responsibilities of the DSMB are to periodically review and evaluate the accumulated study data for safety, quality of study conduct, progress, feasibility, futility, and, when appropriate, efficacy. Based on these reviews, the DSMB makes recommendations to NCCAM/OCRA concerning the continuation, modification, or termination of the study.

FDA: Food and Drug Administration

FISMA: Federal Information Security Management Act

Form FDA 1572: Referred to as a "Statement of Investigator"; it is a requirement of section 505(i) of the Food, Drug and Cosmetic Act and paragraph 312.1 of Title 21 CFR, that an investigator complete this form as a condition for receiving and conducting clinical trials involving investigational drug(s). It includes the investigator's training and experience and provides for legal certifications.

FWA: Federal Wide Assurance

GCP: Good Clinical Practices

HIPAA: Health Insurance Portability and Accountability Act (HIPAA) was enacted in 1996 with the intent of protecting health insurance for workers when they change or lose their jobs as well as requires the establishment of national standards for electronic health care transactions and national identifiers for providers, health insurance plans, and employers. The Administration Simplification provisions also address the security and privacy of health data. The standards are meant to improve the efficiency and effectiveness of the nation's health care system by encouraging the widespread use of electronic data interchange in the U.S. health care system.

ICH: International Conference on Harmonization

IND: Investigational New Drug Application – submitted to the Food and Drug Administration in order to receive an exception from the New Drug Application approval requirements so that experimental clinical trials may be conducted.

IP: Investigational Product

IRB: Institutional Review Board

IMV: Interim Monitoring Visit

IT: Information Technology

MedDRA: Medical Dictionary for Regulatory Activities

MOP: Manual of Procedures- a MOP serves as a reference document for clinical study operations at a site. The MOP is the entire project team's guide for the complete operational management of a clinical research site including administrative and management activities, regulatory affairs, and study implementation. It may serve as a training tool for protocol initiation activities. MOPs are developed and utilized to ensure that at all times the study is conducted in compliance with all application regulations.

NCCAM: National Center for Complementary and Alternative Medicine

NACCAM: National Advisory Council for Complementary and Alternative Medicine

NCCAM Funded: NCCAM is providing financial support for trial or study.

NCCAM Sponsored: NCCAM is responsible for the management (including submission of the Investigational New Drug Application (IND) to Food and Drug Administration (FDA) and initiation of the study) and oversight for the study.

NDA: New Drug Application

NIH: National Institutes of Health

OCRA: Office of Clinical and Regulatory Affairs

PI: Principle Investigator- is a qualified person designated by the applicant institution to direct the research. PIs oversee the scientific and technical aspects of a grant and the day-to-day management of research.

PWI: Project Work Instruction

QA: Quality Assurance- a periodic systematic, objective and comprehensive examination of the total work effort to determine the level of compliance with accepted Good Clinical Practice (GCP) standards. It is an internal audit of various components of the research process to assess adherence to the protocol, local and sponsor policies, and to determine the accuracy of research records.

SAE: Serious Adverse Event

SAS: Statistical Analysis Software

SDMP: Study Data Monitoring Plan- the characteristics of a SDMP are determined by the type of clinical study to be monitored. The intensity of monitoring will primarily depend on the complexity, populations, and risks involved with the study. All clinical studies funded or sponsored by NCCAM that will be monitored by a CRO must have a SDMP approved in writing by the assigned NCCAM COTR before study initiation.

Site: Used as a general term to describe the institution where the patient signed the Informed Consent. Includes: location(s) where subjects are seen, the investigator site file is maintained, the Investigational Product (IP) is stores, or specialized equipment critical to the study endpoints is available, unless otherwise specified by the sponsor.

SIV: Site Initiation Visit

SOP: Standard Operating Procedure

Notes: Reference Web sites

NCCAM Website: http://nccam.nih.gov/

NCCAM-Funded Research: http://nccam.nih.gov/research/clinicaltrials/alltrials.htm

NCCAM Policies and Guidelines: http://nccam.nih.gov/research/policies/index.htm

Code of Federal Regulations: http://www.gpoaccess.gov/cfr/

DHHS Personnel Security/Suitability Handbook: http://www.hhs.gov/ohr/manual/pssh.pdf

Federal Information Security Management Act of 2002 (FISMA), Title III, E-Government Act of 2002, Pub. L. No. 107-347 (Dec. 17, 2002): http://csrc.nist.gov/drivers/documents/FISMA-final.pdf

NIH Computer Security Awareness Training Course: http://irtsectraining.nih.gov/

Required Education in the Protection of Human Research Participants: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-061.html

Revised Policy for IRB Review of Human Subjects Protocols in Grant Applications: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-031.html

Background Information

Since its creation as an independent Center in 1998, the National Institutes of Health (NIH) National Center for Complementary and Alternative Medicine (NCCAM) has developed a broad research portfolio focused on a variety of complementary and alternative medicine (CAM) practices. CAM practices are a group of diverse medical and health care systems, interventions, and products that are not generally considered part of conventional medicine. In view of its expanding portfolio of clinical research, this new solicitation provides for the support of the NCCAM Clinical Studies Monitoring Services (CSMS) Contract to enhance clinical studies oversight by the NCCAM Office of Clinical and Regulatory Affairs (OCRA).

