Supporting Statement A for:

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

OMB Clearance Package

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Yellow highlights indicate changes since the approval of the 2008 submission.

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A. JUSTIFICATION

A.1. Circumstances Making the Collection of Information Necessary

The Early Detection Research Group of the Division of Cancer Prevention, National Cancer Institute (NCI), developed the concept of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial (OMB Number: 0925-0407; Expiration Date: October 31, 2011) in accordance with their mission to develop scientific information and concepts and disseminate the acquired knowledge regarding early detection techniques, practices, and strategies to reduce mortality and morbidity from cancer. To this end, the Research Group sponsors and conducts clinical trials and other appropriate research, fosters technology development, and encourages publication of scientific findings and adoption of proven early detection practices. Section 412 of the Public Health Service Act (42 USC § 285a-1) authorizes the collection of the information.

According to the American Cancer Society "Cancer Facts and Figures 2010" (http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-026238.pdf), in 2010 there were an estimated 51,370 deaths from colorectal cancer and 157,300 deaths from lung cancer. About 13,850 women died from ovarian cancer and 32,050 men from prostate cancer. Lung and colorectal cancers are among the most commonly occurring cancers in the United States, and account for over one-third of all cancer deaths. Successful screening programs for these cancers could possibly have a major impact on overall cancer mortality in the U.S.

OMB first approved the PLCO Cancer Screening Trial in October 1993. Since that initial approval, OMB approved the trial in 1996, 1999, 2002, 2005, and 2008. During the first approval period a pilot study was conducted to evaluate recruitment methods and data collection procedures. PLCO trial recruitment ended in 2001, screening was completed in 2006, and to date, greater than half of participants have completed 13 or more years of follow up. In March 2009, the first report on screening and prostate cancer mortality was published in the *New England Journal of Medicine* (Andriole et al., 2009). In October of the same year, investigators from the Cancer Genetic Markers of Susceptibility (CGEMS) initiative reported in *Nature and Genetics* the results of a third genome-wide association study leading to

the identification of a new prostate cancer susceptibility locus on chromosome 8q24 (Yeager et al., 2009). PLCO biospecimens and data were used in this CGEMS study. Since the inception of the trial, more than 220 articles have been published in peer-reviewed journals; and the number of investigators that submit applications requesting use of PLCO biospecimens and data increases every year. In addition to publications of benefit to the scientific community, data collected will be used to evaluate the effect of screening on the reduction of cancer specific mortality from the four targeted sites: prostate, lung, colorectum and ovary. See **Attachment 2** for a list of users of PLCO scientific findings.

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. 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.

This request is for the ongoing data collection for years nineteen through twenty-one of the study. The contracts for 8 of the 10 Screening Centers (SCs) will end in 2011 and the remaining two sites will close in 2012 and 2014. 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). The CDCC will conduct all active data collection to ascertain cancer and vital status with participants, relatives, physicians, and medical records and pathology departments for those participants who agree to be followed by the CDCC. The CDCC will also conduct passive data collection i.e., submission to tumor registries, vital statistics offices and the National Death Index (NDI), for active participants and participants who are lost to follow up or deceased, and it will coordinate passive data collection by the former SCs for participants who agree to continued follow up, but do not agree to be contacted by a new data collection site.

With the extensive questionnaire and clinical data and the rich collection of biospecimens collected at multiple time points before and after cancer diagnosis, the PLCO Trial has proven to be

extremely valuable resource for research in cancer prevention and molecular epidemiology. Etiologic and early marker studies are being carried out to address hypotheses concerning potential carcinogenic and anti-carcinogenic exposures and genetic susceptibility to disease risk. Biochemical and genetic studies of cancer etiology will typically involve comparison of risk factors between cases and a similar number of comparison subjects. Studies to evaluate the natural history of disease and to characterize early markers will be carried out utilizing previously sequentially collected samples to relate biochemical changes in blood to the pre-diagnostic course of disease development. The etiology and early marker component is fully integrated with the early detection component of the Trial and was explained to participants. They were offered the opportunity to participate in these additional studies of cancer and other diseases which affect their age group. Participation in the additional studies was completely voluntary.

