Supporting Statement B for:

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

OMB Clearance Package

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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 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 locations. 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 154,943 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 13. 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 will reflect 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. Overall compliance has been high averaging 93% for completion of the ASU. The goal for compliance is to achieve an average of 95% for the completion of the ASU. As the study population ages, it is more difficult for the participants to obtain information on the ASU. The SCs have 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 13.

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).

Ten institutions who are under contract to NCI to serve as SCs are responsible for all recruitment, retention, data collection, and data processing activities. A contract has also been established with Westat to serve as the CC for the trial. The CC provided a distributed data entry system for use by each SC. Processed data is sent to Westat with all identifiers removed for preparation of analysis files. The CC is also responsible for assisting in the preparation and documentation of standard procedures and methods for the trial, quality control, coordinator training, and for logistical support for meetings and other activities. University of California at Los Angeles Immunogenetics Center, under a separate contract, is responsible for performing the PSA and CA125 blood tests and reporting results back to the SCs and the CC.

Annual follow-up is conducted with all PLCO participants for at least 13 years from randomization. A brief questionnaire, the Annual Study Update is generally self-administered and sent by mail along with a cover letter (Attachments 3 and 12). Telephone interviews are conducted for non-responders to the mailed questionnaire. Contamination in the control group is measured annually with administration of a Health Status Questionnaire to approximately 100 randomly selected participants in each SC. Contamination is also being assessed in intervention participants who completed screening. The Supplemental Questionnaire administered to all PLCO participants, updates information on demographics, cancer risk factors, and history of cancer screening.

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 7). A letter is sent to the appropriate hospital or physician along with the authorization form to request the records (Attachment 12). Abstraction of medical records is performed by SC 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. Death certificates are obtained for all participants reported as deceased during the entire duration of the trial.

Each SC monitors the quality of its data. Quality control procedures are integrated in the distributed data entry system provided to each SC. The CC regularly monitors SC data by reviewing transmitted data, by regular communication with the SC Coordinators, by reviewing specialized reports as needed, and by accompanying NCI on annual site visits. The Quality Assurance Subcommittee monitors quality control for the overall trial, including training and credentials of PLCO staff.

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

Data collection procedures are designed to maximize response rates. Coordinator training emphasizes methods of gaining respondent cooperation and has included use of role-playing exercises. Coordinators 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 vary by SC and include: sending the national PLCO newsletter to all participants; sending birthday cards, holiday gifts and sympathy cards to participants and their families; issuing clinic visit reminders via postcard or phone; and extending clinic hours to evenings or weekends. Other strategies are under consideration.

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 comprising the PLCO clinical sites are 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 consulted on the design and analysis plan for the

trial were Dr. Robert Connor (retired), Dr. Laurence Freedman (Bar Ilan University, Israel) and Dr. Sylvan Green (Arizona Cancer Center). Dr. Dwight Brock (301/496-9795) of the National Institute on Aging also reviewed the statistical design. 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), Dr. Jian-Lun Xu (301-496-7475), and Dr. Pamela Marcus (301-496-7468).

Ten institutions are under contract to NCI to serve as SCs and 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; with responsibilities including analytic support as needed.