

BACKGROUND INFORMATION/STATEMENT OF WORK

A. Background Information

The primary mission of the Nutritional Epidemiology Branch (NEB) is conducting a high-impact research program that clarifies the role of nutrition in causing and preventing human cancer. The objective of this proposed contract is to provide scientific services in support of this research program.

The belief that nutrition plays an important role in the etiology of cancer is long-standing and widely held. Although many nutrition effects on cancer are likely to be modest, with at most a doubling or halving of risk for those at the highest, compared to lowest, categories of exposure, given the many people who fall into such high- and low-exposure categories, even small relative risks translate into substantial cancer morbidity and mortality. Nevertheless, considerable uncertainty (not to speak of controversy) continues to characterize the nutrition-cancer field. NEB scientists are working to resolve this uncertainty and the proposed Support Services Contract (SSC) is intended to support this effort.

Two areas of emphasis within NEB's research program are especially pertinent to the support services contract:

- *Methodologic research in nutritional assessment.* Scientists in the nutrition and cancer field have become increasingly concerned that traditional epidemiologic assessment methods for diet, body size, and physical activity assessment suffer from substantial measurement error, which limits our ability to detect important but modest relative risks. NEB is internationally recognized as a leader in methodologic research aimed at evaluating existing assessment instruments as well as developing new, more accurate tools for incorporation into ongoing and future studies. The assessment tools resulting from this work are available to and benefit investigators world-wide.
- *Prospective studies.* Given the potential for recall and selection biases in case-control studies and the development in the Division of Cancer Epidemiology and Genetics (DCEG) of prospective cohort studies with a relatively wide dietary intake range, we emphasize prospective investigations of nutrition and cancer. Because of the large size of the Branch's and the Division's cohorts, as well as the emerging opportunities for consortia and data pooling, NEB has been able to undertake detailed examinations of both exposure interactions and end point heterogeneity and thereby make valuable contributions to our understanding of nutrition in relation to overall mortality and several major malignancies. In addition, the Branch has been able to carry out prospective investigations of even less frequently occurring cancers (pancreas, ovary, NHL, and esophagus, for example).

Specific studies supported by this current contract are listed below. Additionally, Table 1 summarizes the study-specific activities.

Navy Adenoma Study

A hospital-based case-control study of colorectal adenomas at the National Naval Medical Center, Bethesda, Maryland was conducted under an earlier support services contract in the Hormonal and Reproductive Epidemiology Branch and continues to be an important resource. Validation of the meat-cooking module as well as biomarker development work in this study has continued under the NEB SSC. One hundred and sixty five healthy volunteers enrolled in the study and completed a 24-hour recall and a food frequency questionnaire (FFQ) including detailed questions on meat-cooking practices. Subjects kept food diaries for 12 days over a 3-month period and recorded how they cooked meat, including its appearance inside and outside. Development of coding for the meat-cooking component of the 24-hour recalls/food-diaries and data entry was conducted by the Contractor. In addition, this study has been utilized as a resource for biomarker development, as detailed below.

NIH-AARP Diet and Health Study

The prospective NIH-AARP Diet and Health Study cohort consists of 566,407 AARP members aged 50-71 originally from eight states (California, Florida, Georgia, Louisiana, Michigan, New Jersey, North Carolina, and Pennsylvania) who satisfactorily completed a food frequency questionnaire (the NCI Diet History Questionnaire [DHQ]) in 1995-96. This is the largest in-depth epidemiologic study of nutrition and cancer ever conducted. A second questionnaire completed by approximately 2/3 of the cohort about 6 months after the baseline instrument provided more detailed information on physical activity, medications and screening experience, family history, meat cooking practices, and earlier life diet and body size.

The study uses state cancer registries to ascertain end points. A validation substudy showed that the registry matching process, designed and implemented by the Contractor, identified approximately 90% of cancers. A second round of cancer registry linkages is currently being carried out and will be completed by early 2007. Mortality end points are ascertained through the Social Security Administration Master Death File and NDI+. The number of incident cancers through the end of 2000 can be found in the Appendix.