A.2. Purpose and Use of the Information

Trials adequate to answer questions of risk and benefit of the screening modalities used in this trial have not been previously conducted in the United States, so there is no other source from which to obtain the data. The scientific goals, design, and clinical process for generating the data have been subjected to multiple peer reviews. Contamination in the control arm and noncompliance in the screened arm were explicitly considered in the statistical design. Anticipated levels of contamination and non-compliance were estimated from available literature and are monitored during the trial. The sizes of the mortality differences between screened and control arms for each cancer site detectable in the trial were determined in the presence of anticipated levels of contamination and non-compliance. The PLCO Screening Trial was designed to achieve maximum financial efficiency while achieving the scientific goals of the research. Separate trials to answer the questions of screening effectiveness in the four cancer sites (prostate, lung, colorectum and ovary) individually would have cost two to four times as much due to replication of study infrastructure. The technologies being tested are of current interest, because they are being considered by clinicians for screening.

The PLCO primary endpoint is cancer-specific mortality for each of the four cancer sites. In addition, cancer incidence, stage shift, and case survival are to be monitored to help understand and explain the results. Biologic prognostic characteristics of the cancers were measured and will continue to be correlated with mortality to determine the mortality predictive value of these intermediate endpoints.

Basic demographic, screening history, and risk factor data for the four cancer sites, as collected from all participants at baseline, will be used to assure comparability between the screening and control groups and make appropriate adjustments in analysis. Further, demographic and risk factor information will be used to analyze the differential effectiveness of screening in high vs. low risk individuals. It is also important to have this baseline data in order to characterize participants who drop out of the study.

To determine if screening reduces the mortality from these four cancers it is critical that the PLCO participants continue to be followed. During the past three years ongoing data collection has consisted of ascertaining and confirming new cancers and determination of vital status for each participant. The data collection instruments include the Annual Study Update (**Attachment 3**), the Health Status Questionnaire (**Attachments 4A and 4B)** and the Supplemental Questionnaire (**Attachment 5**) that are mailed to the participants with cover letters (**Attachment 12**) to be self-administered. The Health Status Questionnaire is gender specific and is mailed only to a subset of 2,000 participants. The Annual Study Update and the Supplemental Questionnaire are mailed to all participants. The Supplemental Questionnaire (SQX) is being re-introduced to provide updated information on demographics, cancer risk factors, and history of cancer screening.

A.3. Use of Improved Information Technology and Burden Reduction

Computer-assisted telephone interviewing for the data collection instruments, including the Annual Study Update (ASU), Health Status Questionnaire (HSQ), and the Supplemental Questionnaire (SQX), was not considered appropriate given their proposed method of administration. These instruments are self-administered and are mailed to the participant to complete at home. This mode of administration is necessary given the large number of participants. Telephone administration is usually limited to non-

responders. In cases where telephone administration is used, the staff person introduces him/herself, explains the reason for the call and asks if it is a good time for the participant to answer a couple of questions (**Attachment 14**). The ASU is read to the participants verbatim, exactly as the data collection items are written.

In addition, for the Annual Study Update, self-administration is advantageous in order to minimize contact with the control group and thus reduce potential for contamination (e.g., controls deciding to have screening examinations because of their involvement with a screening trial).

A previous Privacy Impact Assessment (PIA) was completed and published by HHS on February 22, 2011 for the IT system being used to store and monitor data. The system name is "NIH NCI PLCO Research Database (PLCO)" (**Attachment 15**). The computerized data management system reduces respondent burden. Information collected at baseline is stored in the system. For subsequent annual information collections, information previously supplied by the participant is pre-populated and sent to him/her for confirmation (e.g. name and address of primary care physician and tracing contacts). The participant only needs to indicate whether the information is still correct and not repeat unchanged information. The Annual Study Update shows a computer generated reference date after which the participant is asked to provide cancer diagnosis information; diagnosis information for prior periods need not be repeated.

