Supporting Statement B for:

Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) (NCI)

OMB Clearance Package

Revision Request for OMB #: 0925-0407,

Expiry Date: 9/30/2014

September, 2012

Yellow highlights indicate changes since the approval of the 2011 submission.

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ATTACHMENTS

*Indicates an instrument.

B. COLLECTIONS OF INFORMATION EMPLOYING STATISTICAL METHODS

B.1. Respondent Universe and Sampling Methods

The respondent universe is comprised of the specific populations defined by the original 10 Screening Centers (SCs). As part of the pilot review, it was established that the population base of 55 to 74-year-olds was sufficient to support the recruitment goals in each study location. From these populations, potentially eligible participants were identified and invited to participate in the trial. Each of the 10 SCs recruited between 6,000 and 28,000 participants for a total of 154,910 participants over 8 years of recruitment. Recruitment ended July 2, 2001.

Two changes were made to the eligibility requirements for the trial, which had offsetting effects on sample size requirements. In January 1996, contamination rates were lowered by changing eligibility based on prostate and/or flexible sigmoidoscopy examinations prior to the PLCO trial which, thereby, reduced the required sample size, but age eligibility was subsequently lowered, and this raised the sample size to the original estimate. The DSMB recommended, and the NCI agreed to, lowering the age of randomization to reflect growing knowledge about prostate cancer.

Sample size calculations are provided in **Attachment 14**. Colon cancer affects men and women at roughly the same rates. It is NIH policy (RFP pages 161 and 162, INSTRUCTIONS TO OFFERORS, and page 179, EVALUATION FACTORS FOR AWARD) that offerors for clinical research contracts include women and minorities in study populations so that research findings can be of benefit to all persons at risk to the disease under study. Therefore, a 50/50 gender split has been adopted in PLCO. The racial mix for PLCO reflects the racial compositions of the 10 SCs' geographic areas, because SCs were contractually required to recruit so as to achieve this goal. Additionally, minority recruitment is enhanced by projects supported by the

Centers for Disease Control and Prevention and by PLCO trial-associated RO1 projects supported by NCI.

A consistent gender proportion of 60/40 males to females developed in the early part of the full-scale implementation at most SCs. Strategies were implemented to compensate for the imbalance, and they resulted in an even distribution of males and females enrolled in the trial.

Response rates for the trial are measured as compliance in completion of the Annual Study Update (ASU) questionnaire. To calculate response rates, the number of completed ASU questionnaires is divided by the number of participants who consented to active follow-up by the PLCO Centralized Data Collection Center (CDCC). The goal for compliance is to achieve 90% completion of the ASU. As the study population ages, it is more difficult for the participants to obtain information on the ASU. The CDCC has implemented various strategies to improve retention and compliance, described in section B.3.

B.2. Procedures for the Collection of Information

Stratification at randomization was limited to gender, age, and SC. Analyses will account for this fundamental stratification of trial data. Where appropriate, stratification will be used in analyses for important covariates not included in the stratified randomization. These covariates would include ethnicity or race and smoking history, family history of cancer, dietary factors, previous medical history, and other risk factors for these cancers. Power calculations for the trial are presented in **Attachment 14**.

Vital status follow-up for primary endpoint analysis is expected to be virtually complete. All participants randomized into the PLCO trial are followed annually either by direct contact or indirectly through the National Death Index to obtain vital status data. Based on previous screening trial experience, including the thirteen year results of the Fecal Occult Blood trial at the

University of Minnesota, which uses virtually identical follow-up procedures, only about 1% loss to follow-up is expected.

Analyses of the primary mortality endpoint and secondary survival and staging variables will account for stratification by using the stratified log-rank test and Mantel-Haenszel procedures as well as logistic and Poisson regression techniques (Supporting Statement, Section A.16).

Originally ten institutions under contract to NCI served as Screening Centers responsible for all recruitment, retention, data collection, and data processing activities. A Coordinating Center (CC) contract was also established to provide a distributed data entry system for use by each SC.–Processed data is sent to the Coordinating Center with all identifiers removed for preparation of analytical files.

The NCI seeks to increase the value of PLCO as a resource to intra- and extra-mural researchers by continuing to collect follow-up behavioral data, morbidity and mortality outcomes, and tumor tissue using 1, rather than 10, data collection center. NCI has awarded a contract for continuation of participant follow-up activities to one data collection site named the PLCO Central Data Collection Center (CDCC). Given the advanced age of participants with at least 13 years of follow-up, the PLCO is entering its most productive years of cancer and vital status ascertainment. These additional data will clarify further the long-term effects of screening on cancer mortality, and enable new studies of rare tumors and common tumors in subpopulations.