Over the past decade, the evidence base regarding efficacy and safety of CAM practices has grown substantially in both quality and quantity. Basic research and clinical trials, both large and small, have yielded results—both "positive" and "negative"—that inform consumers' use of and health care providers' recommendations concerning CAM. It is also apparent the nearly 40% of the US public practice some form of CAM therapy on a regular basis. Increasingly, the evidence base is permitting systematic reviews that point toward helpful conclusions regarding safety and efficacy or lack thereof, rather than simple statements that more or better quality research is needed. There is also evidence that this body of research has influenced consumers. For example, both NHIS data and industry sales figures suggest that the results of several large clinical trials have affected both the frequency of use and sales of nonvitamin/nonmineral dietary supplements. In addition, the U.S. Food and Drug Administration (FDA) has taken actions to address concerns about the safety of some CAM products as a direct result of CAM research.

Growth in the quality and quantity of the CAM evidence base reflects substantial growth in CAM research capacity, much of which is a direct result of NCCAM-led and -supported activities to attract scientists to the field, establish multidisciplinary research collaborations, and train investigators in CAM research. In view of extensive use by the public, NCCAM is committed to further research on CAM practices. State-of-the-art research methods and tools are being employed to assess and develop two broad categories of research funded by NCCAM–botanical products & dietary supplements and mind/body & manual therapies. CAM research is now a specific focus of several international organizations, including the Consortium of Academic Health Centers for Integrative Medicine, the International Society for Complementary Medicine Research, and the Society for Integrative Oncology, as well as various national governments (e.g., China and India) and the World Health Organization.

The NCCAM currently funds a broad portfolio of clinical studies that investigate CAM practices with biologically-based or mind/body-based interventions
http://nccam.nih.gov/research/results/spotlight/atoz.htm The biologically-based interventions include those such as dietary supplements (i.e., omega-3 fatty acids, creatine), probiotics, and botanical products (i.e., silymarin, saw palmetto extract). As many of the biologically-based studies funded by NCCAM focus on a specific disease or condition of use, many such studies are conducted under an IND issued by the FDA. By contrast, the mind/body-based intervention studies include modalities such as yoga, Tai

Chi, meditation, acupuncture, massage therapy and chiropractic manipulation. The majority of NCCAM-sponsored clinical research is conducted in single-site studies, and is conducted at academic medical centers, hospitals, clinics and physician offices through a variety of funding mechanisms such as cooperative agreements, grants, and contracts. In addition, several studies are conducted outside of the US, in Canada, Hong Kong, Peru and South Africa. NCCAM also supports an intramural clinical research program at the NIH Clinical Center. The NCCAM clinical research portfolio therefore incorporates many scientific disciplines and includes studies of diverse design, clinical setting, size and complexity.

In view of the diverse scope of NCCAM-funded clinical studies, the NCCAM/OCRA plays a primary role in clinical studies oversight for the approximately 150 ongoing clinical projects. Monitoring of clinical sites is one element of a larger program of clinical studies oversight developed by OCRA to fulfill its responsibilities of ensuring the safety and welfare of participants, of maximizing adherence to appropriate clinical research regulations and guidelines and maximizing data quality from NCCAM-funded studies.

NCCAM has a growing clinical research program that conducts research on promising CAM therapies for treatment or symptomatic relief of numerous diseases and conditions. Such studies of CAM practices involve varying degrees of risks to participants. This relative risk, as well as the scope and complexity of the research will influence the extent of external monitoring required by OCRA. The CAM CSMS Contract will therefore provide support for ongoing site monitoring in NCCAM-funded clinical studies that are identified by OCRA, and addresses the compelling need to provide monitoring to insure that studies are conducted in the most scientifically valid, safe, and efficient manner possible.

1) SCOPE:

A. Scope of Clinical Site and Study Monitoring Functions: The Contractor shall provide comprehensive clinical site and study monitoring services for the NCCAM extramural clinical studies research portfolio. The scope of activities to be performed includes:

(1) site initiation visits prior to clinical study implementation to ensure compliance with NCCAM, U.S. and, where appropriate, country-specific regulatory requirements and guidelines.

(2) routine site monitoring visits for active select phase 0, phase 1, and phase 2 clinical studies to ensure compliance with NCCAM, U.S. and, where appropriate, country-specific regulatory requirements and guidelines, verify the accuracy and completeness of clinical study data, and assess adherence to protocol-specific requirements.

(3) specialized site monitoring visits for a variety of purposes, including regulatory audits, assessments of overall and protocol-specific research pharmacy operations and management of investigational products, and remedial or for cause site visits to implement and ensure adherence to corrective actions required to address site or study deficiencies identified through routine site monitoring.

(4) site closeout visits to ensure appropriate completion of clinical studies, storage of clinical records and disposition of investigational products.

(5) preparation of written reports of all site monitoring visits, including identification of problems and deficiencies and recommendations for remedial actions.

(6) the development and implementation of Standard Operating Procedures for the conduct of clinical site and study monitoring functions, including the components to be reviewed/assessed and the processes to be used for each type of site visit.

(7) the development and implementation of a training plan for site monitors on staff and new hires and for evaluating the effectiveness and efficiency of training activities conducted.

(8) the development and implementation of a Quality Assurance/Quality Control (QA/QC) Plan to ensure the efficient and effective performance of monitoring functions and the appropriate management of the project.

(9) the development and implementation of an Integrated Master Project Plan to provide for the overall management, integration and coordination of all contract activities.

(10) other technical and administrative support to coordinate meetings, teleconferences, review and/or preparation of study-related documents and materials.