The very large size of AARP confers some distinctive advantages, including the ability to investigate prospectively: relatively rare cancers (esophageal, pancreatic, ovarian cancers; lymphoma); a number of potentially biologically important interactions (e.g., energy balance and dietary factors in relation to female malignancies among menopausal hormone users and nonusers); nutritional factors in relation to cancer subtypes, defined on the basis of, e.g., histology (adenocarcinoma vs. esophageal squamous cell carcinoma, stage (localized vs. advanced/fatal prostate cancer, and certain molecular characteristics (e.g., hormone receptor status); nutrition-cancer relations, at least for some cancers, among racial-ethnic subgroups. Participants have a wide intake range: e.g., over 10% of the more than a half million participants report more than 40%, and 10% less than 20%, calories from fat. The incorporation of the more refined meat assessment module into a subcohort of 340,000 permits some especially pertinent analyses. The very large calibration study (the largest in any cohort that entails two administrations of a reference instrument) permits measurement error adjustment; the participation of world-class statisticians working in nutritional epidemiology allows for particularly rigorous analyses and reports. The use of cancer-registries is extremely cost-

effective and is yielding 90% of cancer cases. Finally, the close collaboration with AARP, with its extensive membership infrastructure, permits novel future investigations, such as the incorporation of the multiple 24-hour recalls (in conjunction with other internet-based questionnaires) into the current cohort and potentially, with relatively little added expense, a new wave of AARP members.

Over the last year, in response to the site visit and BSC recommendations, the study has greatly strengthened its oversight, management, cohort maintenance activities, and scientific output. An External Working Group is in place and meets twice a year. The NCI Steering Committee has been expanded to include three senior DCEG epidemiologists. A program analyst has assumed full-time study coordination duties within the Branch. A tenure-track investigator with extensive cohort experience has been made co-PI of the study, with responsibilities for overseeing analysis and scientific productivity. Collaborative relations with AARP have been strengthened (through regular meetings and especially by the emerging study output). Collaborations with universities (e.g., Harvard) and other government agencies (e.g., NIEHS, NIA) have been developed and are expanding. Finally, a steady stream of manuscripts has emerged from the study, with many more in preparation. The analysis and manuscript production involves investigators throughout DCEG and NCI.

A separate contract was established in 1994 through 2003 with a contractor, which served as the coordinating center for the AARP study. Several activities integral to the study were carried out under the SSC during this time. In addition, with the expiration of the original contract, most of the cohort maintenance and other support activities have been carried out under the SSC. Tasks carried out under the SSC included:

- Cohort maintenance and tracing
 - Address updating based on
 - National Change of Address program (NCOA)
 - results of follow-up questionnaire mailing
 - linkage with AARP mailing list
 - email, phone calls, or written correspondence from participants
 - Ad hoc analyses and reports on field work progress
- End point ascertainment
 - Acquisition and maintenance of IRB approvals from each of the original 8 state cancer registries
 - Linkages to the eight state cancer registries through the end of 2000
 - NDI+ through the end of 2001
 - IRB approvals from 3 additional states (Arizona, Nevada, Texas) for possible linkage to areas where AARP members may have moved
 - Acquisition of hormone receptor status data
 - Preparation of manuscript on the Contractor registry linking method
- Preparation of new OMB package for future pilot studies and potential assessment with new automated, internet-based 24-hour recall (ASA-24)
- Liaison activities for ongoing collaborations
 - With Harvard, study of risk factors for Amyotrophic Lateral Sclerosis (ALS)
 - With NIEHS, study of risk factors for Parkinson's disease and ALS
- Design and mailing of newsletter (in conjunction with the Office of Cancer Communications)
- Design of follow-up questionnaire
- Linkage with new AARP-based commercial sociodemographic data base
- Preparation of new newsletter for Fall 2006
- Preparation of materials for External Working Group meetings

Meat Studies

Meat research is a major concentration within NEB (Cross 2004) and the Contractor has been involved in three key areas of this work: meat questionnaire and data base development, biomarker development, and support services for Branch collaborative research.

Questionnaire and data base development. A high proportion of meats consumed in the US and Europe is processed or preserved. Much of the data on processed and preserved meats is obtained from a limited number of questions normally included in the FFQs. Moreover, the combination of foods in any particular line-item within the FFQ is not driven by the way the meats are preserved, which makes it difficult to investigate potential mechanisms.

The Contractor used a national food intake survey to identify representative processed meats consumed in the US. Using the frequency of consumption data from this survey, the Contractor developed 17 main questions and 22 sub-questions for the new comprehensive Meat Module and carried out cognitive testing for the new instrument. Questions on fish consumption were also included in the questionnaire. Contractor staff developed a meat picture card insert of meats cooked to different degree of doneness to be used in

conjunction with the Meat Module; in some cases, they had to have meats cooked and photographed.