A.4. Efforts to Identify Duplication and Use of Similar Information

This trial was four years in design. Consultations with expert groups regarding each of the four cancer sites were numerous. Presentations to professional groups, NCI-sponsored workshops, external and internal peer review of the concept, a comprehensive review of the literature (**Attachment 1**) and interactions with investigators in European countries interested in these research questions, were aggressively pursued in the design and concept development effort. NCI staff involved in design of this trial also participated in the screening evaluation project of the International Union Against Cancer which monitored and assessed the status of cancer screening worldwide. This is the first, and possibly only, study

in the world to evaluate these multiple screening modalities in a randomized, controlled trial. No similar data are available to answer the questions addressed in the PLCO trial. There is no duplication, although since the PLCO trial has entered its main phase, some European countries are collaborating in the evaluation of prostate cancer screening by a protocol unique to their needs, and once-in-a-lifetime screening by flexible sigmoidoscopy is being evaluated in the United Kingdom. In addition, the evaluations of cancer screening programs in Korea and Japan have recently been published.[1,2]

A.5. Impact on Small Businesses or Other Small Entities

This information collection does not involve small businesses or other small entities.

A.6. Consequences of Collecting the Information Less Frequently

Annual follow-up provides timely information on incidence of new cancers and deaths from the cancers of interest. Less frequent follow-up would be deleterious to monitoring requirements. Current participant files are essential for Data and Safety Monitoring Board (DSMB) review and to minimize loss to follow-up and ensure timely acquisition of endpoint events.

A.7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

The proposal is consistent with the information collection guidelines in 5 CFR 1320.5.

A.8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

A 60-day Federal Register notice soliciting comments on the PLCO trial prior to submission to OMB was published in the Federal Register on April 20, 2011, Volume 76, Number 76, Page 22108 and

[1] Jung KW, Shin HR, Kong HJ, Park S, Won YJ, Choi W, Park EC (2010). Long-term Trends in Cancer Mortality in Korea (1983-2007): A Joinpoint Regression Analysis. Asian Pacific Journal of Cancer Prevention, 11, 1451-1457

[2] . Yoshida M, Kondo K, Tada T (2010). The relation between the cancer screening rate and the cancer mortality rate in Japan. The relation between the cancer screening rate and the cancer mortality rate in Japan. The Journal of Medical Investigation, 57, 251-259.

allowed 60-days for public comment. One public comment was received on April 20, 2011 which commented on the government spending money to support NIH.

The PLCO Steering Committee is involved in designing, conducting, and monitoring the PLCO trial. The committee provides overall scientific direction for the study and serves as the major decision-making body for operations. The Steering Committee is composed of the NCI Project Officers, Principal Investigators (PIs) of each of the screening centers (SCs), the Laboratory, the Coordinating Center (CC) and CDCC. See **Attachment 6** for member names, organizations and phone numbers. The following list shows dates of monitoring and review activity since the prior OMB approval:

- Steering Committee Meetings: 3/10-13/2008, 9/15-18/2008, 3/2-4/2009, 9/21-23/2009, 3/26-29/2010, 9/20-22/2010, 5/2-4/2011.
- PI Conference Calls: 6/24/2008, 7/10/2009, 2/14/2011

Data are reviewed on a regular basis by the DSMB for PLCO. The DSMB is comprised of scientists outside of the trial. Extramural consulting specialists also help monitor and evaluate progress and scientific changes.

- DSMB Meetings and Conference Calls: Meetings 11/7/2008, 10/30/2009, 10/4/2010, 12/2/2011, Conference Calls 5/20/2010, 4/12/2011

A.9. Explanation of Any Payment or Gift to Respondents

This information collection does not involve payment or gifts to respondents.