B. Scope of Clinical Studies Programs and Projects: The scope of NCCAM-supported clinical study programs and projects for which clinical site and study monitoring services shall be provided includes the following:

(1) NCCAM Extramural Clinical Studies: On-site monitoring support for contractors, grantees and other clinical investigators conducting selected phase 0, phase 1 and phase 2 clinical , as well as selected observational clinical studies.

(2) Other NCCAM-funded Investigator-initiated Projects: Expanded capability for conducting on-site monitoring to encompass the expanded scope of studies conducted under the auspices of the Intramural Research Program.

2) TECHNICAL REQUIREMENTS:

Independently and not as an agent of the Government, the Contractor shall furnish all the necessary services, qualified personnel, material, equipment, and facilities, not otherwise provided by the Government as needed to perform the Statement of Work below.

A. CLINICAL SITE MONITORING VISITS

The Contractor shall conduct both routine and specialized visits to NCCAM-funded domestic and foreign clinical sites to ensure compliance with: (i) 21 CFR 312 – GCP; (ii) 45 CFR 46 – "Human Subjects Protection"; (iii) the ICH E6-GCP Guidelines (http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm); (iv) country-specific requirements governing human subjects research; (v) protocol-specific requirements; (vi) NCCAM policies and procedures (http://nccam.nih.gov/research/policies/terms-of-awards.htm); and (vii) Office of Human Research Protections (http://www.hhs.gov/ohrp/) . The frequency and intensity of clinical site monitoring visits will be determined by NCCAM on the basis of protocol risk and individual clinical site characteristics. The contractor shall conduct 25-35 on-site monitoring visits per year of investigators conducting phase 0, phase 1 and phase 2 studies assigned by NCCAM for CRA monitoring.

1. Standard Operating Procedures

a. Within twenty-one (21) calendar days of the contract effective date, submit, for COTR review and approval, Draft Standard Operating Procedures (SOPs) governing all aspects of the conduct of both routine and specialized clinical site monitoring visits. The COTR will review and provide comments and revisions to draft SOPs within twenty- one (21) calendar days of receipt. The Contractor shall finalize SOPs within fifteen (15) calendar days of receipt of COTR comments.

(1) Separate SOPs shall be provided for:

(a) site initiation visits prior to clinical study implementation

(b) routine site visits to monitor compliance with Federal and country-specific regulatory requirements, GCP and ICH guidelines, protocol-specific requirements, and NCCAM policies and procedures
(c) remedial or for cause visits
(d) investigational pharmacy operations assessments
(e) protocol-specific investigational drug audits
(f) regulatory reviews
(g) site close out visits at the completion of clinical studies

(2) Each SOP shall address the components listed below. The forms and templates to be used by the Contractor to record site visit data and other information obtained will be provided by the COTR or his/her designee.

(a) a description of each aspect of clinical study conduct and clinical site operations to be reviewed
(b) the sources of data and other information to be used to monitor each aspect of clinical study conduct and clinical site operations
(c) detailed work instructions
(d) the types of clinical site personnel required to participate
(e) scheduling process and procedures for the preparation of participating clinical site staff, including questions and other materials to be provided to clinical site staff in advance of site visits, as well as data, documents and other information to be gathered and made available by clinical sites
(f) the average length of the site visit and the number of Contractor monitors required

(3) SOP Updates: Keep abreast of all changes in Federal and country specific requirements governing human subjects research, GCP and ICH guidelines, and NCCAM policies and procedures; update SOPs, as necessary, within thirty (30) calendar days of the effective date of all such changes, and submit updated SOPs for COTR review and approval. Updated SOPs shall be implemented by the Contractor only after receipt of written COTR approval.

2. Routine Clinical Site Monitoring Visits and Reports

a. The number, frequency and intensity of routine clinical site monitoring visits will be determined by NCCAM on a protocol-specific basis commensurate with the anticipated level of protocol risk and characteristics of the individual participating clinical sites.

Assignments for routine clinical site monitoring visits will be provided to the Contractor no less than quarterly and no less than six (6) weeks in advance of each quarter.

b. Routine clinical site monitoring visits shall encompass the following aspects of clinical study conduct and clinical site operations:

(1) the accuracy and completeness of reportable data on Case Report Forms (CRFs)
(2) adherence to inclusion and exclusion criteria
(3) reporting of protocol violations
(4) accuracy and completeness of the reporting of protocol exemptions approved by the Protocol Team
(5) documentation and reporting of Serious Adverse Events (SAEs)
(6) documentation of informed consent and adherence to informed consent procedures
(7) documentation of objective findings, including verification of endpoints
(8) maintenance of appropriate source documentation
(9) adherence to Federal and country-specific regulatory requirements, GCP and ICH guidelines, and NCCAM policies and procedures
(10) adequacy of pharmacy operations, performance and management related to protocol-specific requirements
(11) regulatory review to assess the adequacy of procedures for ensuring compliance with regulatory requirements
(12) adherence to other protocol-specific requirements, including the collection and reporting of clinical laboratory tests and storage of clinical specimens

c. For all routine clinical site visits, the clinical sites involved shall be provided with a description of the site-specific activities/protocols to be reviewed, data and other information to be collected/assessed, and instructions on the clinical site personnel and materials to be made available. This information shall be provided to the clinical sites no less than twenty-one (21) calendar days prior to the scheduled site visit.

d. Reports of routine clinical site monitoring visits shall be prepared using site visit report templates provided by the contractor and approved by the COTR. Reports shall be e-mailed to the COTR no later than ten (10) calendar days following completion of each site visit.