A Windows-based data base, known as CHARRED (the Computerized Heterocyclic Amines Resource for Research in Epidemiology of Disease) (www.charred.cancer.gov), containing information on heterocyclic amines, polycyclic aromatic hydrocarbons and total mutagenic activity was created by NCI investigators. In providing support for further development of this data base, the meat samples previously prepared were re-examined to include additional components such as heme, inorganic iron, and nitrogenous compounds. In addition to preparing the meat samples, the Contractor performed linkages with the USDA data base, worked with an extramural university to finalize the processing protocol, coordinated shipping and tracking of specimens, and investigated laboratories for measuring nitrite, nitrate and *N*-nitroso compounds. This work demonstrated that combining many of the meats (e.g., ham, bologna, salami and other lunch meats) into one line-item, as is typically done in FFQs, may lead to substantial misclassification in nitrate and nitrite intake.

Biomarker development. To evaluate possible markers of meat intake, urine samples from controlled meat feeding studies were analyzed for carnitine, creatinine, creatine, 1-methylhistidine, 3-methylhistidine, taurine, and nitrogen. The Contractor developed the protocol and collected urine samples for quality control, identified an appropriate laboratory for analysis, prepared the IRB exemption package, and conducted a small pilot study; a manuscript summarizing the findings is in preparation.

Although the results for creatine, creatinine, carnitine, and taurine were distinct across the low, medium, and high meat intake diets in terms of mean levels for each diet, there was substantial dose-response variation across individuals. The findings for urinary concentrations of 1- and 3-methyl-histidine were more promising: not only did the mean values clearly distinguish between the three doses of meat in the diet, but the individual values were distinct for each diet. These findings are now being extended to the urine samples collected in the Navy Adenoma Study.

Support of Branch collaborative research. The Contractor provided materials to extramural investigators at several universities and the American Cancer Society, including printing scannable and PDF versions of the Meat Module and meat picture card, a Spanish translation of the meat picture card, and results from analyses of meat consumption in NHANES. The Contractor recently initiated a feasibility study of using the Meat Module in the AARP study.

India Health Study

To assess whether a prospective cohort study of dietary, lifestyle, environmental, and genetic factors is feasible in India, a multicenter pilot study in Delhi, Mumbai, and Trivandrum has been initiated. The pilot study consists of three parts: 1) evaluation of the socio-demographic characteristics of the proposed study populations and logistical issues involved in conducting a large-scale study; 2) characterization of the composition and variability of the diet, including accuracy of assessment, and 3) evaluation of issues related to follow-up and end-point

ascertainment. Nutritional and disease markers will be measured in the blood, urine and toe nail samples.

Contractor support has been critical to the overall planning and initiation of the study. The Contractor has been able to execute subcontracts and reimburse subcontractors more quickly than government, which has been invaluable in fostering collaboration with our Indian colleagues.

Specifically, the Contractor has supported the development of materials for the implementation of study procedures and protocols, and has assisted in the training of staff in India for this feasibility study of dietary patterns and health and cancer outcomes. The Contractor has advised NCI of the proper procedures for study approval with regard to OMB clearance, ICMR clearance in India, and developed material for the various IRBs. The Contractor has also participated in numerous meetings and conference calls with study collaborators including Capital Technology Information Services, Inc. (CTIS), Information Management Services (IMS), and the Indian site investigators. The Contractor worked with NCI in developing specimen collection procedures and provided NCI with additional information from procedure manuals from other studies regarding specimen collection. The Contractor has worked directly with field site investigators in India to determine the study needs and develop a budget for each field site. The Contractor staff traveled to India with one of the NCI investigators to conduct a site visit in May 2006. All the on-site work is being carried out through subcontracts with the Contractor. Finally, the Contractor was responsible for coordinating a 2003 conference which involved NCI staff, Indian investigators, and international experts on the Steering Committee.

OPEN

OPEN (Observing Protein and Energy Nutrition) was a cross-Divisional study funded by DCEG and the Division of Cancer Control and Population Sciences (DCCPS). The study was initially funded with a stand-alone contract; funds were shared with DCCPS. Several tasks beyond the budget and scope of this initial contract mainly the ReOPEN work) were carried out under the SSC.

The OPEN study was designed to compare two dietary report instruments, the FFQ and 24-hour recall, with two 'recovery' biomarkers: doubly labeled water (DLW) for total energy intake and urinary nitrogen (UN) for protein intake (Subar 2003). The study was conducted in a representative sample of 486 participants (half men, half women) age 40-69 from the Washington, D.C. metropolitan area. Recruitment was surprisingly successful: approximately 75% of those contacted agreed to participate and all but two participants completed the study. Initial study components included two repeat applications of an FFQ, two 24-hour recalls, two 24-hour urine collections (with administration of para-amino benzoic acid to monitor completeness of collection), the DLW procedure, fasting blood specimens, height and weight measurement at the beginning and end of the DLW procedure, a physical activity questionnaire, and a supplemental questionnaire (providing information on correlates of misreporting).