A.10. Assurance of Confidentiality Provided to Respondents

Each participant recruited into the study signs an informed consent that states the voluntary nature of participation and states that the information they provide will be kept private under the Privacy Act (**Attachment 7**). The identity of participants is maintained in a number of different ways.

- Access to study data is limited to the staff working on the study.
- All completed hard-copy data forms are kept in locked filing facilities at CDCC and SC offices.

- Data collected at the CDCC and SCs are maintained in automated information systems physically separate from other institutional systems. Limited (no personal identifiers available) dial-in access is possible through a two-step procedure requiring the CDCC/SC and CC. The systems have the following privacy controls: Access to files is through the use of a password known only to authorized study staff. Names and Social Security Numbers (SSN) are encrypted and stored in separate files from other data and are linked only by the participant identification number. All reports or files (output) with identifiers, produced and maintained at the SCs only, carry the following disclosure statement at the top and bottom of each page: *"This report contains data protected under the Privacy Act of 1975. Please distribute only to authorized personnel and store and dispose of report in a proper manner."*

- The DSMB periodically reviews study procedures, including privacy protection.

- Data collected are maintained at the CDCC and SCs (including identifying information) and at NCI (without identifying information) until completion of the study or until they are no longer required for the research. Data will be destroyed as required by NIH Manual 1743 - "Keeping and Destroying Records".

Each SC had IRB approval, as well as Office of Human Research Protocol (OHRP) certification before beginning participant recruitment. Data transferred from SC to the CDCC does not occur until both organizations have IRB approval. At the time of study initiation, NCI and the Coordinating Center IRBs determined that IRB review was not needed since neither receives any identifying information about the participants. Approvals are kept current by standard procedure and are documented in **Attachment 9**. The data collection is covered by NIH Privacy Act Systems of Record 09-25-0200, "Clinical, Basic and Population-based Research Studies of the National Institutes of Health (NIH), HHS/NIH/OD" published in the Federal Register on September 26, 2002 (67 FR 60776) (**Attachment 10**).

A.11. Justification for Sensitive Questions

Personally identifying information (PII) on PLCO trial participants is collected and maintained by the CDCC and the SCs, and is necessary to allow annual follow-up, to access medical records and to perform National Death Index searches. No identifying information is provided to the Coordinating Center contractor or the government. Data analyses and reports are aggregated without personal identifiers.

The only potentially sensitive question is SSN. SSN is only collected on the Follow-up Locator Form which is the second half of the ASU (**Attachment 3**), and confirmed annually by the participant. SSN is used, as stated on the form, only to help locate participants if no longer at their home address and to search vital records in the future, which is essential to the validity of the study results. It will be used for National Death Index searches. When SSN is requested, the participant is told of the purpose of the data collection, the legislative authority under which the information is being collected, the voluntary and private nature of the survey, and the absence of any penalty for refusal. SSN is not required for participation in the study.

SSN data is maintained at the CDCC and each SC and is stored with other confidential study data and is subject to the same confidentiality procedures and protections as required by the Privacy Act Systems of Record (**Attachment 10**) and as summarized in the study-specific Confidentiality Procedures of Screening Centers (example provided in **Attachment 8**).

A.12. Estimates of Annualized Burden Hours and Costs

Number of respondents sent follow up forms in the PLCO is consistently declining because we are experiencing more deaths with study participants as they age. In the 2008 OMB PLCO Cancer Screening Trial submission, the estimated number of respondents for Year 18 (the current year) was 131,341. However, due to the death rates, there are currently only 122,655 respondents in the trial.