The Contractor shall **immediately notify the Contracting Officer's Technical Representative** by telephone with a follow-up email of any findings suspicious and/or suggestive of intentional misrepresentation of data and/or disregard for regulatory safeguards for **any of the three** (regulatory, pharmacy and participant case) **components of a monitoring visit**. Similarly, critical findings (e.g., any fraudulent findings, prefilling of CRFs, invalid signatures, and unreported Serious Adverse Events) shall be reported to the COTR within 24 hours of site visit completion.

3. Specialized Clinical Site Visits and Reports

The Contractor shall perform a variety of specialized clinical site visits, to be assigned by the COTR on an as-needed basis, designed to focus on specific aspects of clinical study conduct and clinical site operations. Specialized clinical site visits may be conducted either in tandem with other clinical site monitoring visits or as separate, independent visits. The Contractor shall conduct specialized clinical site visits in accordance with the timelines specified in the monitoring assignments provided by the COTR or his/her designee. Scheduling of "for cause" site visits will be determined by the COTR or his/her designee on a case by case basis based on the nature and potential risk characteristics associated with such visits. In addition, forms and

templates specifying the data and other information to be collected, assessed and reported for specialized clinical site visits will be provided by NCCAM.

a. Specialized clinical site visits to be conducted include the following:

(1) *Site Initiation Visits* prior to clinical study implementation to ensure site compliance with all Federal and country-specific regulatory requirements, GCP and ICH guidelines, and NCCAM policies and procedures.

(2) *Site Closeout Visits* after clinical study completion to confirm that the proper closeout of clinical studies has been accomplished in accordance with established policies and procedures, including storage of study records and disposition of any remaining supplies of investigational products.

(3) *Specialized Pharmacy Visits* to assess the appropriateness and adequacy of overall research pharmacy operations and management, and/or research pharmacy performance in adhering to protocol-specific requirements for the receipt, labeling, storage, dispensing and inventory of investigational products.

(4) *Specialized Regulatory Review Visits* to assess the appropriateness and adequacy of established procedures for ensuring compliance with Federal and country-specific regulatory requirements, and NCCAM policies and procedures for monitoring adherence on the part of clinical site personnel, and for maintaining a system of records for regulatory documentation.

(5) *Remedial or "For Cause" Visits* to assist clinical site personnel in developing and implementing corrective and remedial actions for identified deficiencies and for other "for cause" reasons, such as scientific misconduct or fraud.

b. Specialized Site Visit Plans and Reports

(1) For all specialized site visits, the clinical sites involved shall be provided with a description of the site-specific activities/protocols to be reviewed, data and other information to be collected/assessed, and instructions on the clinical site personnel and materials to be made available. This information shall be provided to the clinical sites no less than twenty-one (21) calendar days prior to the scheduled site visit.

(2) Brief summaries of the results of specialized visits shall be prepared and submitted to the COTR within five (5) calendar days of visit completion. Critical findings (e.g., any fraudulent findings, prefilling of CRFs, invalid signatures, and unreported Serious Adverse Events) shall be reported to the COTR within 24 hours of visit completion. Unless otherwise specified, specialized site visit report templates will be provided by the COTR. Completed reports of specialized site visits shall be sent via e-mail to the COTR within fourteen (14) to twenty-one (21) calendar days depending on complexity of site visit completion.

B. TRAINING

1. Within twenty-one (21) calendar days of the contract effective date, submit, for COTR review and approval, a Draft Training Plan delineating all training activities to be conducted for site monitors on staff as well as newly hired site monitors. The Draft Training Plan shall include the following:

    a. plans for initial and continuing training activities to be carried out both in-house and through non-Contractor organizations

    b. frequency of training

    c. training methods/approaches (e.g., workshops, videocasts, written materials, etc.)

    d. training curricula, duration and instructors both on staff and from other non-Contractor sources

    e. provisions for ensuring that experienced monitors accompany new monitors on initial site visits – both routine and specialized

    f. plans for evaluating the training activities conducted, including evaluation and performance metrics to assess outcomes, effectiveness, and efficiency and identify areas for improvement

    g. information Security Training. HHS policy requires Contractors/Subcontractors receive security training commensurate with their responsibilities for performing work under the terms and conditions of their contractual agreements.

    The successful Contractor will be responsible for assuring that each Contractor/Subcontractor employee has completed the NIH Computer Security Awareness Training course at: http://irtsectraining.nih.gov/ prior to performing any contract work, and thereafter completing the NIH-specified fiscal year refresher course during the period of performance of the contract. The successful offeror shall maintain a listing of all individuals who have completed this training and shall submit this listing to the COTR.

    Additional security training requirements commensurate with the position may be required as defined in NIST Special Publication 800-16, Information Technology Security Training Requirements (http://csrc.nist.gov/publications/nistpubs/800-16/800-16.pdf). This document provides information about information security training that may be useful to potential offerors.

The Draft Training Plan shall be revised, as necessary, in accordance with COTR comments, and the Final Training Plan shall be submitted to the COTR and implemented within forty (40) calendar days of receipt of COTR comments.

2. Provide to the COTR written assessments of training activities conducted at a minimum of semi-annually, along with recommendations for modifications to the approved Training Plan to improve effectiveness and efficiency and to incorporate additional training activities relevant to changes in

Federal and country-specific regulatory requirements, GCP/ICH guidelines, and NCCAM policies and procedures.