OPEN showed that relative risks would be severely attenuated (relative risk of 2.0

becomes 1.0-1.1) if based on absolute intake reported on the FFQ. The OPEN data also showed, for the first time, that energy adjustment reduces attenuation due to measurement error in the FFQ, although the attenuation is still considerable (RR of 2.0 becomes 1.2-1.3). OPEN provides direct evidence that multiple 24-hour recalls will perform more accurately as a primary assessment tool than a FFQ. However, 24-hour recalls may not be a valid reference instrument to evaluate the accuracy of a FFQ and adjust observed relative risks for measurement error. For example, as compared to biomarkers, 24-hour recalls underestimate attenuation by 60% for energy-adjusted protein intake. OPEN also engendered several ancillary studies.

REOPEN is a recent extension of OPEN that evaluates performance of a four-day food record (4DFR), a 7-day Daily Food List ('checklist'--an instrument that records the number of times a limited number of food categories are consumed), and another FFQ among the original members of OPEN. Support for the study was provided by the SSC and with funds provided by DCCPS. Although assumptions need to be made about the relevance of the original DLW data to current energy expenditure--current weight and physical activity measured by questionnaire are available--this study will provide useful information about accuracy of the 4DFR and the combined FFQ plus checklist.

CONCeRN

The CONCeRN (COlorectal Neoplasia screening with Colonoscopy in asymptomatic women at *Regional Navy/army* medical centers) study is a multi-center screening study initially designed to quantify the relative benefits of colonoscopy as compared to sigmoidoscopy as a modality for colorectal cancer screening. NEB added an etiologic component to the study for the investigation of several hypotheses relating diet, genetic susceptibility and other risk factors for colorectal neoplasia, as well as the creation of a blood and tissue repository for future analyses. There were approximately 1,400 women enrolled in the main clinical study and 900 of these in the etiologic sub-study; those in the sub-study also returned a self-administered FFQ (the NCI-DHQ) to assess usual dietary intake in the previous year and a more-detailed general risk factor questionnaire. During the colonoscopy, three pairs of pinch-biopsies of apparently-normal tissue were taken and all polyps were removed, with their size and location recorded.

The questionnaires were developed, produced, distributed and collected using the Support Services Contract and then processed and coded to form a working dataset. Continued support included management of sub-studies and the initial coordination of the addition of CONCeRN to the Arizona Cancer Center pooling project.

The main findings from the CONCeRN study showed that sigmoidoscopy would miss a substantial proportion of advanced neoplasms in the proximal colon, suggesting colonoscopy as the preferred method of screening for colorectal cancer in women. In addition, CONCeRN has fostered substudies of insulin-like growth factors, one carbon metabolism, including analyses of tissue level folate and DNA markers of methylation, and specific dietary components, such as meat.

Agricultural Health Study (AHS) – Administration of DHQ

The AHS explores potential causes of cancer and other diseases among farmers and their families and among commercial pesticide applicators. A collaborative effort involving NCI, the National Institute of Environmental Health Sciences (NIEHS), and the U.S. Environmental Protection Agency (EPA), the AHS began in 1994 in North Carolina and Iowa and continued to gather information about the health of pesticide applicators and their families, details on occupational practices, and information on lifestyle and diet on a periodic basis. The cohort includes 89,658 private pesticide applicators, spouses of private applicators, and commercial pesticide applicators recruited within Iowa and North Carolina. Cancer incidence and mortality data are obtained from the Iowa and North Carolina cancer registries; mortality is also ascertained through NDI.

Phase I, initial cohort recruitment, began in 1993 and concluded in 1997. Phase II follow-up began in 1999 and concluded in 2003. Phase I included a limited diet and supplement use assessment; Phase II included a mailed FFQ (the NCI DHQ), with a detailed evaluation of meat-cooking practices.

The Contractor has been responsible for carrying out the Phase II dietary assessment. Through December, 2005, approximately 35,000 FFQs were collected. Among those completing this instrument, the incidence yield was 344 breast, 155 colon, and 544 prostate cancers. Analyses of meat cooking practices from Phase I for prostate cancer are ongoing and will be compared to data from Phase II FFQ. Over the next several years, with longer follow-up and aging of the population, the number of cancers accrued will increase substantially, making this a useful resource for the Division. We are using dietary variables as potential confounders in ongoing studies in the AHS.