For this submission, it is anticipated that 80% of the participants at the 8 SC will agree to be followed by the CDCC and the other two SC participants will decrease slightly due to death rates yielding approximately 96,844 respondents for Year 19 (the first year after OMB approval for the

2011submission) to complete the Annual Study Update (ASU) and the Supplemental Questionnaire in Year 19, 92,049 in Year 20 and 89,929 in Year 21. Over the course of 3 years, the total number of respondents will be 278,822, with an annual average of 92,941. Of the 278,822 respondents, 6000 respondents (2000 for each year) will also complete the Health Study Questionnaire (HSQ).

It is estimated that the annualized burden to complete the ASU, HSQ, SQX and the follow-up telephone script for ASU non-responders will be 54,692 hours. This amounts to an estimated total of 164,076 burden hours for the respondents over the 3 years of data collection (Table A.12-1).

Table A.12-1 Estimates of Annual Burden Hours

Type of Respondents	Survey Instrument	Number of Respondents	Frequency of Response	Average Time Per Response (Minutes/Hour)	Annual Burden Hours
Male and Female Participants	ASU (Attachment 3)	92,941	1.00	5/60 (0.08)	7,745
	Script for ASU Non-response (Attachment 14)	3,718	1.00	5/60 (0.08)	310
	HSQ (Attachment 4A or 4B)	2,000	1.00	5/60 (0.08)	167
	SQX (Attachment 5)	92,941	1.00	30/60 (0.50)	46,471
Total		234,352			54,692

The annualized respondent burden is estimated at 54,692 hours at $20.90/hour, amounting to an annualized cost to respondents estimated to be $1,143,065 (Table A.12-2). For the 3 years of data collection, the total estimated cost to respondents will be $3,429,194.

Table A.12-2 Annualized Cost to Respondents

Survey Instrument	Total Annual Burden Hours	Hourly Wage Rate[3]	Annualized Cost to Respondents by Year

[3] Updated the hourly wage rate based on the May 2010 Bureau of Labor Statistics: http://www.bls.gov/oes/current/oes_nat.htm. The respondents are the general public, so the mean hourly for all

ASU	7,745	$20.90	$161,872.24
Script for ASU Non-response	310	$20.90	$6,475.52
HSQ	167	$20.90	$3,483.33
SQX	46,471	$20.90	$971,233.45
Total	54,692		$1,143,064.54

A.13. Estimate of Other Total Annual Cost Burden to Respondents and Record keepers

There is no other total annual cost burden to respondents or record keepers for capital or start-up costs, or for operation, maintenance, or purchase of services.

A.14. Annualized Cost to the Federal Government

Annual costs include costs for contractors: the CC, the CDCC and the 10 SCs; NCI staff time to carry out planning and design activities, monitor the project and conduct analyses, estimated at seven full-time equivalents (approximately $110,539 per staff year); and non-NCI consultants to provide expertise relevant to the project and serve on the DSMB are estimated at $11,314 annually. The total cost to the Federal Government for the proposed 3-year period is $19,429,146 making the annualized cost to be $6,476,382 (Table A.14.1). These figures include direct and indirect costs.

Table A.14-1 Annual Cost to the Federal Government

	YEAR 19	YEAR 20	YEAR 21
Coordinating Center	$1,808,319	$1,924,613	$1,336,659
Screening Centers	$3,371,073	$1,115,288	$1,134,293
Central Data Collection Center	$2,139,626	$2,120,684	$2,123,330
TOTAL CONTRACTOR	$7,319,018	$5,160,585	$4,594,282
NCI Staff	$768,649	$768,649	$784,021
Non-NCI Consultants	$11,314	$11,314	$11,314
ANNUAL COST	$8,098,981	$5,940,548	$5,389,617

occupations was used, which is now $20.90.

TOTAL COST	$19,429,146

A.15. Explanation for Program Changes or Adjustments

This is a program change of the previously approved study due to OPDIV discretion; also considered a revision. Both the total number of respondents and the total burden hours have increased since the last submission due to the re-introduction of the Supplemental Questionnaire (SQX). The SQX substantially increases the average time per response. This questionnaire updates information on demographics, cancer risk factors, and history of cancer screening. The addition of a telephone script to contact respondents who do not return the ASU also contributed to the increase in respondents and burden hours.