3. At the end of each year of the contract period of performance, provide to the COTR a listing of all training activities conducted and the names of Contractor and any subcontractor staff completing each training program.

4. The Contractor shall provide trained professional monitors to perform the work. If the contractor can not recruit fully trained and qualified individuals and needs to train them to carry out the work, the cost of that training shall be at the expense of the contractor, not NCCAM.

C. CLINICAL AND TECHNICAL PERSONNEL

The Contractor shall provide clinical and technical personnel with appropriate training, expertise and experience to carry out the functions of the contract. This includes the following personnel:

1. Site Monitors:

a. The Contractor shall provide and maintain a cadre of site monitors with the training, experience and capabilities to perform clinical site and study monitoring functions for the full scope of NCCAM supported clinical studies and clinical sites. These site monitors should possess: (i) training and experience in monitoring phase 0, phase 1, and phase 2 clinical studies; (ii) training and experience in monitoring clinical studies conducted at domestic sites, at foreign sites in resource-limited countries, and in a variety of community- and hospital-based settings; (iii) knowledge of country-specific health care systems and clinical research regulations; and (iv) proficiency in the language of countries where clinical records are not maintained in English.

b. Additional in-country site monitors may be used to resolve workload and scheduling conflicts. In such instances, the Contractor shall submit, for COTR review and approval, a written justification for the use of in-country site monitors and documentation of the training, expertise and experience of the site monitors recommended.

2. Supervisory Site Monitor with responsibility for overseeing the clinical site monitoring activities carried out by the site monitors, including tracking site visit assignments, assigning monitors, developing and maintaining site visit schedules, resolving scheduling conflicts, ensuring completion of appropriate pre-site visit activities and correspondence, and assisting in the assessment of the performance of site monitors and the quality of site monitoring activities carried out.

3. IT Manager with the training, experience and capabilities to ensure appropriate adherence to FIMSA policy and regulations.

Note: Key personnel shall not be consultants. Offerors should indicate the total FTEs assigned to the project and specify the FTE distribution for each task outlined in the Statement of Work. Provide a Personnel Ranking Matrix which indicates the hierarchical line of supervisory authority, and indicate which Contractor position(s) will perform the various tasks.

D. QUALITY ASSURANCE/QUALITY CONTROL PLAN

1. Develop and implement a Quality Assurance/Quality Control (QA/QC) Plan designed to: (i) standardize contract processes; (ii) ensure that the conduct of all contract activities complies with domestic and country-specific regulations governing human subjects research, GCP and ICH guidelines, and NCCAM policies and procedures; and (iii) provide for the assessment of Contractor performance and the quality of clinical site monitoring activities conducted. Specifically, the Contractor shall:

    a. Within six (6) weeks of the contract effective date, develop and submit, for COTR review and approval, a Draft QA/QC Plan detailing the following:

        (1) Standard processes to be used to ensure internal QA/QC with respect to the timeliness, accuracy and completeness of the clinical site monitoring activities performed

        (2) Measures/metrics to be used to assess performance and the quality of clinical site monitoring activities

        (3) Approaches/methods to document and address problems and deficiencies identified, including improvements in the internal QA/QC Plan

        (4) Plans for training of Contractor staff on standard processes and measures used for internal QA/QC COTR comments on the Draft QA/QC Plan will be provided within eight (8) weeks of receipt, and the Final QA/QC Plan shall be submitted within four (4) weeks of receipt of COTR comments.

    b. Provide quarterly reports on the results of internal QA/QC to the CO and COTR, including all deficiencies and problems identified, recommended approaches/actions to be taken to correct deficiencies and resolve problems, and any recommended modifications to the QA/QC Plan. All QA/QC Plan modifications must be approved by the COTR prior to implementation.

    b. Any major QA/QC deficiencies/problems (e.g., lack of training as provided for in the approved Training Plan, late submission of clinical site monitoring visit reports, inadequate technical knowledge of the Federal and/or country-specific regulations, etc.), as defined in approved SOPs, shall be reported to the COTR within 24 hours of identification and shall include Contractor recommendations for resolution. A brief report on the implementation of COTR-approved resolution actions shall also be submitted within time frames to be specified in the approved QA/QC Plan.

2. The COTR may authorize, at any time during the contract period of performance, independent audits, including: (i) review of both routine and specialized visits at clinical sites; (ii) review of Contractor processes, procedures and operations at the central office; and (iii) review of processes, procedures and operations at regional domestic and foreign offices. The COTR will notify the Contractor of plans for independent audits two (2) weeks in advance of the scheduled audit. For audits conducted at Contractor facilities, the Contractor shall ensure that appropriate staff and all necessary information/documentation are available. For cause audits may be performed at any time and without advance notice to the Contractor in instances of suspected non-performance and/or non-compliance with Federal and/or country-specific regulatory requirements.

F. PROJECT MANAGEMENT

1. Overall Project Management

a. Provide for the overall management, integration and coordination of all contract activities, including the management and coordination of activities carried out in collaboration with other NCCAM contractors and grantees and the management of functions and activities carried out by subcontractors. This shall include the development, implementation and updating, as necessary, of an **Integrated Master Project Plan (IMPP)** consisting of the following components:

(1) *Management Structure*: The management structure for the entire project, including: (i) a description of the roles and responsibilities of Contractor and subcontractor staff; (ii) delineation of lines of authority; and (iii) plans for achieving appropriate and ongoing communications among project staff. This component of the Integrated Master Project Plan shall be submitted in draft form, for COTR review and approval, within four (4) weeks of the contract effective date, revised in accordance with COTR comments, and submitted in final form within eight (8) weeks of the contract effective date.