Annual follow-up is conducted with all PLCO participants who consent to be in the active follow-up group. A brief questionnaire, the Annual Study Update is generally self-administered and sent by mail along with a cover letter (**Attachments 2 and 4**). Telephone interviews are conducted for non-responders to the mailed questionnaire (**Attachment 14**). All participants who consent to be in the active follow-up group will also receive the Medication Use Questionnaire (**Attachment 5**), a self-administered questionnaire used to obtain information regarding the use of

NSAIDs, acetaminophen, aspirin, and current prescription medications. In addition to requesting information regarding medication use, the first mailing of the Medication Use Questionnaire also asks participants to provide consent to use their personal information to attain health information from electronic records such as Medicare and Medicaid. The information from Medicare and Medicaid will be used to evaluate screening modality processes by intervention arms in the PLCO study ad its association with cancer outcomes. For example, to evaluate the association between colonoscopy procedures and the risk of colon cancer by intervention arm and to evaluate the association between chest x-ray procedures and the risk of lung cancer by intervention arm. The data obtained from Medicare Medicaid will also be used to explore the association between risk factors and non PLCO health outcomes such as the association between oral microbial content and CVD risk. Contamination in the control group is measured annually with administration of a Health Status Questionnaire to approximately 2000 randomly selected participants (**Attachment 3a and 3b**).

Data documenting cancer diagnosis and treatment are collected through abstraction of medical records. Participants are asked to sign an authorization to release medical records (**Attachment 9**). A letter is sent to the appropriate hospital or physician along with the authorization form to request the records (**Attachment 4**). Abstraction of medical records will be performed by CDCC staff. Deaths are ascertained through the annual follow-up process and the National Death Index. These activities are done by each SC so that no identifying information need be released to any other organization.

The CC will continue to monitor the quality of the data. Quality control procedures are integrated in the data entry process. The CC regularly monitors data by reviewing data, by regular communication with the data collection staff, and by reviewing specialized reports.

B.3. Methods to Maximize Response Rates and Deal with Non-response

Data collection procedures are designed to maximize response rates. Retention training emphasizes methods of gaining respondent cooperation and has included use of role-playing exercises. Study staff are provided with answers to many typical respondent questions and encouraged to practice with these until they are comfortable with their ability to explain the study and encourage participation. We expect interest in the trial will continue to be strong, with refusals more likely to occur with completing the annual health survey. Response rate is improved through careful tracing, second mailings and telephone follow-up with non-responders to the mailings.

With the conclusion of screening exams and participant recruitment, resources are focused on retention of PLCO participants. Retention strategies in use include: sending the national PLCO newsletter to all participants; sending birthday cards, holiday gifts and sympathy cards to participants and their families.

Regarding biases, as is true with every study, the participants in this trial are probably not completely representative of the general U.S. population. However, the 10 SCs that comprised the original PLCO clinical sites were distributed nationwide, and include black, Hispanic, and Asian American minorities. Furthermore, baseline data collected from the participants includes demographic, socioeconomic, occupational, and risk factor information, so stratified and adjusted analyses can be performed. Detailed diagnostic and prognostic information for cancer cases and cause of death information will be collected for similar uses. Beyond this, because of the randomized nature of this study, comparisons between the arms of the trial are unbiased. There is no selection bias within the trial.

B.4. Test of Procedures or Methods to be Undertaken

There are currently no plans for the PLCO Trial to test procedures or methods.

B.5. Individuals Consulted on Statistical Aspects and Individuals Collecting and/or Analyzing Data

Senior statistical collaboration and guidance for the PLCO Trial is provided by the NCI. Dr. Philip Prorok, Chief, Biometry Research Group, DCP, NCI (301-496-7709) is associate Project Officer for the study. NCI statisticians involved in the analysis are Dr. Richard Fagerstrom (301-496-7458), Dr. Grant Izmirliam (301-496-7519), Dr. Paul Pinsky (301-402-6480), Dr. Ping Hu (301-496-8553), and Dr. Jian-Lun Xu (301-496-7475).

The CDCC and two remaining SCs under contract to NCI are responsible for the data collection and data processing activities. Information Management Services, Inc. is under contract to NCI to provide analytic support. Westat is under contract to NCI as the CC and CDCC; with responsibilities including analytic support as needed.