In addition to an increase in burden, another change from the 2008 application is that the Prostate Cancer Reoccurrence Questionnaire (PCR) project will be completed under the current approval period. The PCR Questionnaire will no longer be administered and has not been included in this submission. The PCRQ is no longer being used since that data collection effort will be completed by September 29, 2011.

A.16. Plans for Tabulation and Publication and Project Time Schedule

Methods to be employed in the analysis of the study will include standard descriptive statistics and analytic techniques such as regression, analysis of variance and covariance, analysis of proportions, and contingency tables. New methods of analysis or modeling will be developed and applied as needed. Using the distributed data entry system, data are optically scanned and, when appropriate, manually entered daily at the SCs. These data are uploaded to NCI computers monthly for analysis. Intra- and inter-center comparisons in the above mentioned areas are accomplished using descriptive statistics to monitor progress and practices. Proportions complying and contamination can be compared using

standard Chi-square ($\chi 2$) tests. Quality assurance is monitored locally and via periodic central review, including summary statistics on screening results and problems.

Data are presented on an annual schedule for evaluation by the DSMB. The DSMB examines the operation and data of the trial and offers advice regarding modification and continuation. In the Final Phase (19th year through completion), topics addressed include:

- Quality assurance, retention, delivery, follow-up, contamination, compliance, and information system evaluation;
- Determination of screening test characteristics, including sensitivity, specificity, predictive value;
- Prevalence and incidence;
- Characteristics of cases, including stage, histology, survival, and interval versus screen detected cases;
- Rate of advanced stage disease;
- Cause specific and all-cause mortality;
- Lead-time estimation and modeling; and
- Complications of interventions.

Sensitivity, specificity and predictive value will be calculated for each test and test combination for each cancer site for each screen. At the completion of screening, overall calculations of these parameters will be made. Prevalence will be calculated as the number of cancers detected per 1000 individuals screened on the first screen for each cancer site and SC and pooled to indicate overall prevalence. Incidence will similarly be calculated as the number of cancers per 1000 person years at risk. Incidence rates will be calculated yearly and cumulatively over the course of the trial. The ratio of prevalence to incidence will be used as an estimate of the mean duration of pre-clinical disease.

For cancer case characteristics such as histology and stage which carry prognostic implications, the distribution of each characteristic will be calculated for each cancer site among control group cases, all screened group cases, screen detected cases and interval cases. The distributions can be compared using Chi-square (χ^2) tests. Survival distributions will also be calculated for the same subsets of cancer

cases using the Kaplan-Meier method and compared using the log rank test and Cox proportional hazards regression methods. These distributions will be calculated cumulatively each year of the trial to assess possible screening benefit. These intermediate endpoints cannot be relied upon for definitive evaluation, however, because they are subject to lead time and length biases.

Lead time is the amount of time by which a cancer is diagnosed earlier in a screening program relative to the time when it would present clinically in the absence of screening. If survival is measured from time of diagnosis, cases of disease detected by screening will automatically have longer survival, even if length of life is not increased, because of the inclusion of the lead-time. This is lead-time bias. Length bias is related to the fact that in a population of individuals with a disease, there is a distribution of times or durations which the diseased individuals spend in a pre-clinical disease state in which the disease is asymptomatic but detectable by screening. Individuals with longer duration and therefore slower growing, better prognosis disease are more likely to be in the pre-clinical detectable state at the time of a screen. As a result, cases of disease which have a better prognosis even in the absence of screening are over-represented among the screen-detected case group. Any measure of staging or survival is improved as a consequence of this length bias even if screening has no effect on disease outcome.