Support for Development of an Automated, Internet-Based 24-Hour Recall

ASA-24 is an automated, self-administered, internet-based 24-hour dietary recall that is being developed at NCI. Primary funding has been through a contract awarded by DCCPS with a contractor; additional support was provided by NEB to advance the work before the DCCPS was operative. Tasks carried out by the Contractor as part of this developmental effort include data base review, and input, and cognitive testing. Evidence from OPEN and other studies suggests that multiple 24-hour recalls will achieve greater assessment accuracy than the traditional FFQ, but incorporation of multiple recalls into large prospective studies has been prohibitively expensive. The new internet-based instrument could be administered several times over a year with minimal expense and has the potential to qualitatively improve dietary assessment in epidemiologic studies.

Glycemic Index/Load Estimation

The SSC supported work that was vital in the development of a systematic method for deriving an individual's glycemic index (GI) and glycemic load (GL) values from completed FFQs in several DCEG prospective studies, including the Polyp Prevention Trial (PPT), PLCO, BCDDP, and AARP studies. This work has now been reported (Flood 2006) and the method has been made available on the DCEG intranet site. A recent publication from PLCO reported that GI and GL were not directly related to colorectal adenoma risk (Flood, in press).

Table 1: Specific Contract-Supported Activities Under Current Contract

STUDY	Support Activities									
	A	B	C	D	E	F	G	H	I	J
Navy Adenoma Study									X	
NIH-AARP Diet and Health	X	X	X	X	X	X	X	X	X	X
Meat: Questionnaire Development		X	X	X		X				
Meat: Biomarker Development	X		X		X		X			
India Health Study	X	X	X	X					X	
OPEN	X	X	X		X			X	X	X
Concern	X			X	X	X				
Agricultural Health Study		X			X			X		
ASA-24 (automated 24-hour recall)	X	X	X	X	X	X		X	X	

- A: Field supervision or project management
- B: Form development
- C: Study participant selection
- D: Interviewer/abstractor/measurer training
- E: Interviewing or form administration
- F: Record abstraction and coding
- G: Biologic specimen collection/processing
- H: Data processing
- I: Quality control
- J: Tracing and follow-up

The new contract is intended to provide resources, expertise, and administrative flexibility to enable the Nutrition Epidemiology Branch (NEB) investigators to make headway in understanding the nutritional causes of malignant disease. NEB seeks to establish a contract with an organization highly experienced in providing technical support services for both methodologic and substantive research projects in the nutritional epidemiology of cancer. Activities to be performed under the contract include designing data

collection instruments; creating newsletters; hiring and training of interviewers and abstractors; administering dietary assessment instruments, including Food Frequency Questionnaires (FFQs), food records, and dietary recalls; tracing individuals; conducting cancer registry matching and National Death Index (NDI) searches; collecting, keying, editing, updating, and coding data; monitoring data collection activities and quality control procedures; creating and manipulating data files; developing and running analytic programs; arranging for the collection, processing, transport, and storage of biological specimens; preparing OMB clearance packages; managing study oversight committee reviews; establishing and managing collaborations with foreign investigators.

Although the scientific design and oversight of research projects are the responsibility of the Nutritional Epidemiology Branch, the contract will provide the following general activities:

- 1) Development of coordination and liaison at a local or international level with collaborating investigators or institutions whose cooperation is needed for the conduct of a study.
- 2) Assistance in the design and pilot testing of forms required for field investigations (e.g., questionnaires, abstracting forms, coding forms, manuals for field procedures and other documents).
- 3) Hiring, training and supervision of field personnel (interviewers, abstractors, and others).
- 4) Identification and location of study subjects.
- 5) Supervision and management of field operations.
- 6) Collecting data (interviewing/record abstraction, biologic specimen collection and processing).
- 7) Data entry and maintenance of tracking systems for data and biologic specimens.
- 8) Data reduction activities (coding, keying, and editing) of data collected into a format suitable for computer analysis.
- 9) Quality control and standardization for producing appropriate and valid data.

Specific activities in support of NEB's major research concentrations include:

Meat methods research

- Provide support for data base development, including iron (heme and non-heme in meats cooked by varying methods), processed meat (nitrite, nitrate, *N*-nitroso compounds), and fish (heterocyclic amines, polycyclic aromatic hydrocarbons, nitrite, nitrate, nitroso-compounds).
- Give support to specific studies evaluating novel biomarkers, including 1- and 3-methyl histidine in urine, O⁶ carboxy-methylguanine adducts in blood and biopsy tissue, and sSalivary *N*-nitroso compounds
- Maintain the evolving data base maintenance and review appropriate literature in support of NEB research on probiotics.

- Provide technical support for an evaluation of meat consumption trends in the US from National Surveys.