(2) *Site Monitoring Services Distribution:* Plan delineating the proposed number and location of site monitors, domestically and internationally, and the rationale for the establishment of both U.S. and foreign regional and/or local field offices based on expected cost and performance efficiencies to be achieved. This component of the Integrated Master Project Plan shall be submitted in draft form, for COTR review and approval, within four (4) weeks of the contract effective date, revised in accordance with COTR comments, and submitted in final form within eight (8) weeks of the contract effective date.

(3) *Project Implementation and Management*: Plans for implementing and managing all contract activities and assessing the efficiency of internal project management procedures, including: (i) internal timelines for planning and implementing contract assignments and metrics to be used to assess efficiency and timeliness with respect assignment planning and implementation; (ii) personnel and other resources required; (iii) methods to assess the adequacy of the resources devoted to the contract and for determining the need to reduce or expand contract resources as necessary to

accommodate workload; (iv) the overall monitoring strategy for the efficient scheduling and completion of clinical site monitoring visits (e.g., bundling visits in geographic areas); (v) identification of project risks and risk management and mitigation strategies to address issues such as staff turnover, workload and scheduling problems; (vi) plans for initial and ongoing training of technical and administrative staff on the plans, procedures and timelines provided for in the Integrated Master Project Plan; and (vii) procedures to ensure that all Contractor and subcontractor staff safeguard intellectual property, the confidentiality of human subjects and other data, and other information provided by third parties or by the Government, as well as data generated through this contract. This component of the Integrated Master Project Plan shall be submitted in draft form, for COTR review and approval, within eight (8) weeks of the contract effective date, revised in accordance with COTR comments, and submitted in final form no later than three (3) months from the contract effective date.

(4) *Annual Integrated Master Project Plan Review:* The approved Integrated Master Project Plan shall be reviewed on an annual basis and recommendations for modifications shall be provided to the COTR, including the incorporation of additional domestic and/or foreign regional and local field offices, the discontinuation of established domestic and/or foreign regional and local field offices, and any proposed changes in the number or location of monitors.

At the time of the annual IMPP review the Contractor shall be responsible for:

a. Developing and submitting the agenda for COTR review and approval no later than four (4) weeks prior to the date of the meeting
b. Developing additional materials and data pertinent to the review of contract progress, performance, efficiency and resource utilization
c. Distributing agendas and additional materials to meeting participants no later than seven (7) calendar days in advance of the meeting date
d. Developing oral presentation materials
e. Making logistical arrangements for all participants for meetings conducted at the Contractor's central office
f. Preparing and submitting Review Meeting Reports, for COTR and Contracting Officer review and approval, within four (4) weeks of completion of each meeting

b. Provide a Technical and Administrative Infrastructure to ensure the efficient planning, initiation, implementation, coordination, management and timely completion of all projects carried out under this contract and effective communications with the COTR and the Contracting Officer. This infrastructure shall include:

(1) A Program Director with responsibility for overall project management and communications, tracking, monitoring and reporting on project status and progress, and recommending modifications to project requirements, timelines, and procedures, including work undertaken by subcontractors.

(2) A Senior Project Manager with responsibility for overseeing the daily operations of the contract, tracking assignments, ensuring adherence to internal policies and procedures and NCCAM established timelines, and reporting on and, in collaboration with the Program Director, resolving deficiencies and problems.

(3) Administrative personnel with responsibility for financial management and financial reporting on all activities conducted by the Contractor and subcontractors.

2. Meetings and Teleconferences

a. Contract Initiation Meeting

Within four (4) weeks of the effective date of the contract, participate in a one-day Contract Initiation Meeting with the COTR, the Contracting Officer, other NCCAM staff designated by the COTR, the Program Director, the Lead Site Monitor and the Senior Project Manager, to be held at the Contractor's site. The purpose of the Contract Initiation Meeting shall be to orient the Contractor to NCCAM contract procedures, discuss Initial Transition plans, if appropriate, review the status of site monitors on staff and recruitment efforts to hire 100% of monitors within specified timelines, and review current and upcoming clinical site monitoring assignments.

b. Monthly Contract Progress Review Meetings/Teleconferences

Plan and conduct Contract Progress Review Meetings or Teleconferences, at a minimum of monthly intervals, to review: (i) the status of ongoing and future clinical site monitoring assignments; (ii) any issues pertaining to contract staffing and turnover, workload and scheduling; (iii) any significant findings resulting from clinical site monitoring visits conducted over the preceding month and the status of their resolution; (iv) upcoming clinical site monitoring assignments; and (v) project management procedures and assessment of the efficiency and quality of the clinical site monitoring activities conducted.

Monthly Contract Progress Meetings/Teleconferences shall include the Contract Program Director and Senior Project Manager, the COTR, other NCCAM staff as necessary and as designated by the COTR, and the Contracting Officer as necessary to discuss contractual matters. The meeting/teleconference schedule will be established by the COTR post-award. The Contractor shall be responsible for preparing and distributing agendas and other meeting/teleconference materials within seven (7) calendar days of the meeting date, and for preparing and distributing to participants written summaries of all action items and decisions resulting from these meetings/teleconferences within seven (7) calendar days of meeting/teleconference completion.

c. Additional Meetings and Teleconferences At the request of the COTR, the Contractor shall arrange teleconferences and/or meetings with the COTR to discuss specific clinical site monitoring assignments, including recently completed and upcoming clinical site monitoring visits. For each such meeting/teleconference, the Contractor shall be responsible for preparing and distributing the

agenda and other materials, including site visit reports and recommendations for improvements or corrective actions. The Contractor shall also prepare brief summaries of the major decisions and action items resulting from these meetings and teleconference and submit to the COTR within seven (7) calendar days of meeting/teleconference completion.