Estimation of lead-time is an important intermediate indicator of early detection capability of the screening procedures. Average lead-time will initially be estimated using the prevalence to incidence ratio under the assumption of an exponential distribution of pre-clinical duration. Other modeling approaches to lead time estimation also will be employed. These include the Day-Walter model (Am J Epidemiol 118:865-886, 1983 and Biometrics 40:1-14, 1984) which allows estimation of the lead time distribution, and newer approaches under development which examine differences in long term case survival rates to estimate mean lead time. The assumption of an exponential distribution is justified by several analyses of screening data, using the Day-Walter model and other approaches, in which the exponential was the best fitting distribution. Other, more general, lifetime distributions will also be considered including the Weibull, gamma, and generalized gamma distributions.

As with incidence rates, the rate of advanced stage disease and the cause-specific and all cause mortality rates will be calculated as the number of events per 1,000 person years at risk. These will be calculated yearly and cumulatively for each successive year of the trial, and relative to each of the four cancer sites under study. The rate of advanced stage disease is thought to be an indicator of changes in disease specific mortality, while the cause specific death rate is the primary endpoint in this trial. These rates will be compared using Poisson tests and Poisson regression analysis. All cause mortality is examined as an indicator of comparability of the randomized arms of the trial.

Sequential monitoring is an integral part of this trial. The possibility exists for the trial to be stopped early either because overwhelming evidence of a screening effect emerges or because interim data show essentially no evidence of an effect of the screening and there is a very slim chance of detecting an effect (even if one exists) by the planned end of the study. Statistical monitoring guidelines were established by the DSMB to use in its periodic examinations of the emerging data from the trial to decide upon continuation or termination. The procedures used include the sequential technique of Lan and DeMets (Biometrika 70:659-663, 1983) as well as stochastic curtailment methods (Lan, Simon, and Halperin, Communications in Statistics C1: 207-219, 1984). Monitoring is conducted separately for each cancer site under investigation in the trial.

Complications of the screening and diagnostic procedures administered to trial participants were recorded and monitored very closely during the active screening phase of the trial. These include any medical complications or risks and any mortality potentially related to study procedures, particularly the more invasive procedures such as colonoscopy or laparotomy, which might follow a positive colorectal screen or ovarian screen, respectively. These were examined for each cancer site at each SC for up to one year after a screening episode. Cancer incidence is also tracked to alert investigators to possible substantial over-diagnosis of one of the cancers being studied. This is thought to be a problem particularly for prostate cancer. Guidelines for termination in the event of adverse effects of the screening process were developed by the DSMB.

The PLCO trial was designed to obtain a racially mixed study population which will permit valid scientific evaluation of each of the screening modalities under study for all races combined. In designing this trial, it was not considered feasible to conduct mortality endpoint trials by minority subgroup. Such an objective would have necessitated running an equivalent trial for each of the subgroups. Race was recorded at baseline for all PLCO trial participants. Post hoc subgroup analyses to ascertain the degree to which effectiveness is equivalent or different in racial subgroups can therefore be conducted. If all race specific findings are consistent with the overall finding, generalization of the overall results to all racial groups would be valid. If not, additional research hypotheses can be considered.

Publications addressing all of the above topics will be submitted to appropriate medical, statistical, and clinical trials journals as the relevant data reach maturation. A steady stream of publications is anticipated as the trial progresses to ensure that the medical and scientific communities are kept fully informed. To date, 263 articles and book chapters have been published from PLCO data (**Attachment 11**).

The time schedule for the ongoing project is provided below.

Activities	After OMB Approval (Months)
Continued Cancer Ascertainment	0-36 months
Continued Vital Status Ascertainment	0-36 months
Continued Data Editing	0-36 months
Continued Data Analysis	0-36 months
Continued Publication of Findings	0-36 months

A.17. Reason(s) Display of OMB Expiration Date is Inappropriate

This study will display the expiration date for OMB approval of the information collection.

A.18. Exceptions to Certification for Paperwork Reduction Act Submissions

PLCO complies with 5 CFR 1320.9, the Certification for Paperwork Reduction Act Submissions.