Evaluation and application of ASA-24

With the completion of the initial version of ASA-24 (anticipated Summer 2007), additional developmental work and application to epidemiologic studies will be carried out under the SSC:

- Provide support for a pilot study of the response to ASA-24 in the existing AARP study cohort.
- Evaluate the possibility of using AARP infrastructure to administer ASA-24 to additional AARP members not in the original cohort, including those residing in additional states with strong cancer registries.
- Coordinate an investigation of possible ASA-24 incorporation in other intramural and extramural prospective cohorts.
- Coordinate administrative and technical aspects of a biomarker-based validation study within the AARP study and possibly other prospective cohort studies.

NIH-AARP Diet and Health Study

Study activities to be carried out under the support services contract include:

- Tracing cohort participants
- Conducting periodic validation studies of the SS MDF (vs. NDI) in an (the External Working Group recommended this be done approximately every 3 years)
- Performing NDI+ search (at approximately 10 years of follow-up)
- Carrying out cancer registry matching for additional incident cases
- Administering the automated 24 hour recall to the AARP population (contingent upon results of pilot study evaluations of ASA-24). This includes preparation of an OMB package
- Producing and distributing regular newsletters to cohort
- Coordinating External Working Group reviews
- Evaluating possible Medicare record linkage
- Providing support services for participation in consortial and collaborative projects:
 - Parkinson's disease project (led by NIEHS)
 - The extramurally-based Harvard Pooling Project
 - The extramurally-based ALS project
 - DCEG cohort consortium (e.g., ovarian cancer study)
 - New intra-, extramural cohort consortium (e.g., for pancreatic cancer)
- Maintaining liaison with AARP staff

India Health Study

We anticipate that the India Health Study pilot will be completed under the new SSC. In addition, the SSC will facilitate the construction of a dietary data base for Indian foods.

CONCeRN

The Contractor will be responsible for ongoing study management, including support for CONCeRN's participation in the Arizona polyp study pooling project. In addition, the Contractor will handle data management for future biospecimen analyses.

Esophageal adenocarcinoma collaboration with Kaiser Permanente and other HMOs

Coordinate the establishment of a collaboration with one or more large HMOs for facilitating etiologic studies of esophageal adenocarcinoma, especially in women. (This is a new and as yet unapproved project.)

B. Statement of Work

Independently and not as an agent of the government, the Contractor shall be required to furnish all the necessary services, qualified personnel, material, equipment, and facilities, not otherwise provided by the government, as needed to perform the work identified herein. Types of support to be provided by the Contractor in the conduct of studies may vary. The Contractor shall be responsible for simultaneously managing concurrent, multiple, domestic (including international) studies. The time line or schedule for support activities will be specified by the NCI Project Officer based on the study. The Contractor shall inform the NCI Project Officer of any unforeseen circumstances that may delay timely completion or progress of study activities. All study activities, documents, and procedures must be approved by the Project Officer prior to implementation. The Contractor shall perform some or all of the following support activities as may be specified by the NCI Project Officer in the conduct of each study:

1. Study Initiation and Liaison

- a) Obtain necessary information to determine effective study resources (e.g., capabilities of collaborating institution, numbers of eligible study subjects, etc).
- b) Determine parties whose cooperation and approval is necessary for implementation of the study (e.g., federal or state agencies, universities, hospitals, medical offices, laboratories, other NCI Contractors, etc.).
- c) Arrange for communication and meetings between the NCI research investigators and agents for those parties whose cooperation or approval is needed.
- d) Attend such meetings, provide background information required, and take appropriate action on recommendations, as applicable. Document proceedings and action items as requested by NCI staff.
- e) When multiple institutions are involved on a multi-center study, develop procedures to assure that the investigation is being conducted in standard ways at all sites.
- f) Make arrangements for translations for necessary transactions to initiate studies in foreign settings.
- g) Negotiate and manage all financial and administrative matters related to the collection of data and specimens with the various collaborating centers (e.g., subcontracts, purchase of equipment, other compensation).
- h) Assist in development of protocols and completion of forms as may be required for various committees, such as Institutional Review Boards. Attend such committees if requested by the Project Officer (or a designate representative-hereafter referred to only as the Project Officer)

