Supporting Statement A for:

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

OMB Clearance Package

OMB #: 0925-0407

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ATTACHMENTS

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, 2008) 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 2007" (www.cancer.org/downloads/STT/CAFF2007PWSecured.pdf), in 2007 there were an estimated 52,180 deaths from colorectal cancer and 160,390 deaths from lung cancer. About 15,280 women died from ovarian cancer and 277,050 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. Death rates for prostate and colorectal cancers have declined slowly for many years, while the death rate for lung cancer has declined in men while it has continued to increase in women but is approaching a plateau. Successful screening programs for these three cancers could possibly have a major impact on overall cancer mortality in the U.S. The death rate for ovarian cancer is remaining level. Since the majority of ovarian cancers present as advanced disease with poor prognosis, while recent reports indicate that early disease

may have as much as a 93 percent 5-year survival rate, successful screening for ovarian cancer might substantially reduce mortality from this disease.

Medical literature review supports the view that screening modalities for those cancers may be effective, but no previous research has evaluated them in the framework of a definitive epidemiological study such as PLCO (Attachment 1). Uncertainty among clinicians and scientists regarding the health benefits and risks of screening for these cancers has resulted in conflicting positions in the medical community and confusion in populations at risk. The scientific basis for determining risks and benefits is inadequate. A long-term randomized controlled trial with adequate statistical power is necessary to resolve the uncertainties by determining the effects of screening on disease-specific mortality. The NCI will issue factual information on the medical benefits and risks of these screening examinations, as scientific evidence is obtained and published. These facts will be in the form currently available for other cancer sites through the Physician Data Query (PDQ) system and promulgated by the NCI Office of Communications. The PDQ is available to the public and to health care providers.

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.

OMB first approved the PLCO Cancer Screening Trial in October 1993. Since that initial approval, OMB approved the trial in 1996, 1999, 2002 and 2005. During the first approval period a pilot study was conducted to evaluate recruitment methods and data collection procedures. Recruitment was completed in 2001 and data collection continued through 2005. When participants enrolled in the trial they agreed to be followed for at least 13 years from the

time of enrollment. This request is for the ongoing data collection for years sixteen through eighteen of the study. During this period, participants will continue to be followed to ascertain cancer ascertainment and vital status through the administration of the Annual Study Update form. This form is administered to every participant every year during their participation in the study.

As the Trial progresses, 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 is, however, completely voluntary and has no impact upon their ability to have taken part in the screening component of the trial, which is now concluded.

A.2. Purpose and Use of the Information

Trials adequate to answer questions of risk and benefit have not been conducted, 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 sites 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. Refined technologies which may become available during the trial can be considered for inclusion in the protocol.

The PLCO primary endpoint is cancer-specific mortality for each of the four cancer sites (prostate, lung, colorectum and ovary). 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 will be measured and 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. The data collection instruments include the Annual Study Update (Attachment 3) and Health Status Questionnaire (Attachment 4A and

4B) which are mailed to the participants to be self-administered. The Health Status Questionnaire is gender specific and is mailed only to a subset of 2,000 participants.

During the past three years ongoing data collection has consisted of ascertaining and confirming new cancers and determination of vital status for each participant. To determine if screening reduces the mortality from these four cancers it is critical that the PLCO participants continue to be followed.

In addition to the standard follow-up procedures that have been in place since the inception of the trial, more information will be obtained from men who were diagnosed with prostate cancer. Except for information on death due to prostate cancer, we currently do not collect any further information on the clinical course of this disease, subsequent to the year in which the case was initially diagnosed. We now plan to complete the information on prostate cancer in selected PLCO trial participants. The Prostate Cancer Recurrence Questions (PCRQ) (Attachment 5) will be administered twice: once at 5-years post-diagnosis and again at 10-years post-diagnosis. The additional information collected will provide expanded opportunities to evaluate the efficacy of prostate cancer screening, with respect to non-mortal post-diagnosis clinical status, and to evaluate risk determinants of prostate cancer recurrence and spread.

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 Prostate Cancer Recurrence Questionnaire (PCRQ) were 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. The ASU is read to the participants verbatim, exactly as the data collection items are written; no other script is required.