3. Additional Reports

At the request of the COTR, the Contractor shall prepare and submit the following ad hoc reports including, but not limited to:

a. *Quarterly List of Site Monitoring Special Assignments* – providing an inventory of all forthcoming special assignments requested
b. *Bi-monthly Institutional Review Board (IRB) Lapse of Review Report* - providing an inventory of all lapses of IRB review with regard to lack of compliance to GCP guidelines
c. *Quarterly Co-monitoring Requests Report* - providing an inventory of all quarterly site monitoring assignments with 2 monitors designated for the assignment

G. OTHER TECHNICAL AND ADMINISTRATIVE SUPPORT

1. Coordinate and provide technical and administrative support for the activities of the NCCAM-established Clinical Studies oversight entities, including Data and Safety Monitoring Boards (DSMBs) Meetings, Steering Committee Meetings, and designated NCCAM Investigator Meetings. This shall include:

a. Schedule, arrange transportation and lodging, and meeting room facilities, and arrange teleconferencing services for:

(1) three face-to-face meetings per year in the Washington DC Metro area;
(2) five telephone conference call meetings for NCCAM safety oversight structures;
(3) periodic teleconferences for NCCAM-funded investigators and NCCAM staff.

b. Independently prepare, or assist in the preparation of, and distribute a variety of materials for meetings and teleconferences. This shall include:

(1) proposed Concept Proposals for clinical trials, clinical studies and primary and ancillary mechanistic studies;
(2) detailed draft protocols for all such clinical trials and clinical studies;
(3) proposals for modifications in the design of all such clinical trials and clinical studies;
(4) status of and issues surrounding FDA approval of INDs or IDEs;
(5) status reports on the implementation of approved clinical studies, including accrual, retention, loss to follow-up, and problems and issues with respect to data management and quality assurance.

c. At the discretion of the COTR, provide the following training to NCCAM staff and investigators specified by NCCAM including but not limited to: Good Clinical Practice guidelines (GCP), Informed Consent process, or other clinical studies-related training.

d. Prepare brief summaries of all decisions, recommendations and action items resulting from meetings and teleconferences within three (3) business days of meeting/teleconference completion, and distribute to the COTR, other NCCAM staff, and meeting participants.

e. Assist the COTR, NCCAM staff and investigators specified by NCCAM, in the preparation, review and revision of study-related documents and materials, including but not limited to:

a. Manuals of Procedures (MOPs) with specific instructions, requirements and guidelines for study conduct, including the clinical protocol, study forms, procedures for the collection, testing, storage and shipping of patient samples, and procedures for data collection, entry, verification and storage;
b. Investigator Brochures (IBs) as described in 21 CFR 312.23 (a) (5), (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr= 312.23) using results of pre-clinical and clinical testing from reports, reprints and other data available from investigators;
c. electronic or paper Case Report Forms (CRFs) and worksheets;
d. informed consent forms;
e. source documents, questionnaires, memory aids and subject instructions;
f. screening and recruitment logs; and
g. investigational product accountability logs.

H. INITIAL AND FINAL TRANSITIONS

1. Initial Transition

In the event of a new contractor, the Contractor shall ensure the orderly, efficient and safe transition of all contract activities and materials three (3) months prior to the new contract effective date. This shall include the following Initial Transition activities and plans:

a. Within fourteen (14) calendar days of the contract effective date, develop and submit, for COTR review and approval, a Draft Initial Transition Plan to ensure full assumption of all contract responsibilities and functions no later than three (3) months following the contract effective date. The Draft Initial Transition Plan shall delineate the transition activities to be undertaken, timelines for the completion of each transition activity, and the staff to be assigned. Revise the Draft Initial Transition Plan to accommodate COTR comments, and submit the Final Initial Transition Plan no later than six (6) weeks after receipt of COTR comments.

b. Develop materials for and conduct orientation briefings for contract technical and administrative staff within six (6) weeks of the contract effective date. Work with the COTR to incorporate into these orientation briefings information on NCCAM policies and procedures.

c. Participate in a series of joint meetings with the incumbent contractor, the COTR and his/her designees to: (i) review the status of existing clinical site monitoring assignments to be completed, including scheduled site visits to be conducted; (ii) review clinical site monitoring

assignments for the first quarter of the contract period of performance; (iii) discuss overall performance of the clinical sites monitored to date, as well as site-specific deviations, deficiencies and problems identified over the past year, NCCAM-approved corrective/remedial actions, and the status of implementation of all NCCAM-approved corrective/remedial actions; and (iv) document process changes with respect to planning and implementing clinical site monitoring assignments, developing performance measures and assessing the quality of clinical site monitoring activities conducted, contract staffing and turnover, and other project management issues.

d. Contract materials and plans currently in use by the incumbent contractor shall be provided to the Contractor within fourteen (14) calendar days of the effective date of the contract. This includes: SOPs, project management and staffing plan, QA/QC plan, training plan, and overall monitoring strategy. Site monitoring visit reports and other monitoring materials shall be available to the Contractor via a method proposed by the contractor and approved by the COTR.