2. Preparation of Study Materials and Procedures

- a) Prepare, pretest, and produce data collection forms (e.g., abstract forms, follow-up forms, coding forms, questionnaires and exposure assessment forms).
- b) Prepare training programs and materials. Conduct training for new staff in a timely manner and update training for all staff as needed.
- c) Prepare procedure manuals for nurses, research assistants, abstractors, coders, interviewers, tracers, supervisors, data editors, and other personnel as needed.
- d) Prepare procedure manuals for the collection of biological specimens, shipment of biological specimens, submission of specimens to repositories, and tracking of specimens and laboratory results.
- e) Prepare manuals for obtaining and handling medical records, pathology specimens and reports, submission of pathology specimens for review, and collection of death certificates or cause of death.
- f) Develop or adapt existing schemes of coding for categorizing occupational, industrial, nutritional, and medical information.
- g) Translate data collection instruments or manuals into appropriate languages for foreign studies. Under the direction of the Project Officer, back-translate either a portion of the material or all the material into English to assure that the original material has not been changed by the translation.
- h) Given the similarity of activity across studies, design or utilize systems and approaches that can serve as a “shell” or “template” for future work to avoid reinventing such system for each study or project.
- i) Contribute to preparation of newsletters and brochures for informing participants of study findings and eligibility.
- j) Prepare large mailings for subjects participating in ongoing studies.
- k) Assist in the preparation of study-specific packages for OMB, IRB, and/or OHSR reviews.

3. Subject Identification, Selection, Tracing, and Endpoint Ascertainment

- a) Identify study subjects who meet NCI criteria for being included in studies, particularly women, minorities, and children, as appropriate. This includes random digit dialing (RDD) and other methods of selecting controls from the general population and from hospitals or clinics.

- b) Acquire appropriate population rosters or files to identify selected series of potential study subjects.
- c) Locate study subjects or their next of kin for study inclusion.
- d) For retrospectively ascertained subjects, utilize a variety of tracing techniques to ascertain current vital status. For living subjects, locate their current whereabouts so that they can be included in studies.
- e) Perform linkage to a variety of sources including vital status, cancer status, census tracts, etc. Linking should be done using a quality controlled method that has gone through rigorous testing. Linking should be able to handle, partial and fuzzy data.
- f) Creation of study participant ID's as needed.

4. Interview and Abstracting Data Collection

- a) Train abstractors, interviewers, telephone screeners, coders, phlebotomists and others who will be involved with acquiring and assembling data.
- b) Obtain the necessary permissions and/or consents and then interview subjects or their family members using mail, telephone, or in-person questionnaires. Computer assisted interviews may be necessary, depending on the study. Verify a sample (determined with the NCI investigator) of completed questionnaires. Questionnaire content will be provided by the NCI Project Officer and will be jointly modified, if necessary.
- c) Abstract and photocopy records (clinic or office medical records, hospital charts, vital records, job records, etc.). Maintain quality control over the abstracting and copying process. Verify the accuracy of an appropriately sized sample of abstracts (determined by the Project Officer) by independent reabstracting. Accuracy is to be maintained at a 98% level.
- d) Procure death certificates from state vital records departments. The Contractor shall be responsible for determining details of and payment for death certificate procurement from each state. The Contractor shall also be responsible for complying with state requirements regarding retention of such records in consultation with the Project Officer.
- e) Purchase other data, materials, and/or services as necessary.
- f) Develop tracing management system to generate participation loss rates for all data collection efforts.

- g) Validate exposure or disease histories obtained in interviews by obtaining copies of original records.
- h) Obtain copies of imaging studies, radiographs, or other clinical tests (e.g. electrocardiograms) and the associated reports as needed for specific studies.
- i) Create web-based and/or email questionnaire.

5. Specimen Collection, Processing, and Shipment

- a) After obtaining necessary and appropriate informed consent, obtain biological specimens from study subjects. Divide samples in appropriate sample aliquots.
- b) Collect and deliver biologic specimens (blood, urine, tumor, etc.) in appropriate shipping containers and under appropriate shipping conditions with necessary documentation to designated laboratories or investigators for storage and/or analysis. This includes transport of biologic specimens from international studies with necessary customs clearances. Verify safe arrival of specimens to the destination.
- c) Arrange for specimen storage and/or standard laboratory tests or assays on biologic specimens (in one or several laboratories or repositories), as designated by the Project Officer or NCI investigator(s).
- d) Perform other support activities involving specimen collection, storage, tracking and/or dispersal to laboratories as requested by the Project Officer or NCI investigator(s).
- e) Report to the appropriate Project Officer or Alternate Project Officer all irregularities, delays, losses, deteriorations, unplanned defrosting, accidents, mishandling, errors, discrepancies, and inefficiencies connected with any specimen collection, handling, delivery, storage, or testing activity as soon as it becomes known to the Contractor.
- f) Maintain an inventory of specimens sent to laboratories and monitor discrepancies.
- g) Obtain all necessary laboratory reports of results or progress and deliver that to the Project Officer in a timely manner.

6. Data Preparation

- a) Code information into computer-readable form. Verify a 10 percent (or higher as requested by Project Officer) sample for accuracy of the coding by independent recoding. Accuracy is to be maintained at 98% level.

- b) Develop documentation of codes used and listing of unusual responses.

7. Computer Programming and Data Processing

- a) Maintain secured network, server, computer databases and associated reporting software and maintain protection of subjects identity. When sharing data the information should be transferred with no link to subject information.
- b) Prepare edit programs, edit data, and correct computer files where necessary.
- c) Use modifiable data management and tracking systems that can be applied across studies. Minimize creation of unique study-specific management and tracking systems. Such systems must be approved by the Project Officer. Systems should be compatible with the Biospecimen Inventory II, Laboratory Information System of the Core Genotyping Facility or others as appropriate and specified by the Project Officer.
- d) Provide capability of creating datasets with up to hundreds of thousands of study subjects and tens of thousands of variables in SAS, STATA, or other programs as requested by the Project Officer. All data processing, storage, and transfer must be in compliance with US government standards of privacy and confidentiality.
- e) Maintain adequate backup of study data and secure storage of back up media. Frequency of backup may vary by specific study, but will be determined by Project Officer. Report verification rates, discrepancy rates, and error rates for data collection, preparation and keying following the schedule agreed upon with the Project Officer. An unusual problem should be brought to the immediate attention of the Project Officer.
- f) Enter coded information onto suitable computer devices.
- g) Update files with follow-up data, error correction, etc. as directed by the Project Officer. Maintain clearly documented history of development and updating of databases.
- h) Prepare datasets suitable for analyses for transfer to personal computers, as specified by the Project Officer.
- i) Respond to priority requests and changes of direction rapidly by appropriate activities and use of personnel.
- j) Create datasets comprising hundreds of thousands of data items. Include web based preparation of materials.

8. Study Monitoring, Quality Control, and Reporting

Quality control of all aspects of data collection and management is a crucial activity. NCI will carefully review studies to ensure that the data are sound. At the beginning of each study, the NCI investigator responsible for the study will approve a plan prepared by the Contractor's study manager for the schedule and contents of reports needed for quality control. Quality controls will require that the Contractor:

- a) Document each step in a specific study and maintain, in an orderly arrangement, all relevant material so that any aspect of a study may be reviewed and evaluated by the NCI staff at any point in time. Involved are the following:
 - (i) Type letters and prepare forms and other documents necessary in the conduct of a study.
 - (ii) Duplicate study documents when the original sources cannot be retained.
 - (iii) Maintain a filing system of all materials relevant to a particular study, cross referenced in a manner so as to make all of the material easily accessible. These materials shall be maintained under security in accordance with requirements of the Privacy Act as it applies to Contractors.
 - (iv) Maintain a log of decisions made during each study that affect the design, conduct, or analysis. Each entry shall include a brief explanation and date of the problem, the decision made, and the name of the NCI staff member who authorized the change.
 - (v) Prepare budget reports by study and by projects.
- b) Develop and use internal record-keeping procedures for assessing the progress and status of data collection, preparation and entry. These record systems may be paper files or computer systems.
- c) Monitor and document the performance and progress of any work done under subcontract in the performance of a study.
- d) Develop quality control procedures for the handling of biologic specimens specific for needs of each study.
- e) Report verification rates, discrepancy rates, and error rates for data collection, preparation and keying following the schedule agreed upon with the Project Officer. Any unusual problems shall be brought immediately to the attention of the Project Officer.

- f) Provide monthly, semi-annual, and final technical progress reports and monthly budget reports in the format specified by the NCI Project Officer and/or designated representative.
- g) Meet with Government Project Officers on a nearly daily basis, to monitor and review progress on contract activities.

9. Transition

In the event a new contractor is selected for the recompetition of this work, the current contractor shall carry out transition activities. During the first four weeks of the new contract, the Contractor shall effect a smooth transition of the management and operations of the existing support provided by the current Contractor to the new Contractor without prolonged interruption of the normal day-to-day provision of support services including: a) study initiation, liaison and administrative management; b) preparation of study materials and procedures; c) identifying and tracing study subjects; d) interview and abstracting data collection; e) clinical support activities; f) laboratory aspects involving biologic specimens, tests and laboratory data; g) data preparation; h) computer programming and data processing;; and i) study monitoring, quality control and reporting. During this period, the Contractor shall establish a working relationship with the new Contractor. In particular, transfer of all current datafiles should occur within two weeks of the new contract award.