2. Final Transition

The Contractor shall develop and implement a Final Transition Plan to ensure the orderly, efficient and safe transition of all contract activities and materials. This shall include the following:

a. Within six (6) months of the completion date of the contract, develop and submit, for COTR review and approval, a Draft Final Transition Plan delineating the transition activities to be undertaken, timelines for the completion of each transition activity, and the staff to be assigned. The Draft Final Transition Plan shall include a listing of and plans for transferring contract-generated materials, e.g., SOPs, training plan, QA/QC plan, and methods proposed to plan and conduct thorough briefings on the status of current and future assignments, overall assessment of the performance for clinical sites monitored, and site-specific deviations, deficiencies and problems and the status of their resolution. Revise the Draft Final Transition Plan to accommodate COTR comments, and submit the Final Transition Plan no later than four (4) months prior to the completion date of the contract.

b. Implement the approved Final Transition Plan to ensure the completion of all transition activities and the transfer of contract RFP- generated materials to a new contractor by the completion date of the contract.

c. Maintain contract operations at full staffing levels during the Final Transition period.

I. Section 508 Compliance Requirements

All products and deliverables associated with the tasks described within this Statement of Work that are intended for distribution via the Internet or have the potential for access through the Internet must be complain with requirements specified in Section 508 of the Federal Rehabilitation Act, as amended in 1998. This Act addresses any/all electronic and information technology (EIT). As such, those procured through this effort must meet the applicable accessibility standards at 36 CFR 1194. 36 CFR 1194

implements Section 508 of the Rehabilitation Act of 1973, as amended, and is viewable at http://www.section508.gov. The Contractor is responsible for reviewing this regulation which can also be reviewed on http://www.access-board.gov/sec508/guide/act.htm.

The following Section 508 standards may apply to this project:

TBD

[END OF STATEMENT OF WORK FOR BASE PERIOD and Option Years, if exercised.]

3. OPTIONS

In addition to the above functions and services to be provided for the Period of Performance for each year of the contract, Options to increase the level of effort may be exercised at the discretion of the Government. These Options are defined as follows:

OPTIONS FOR ADDITIONAL CLINICAL SITE AND STUDY MONITORING

A. TECHNICAL REQUIREMENTS: Under these Options, the Contractor shall plan for, staff and carry out all clinical site and study monitoring functions, as specified above, for selected phase 0, phase 1, and phase 2 clinical studies.

The Contractor shall perform additional on-site monitoring visits if this option is exercised. This Option may be exercised multiple times within a given contract year should the need arise. The option will be exercised no later than six months after the effective date base contract period of performance or successive option period, if exercised. The monitoring visits exercised during the period of performance must be completed by the expiration date of that same period of performance.

1. This option may be exercised in increments of ten (10) monitoring visits above a base of 25-35 monitoring visits per year as part of the contract with a maximum of one (1) increment (10 total additional monitoring visits) for each of years 2012-2015. The expansion of the number of monitoring visits per year may be initiated to accommodate a larger number of studies as directed by the COTR.

2. The Contractor shall follow the requirements as outlined in section 2.A “Technical Requirements” items 1, 2, and 3 of the Statement of Work in conducting the site monitoring visits.

If the NCCAM/NCI elects to exercise any of these Options, the Contractor
Shall develop the following plans:

1. Draft Option Implementation Plan: Within six (6) weeks of the exercise of an Option, develop and submit, for COTR and Contracting Officer review, a Draft Option Implementation Plan consisting of the following:

a. Staffing plans to include the following positions and the percent effort for each: (i) the total number of site monitors required; (ii) the names and geographic locations of site monitors currently employed by the Contractor and proposed to perform clinical site and study monitoring functions for each Option; (iii) the number of additional site monitors that may be required and proposed plans and timelines for advertising, recruitment, hiring and training of additional site monitors, or for the provision of services through subcontracts/consultants; (iv) provisions for a Lead Site Monitor to coordinate performance of all clinical site and study monitoring functions, including assignment of the Lead Site Monitor for the Base Period, assignment of another member of the Contractor staff to serve as Lead Site Monitor, or proposed plans to hire an additional staff member to perform this role; and (v) the names and roles of other Contractor technical and administrative staff to be assigned to the project, identification of any additional technical and administrative staff positions needed, and plans and timelines for advertising, recruitment, hiring, and training of any additional technical and administrative staff.

b. Plan for the management, oversight and coordination of Option clinical site and study monitoring functions to include: (i) an organizational chart showing all proposed personnel/positions; (ii) a description of roles and responsibilities; (iii) an administrative framework showing clear lines of authority and responsibility for monitoring and assessing performance, adherence to established policies, procedures and regulatory requirements and guidelines, and adherence to established timelines for all required functions.

c. A discussion of any anticipated changes to existing SOPs or development of new SOPs that may be necessary, any anticipated problems relating to expanding clinical site and study monitoring services, and recommendations for problem resolution/mitigation.

d. Identification and description of any additional facilities, including establishment of new local/regional offices, equipment and other resources required.

e. A proposed timeline for completion of all hiring, training, and any additional start-up activities necessary.

2. Final Option Implementation Plan: The COTR and the Contracting Officer will review and provide comments on the Draft Option Implementation Plan within four (4) weeks of receipt. The Contractor shall revise the Draft Option Implementation Plan to address comments and modifications received, and submit the Final Option Implementation Plan within three (3) weeks of receipt of comments.

[END OF STATEMENT OF WORK FOR OPTIONS]