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 on August 10, 2007 for the IT system being used to store and monitor data. The system name is NIH NCI PLCO Research Database (PLCO). A revised PIA needs to be completed and is underway. 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 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.

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 June 6, 2008, Volume 73, Number 110, Page 32338. In response to the notice, there were no public comments received.

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 10 screening centers (SCs), the Laboratory, and Westat, the Coordinating Center (CC). 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: 4/4-7/2005, 9/19-22/2005, 3/25-28/2006, 9/25-28/2006, 3/26-29/2007, 9/17-20/2007, 3/10-14-2008.
- PI Meetings and Conference Calls: 2/4/2005, 1/31/2006, 1/30/2007, 7/27/2007.

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: 11/10/2005, 5/4/2006, 11/9/2006, 10/30/2007.

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

Personally identifying information on PLCO trial participants is collected and maintained by the individual 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 (Westat) or the government. Data analyses and reports are aggregated without personal identifiers.

In addition, each participant recruited into the study signs an informed consent which states the voluntary nature of participation and provides the required assurances of confidentiality protection (Attachment 7). Confidentiality of 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 SC offices.
- Data collected at the 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 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 confidentiality protection.
- Data collected are maintained at the 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".

A model of the confidentiality protection procedures employed at the SCs is presented in a memorandum from the University of Minnesota (Attachment 8). Each SC had IRB approval, as well as OHRP certification before beginning participant recruitment. At the time of study initiation, NCI and Westat's IRBs determined that IRB review was not needed since neither receive 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" (Attachment 10).

A.11. Justification for Sensitive Questions

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 confidential 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 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 (Attachment 8).

A.12. Estimates of Annualized Burden Hours and Costs

Estimated burden hours for this OMB cycle have dropped considerably because we are experiencing more deaths with study participants as they age. In the 2005 OMB PLCO Cancer Screening Trial submission, the estimated number of respondents for Year 15 (the current year) was 145,352. However, due to the death rates, there are currently only 136,341 respondents in the trial.

For this submission, it is anticipated that there will be 135,341 respondents for Year 16 (the first year after OMB approval for the 2008 submission) which amounts to 1000 fewer respondents due to death. In previous submissions, the rate of deaths was based on estimations made much earlier in the study. The new estimations for Years 16, 17 and 18 are a more accurate reflection of the rate in which respondents are dying each year. Based on an anticipated death rate, there will be an estimated 135,341 respondents to complete the Annual Study Update (ASU) in Year 16. This will be reduced by 2,000 respondents for each subsequent year, which includes Years 17 and 18. So the anticipated number of respondents is expected to be 133,341

and 131,341 for Years 17 and 18. Over the course of 3 years, the total number of respondents will be 400,023, with an annual average of 133,341.

Of the 400,023 respondents, 4000 respondents (2000 for Year 16 and 2000 for Year 18) will also complete the Health Study Questionnaire (HSQ), and 3,200 respondents (1,200 for Year 16, and 1,000 for each of the Years 17 and 18) will complete the Prostate Cancer Recurrence Questionnaire (PCRQ). The annualized number of respondents completing the HSQ is 1,333 and for the PCRQ it is estimated at 1,067 (based on a 3-year data collection period).

The total annualized burden hours is estimated to be 11,401 for respondents to complete the ASU, HSQ and the PCRQ. This amounts to an estimated total of 34,202 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)	Total Annual Burden Hours
Male and Female Participants	ASU	133,341	1.00	5/60	11,111.75
	HSQ	1,333	1.00	5/60	111.08
Male Participants	PCRQ	1,067	1.00	10/60	177.83
Total					11,400.66

The average burden hours for the instruments differ from the 2005 OMB submission due to rounding errors that have been corrected for this submission.

The total annualized respondent burden is estimated at 11,400.66 hours at $19.29/hour, amounting to an annualized cost to respondents estimated to be $219,919 (Table 12-2). For the 3 years of data collection, the total estimated cost to respondents will be $659,756.

Table 12-2 Annualized Cost to Respondents			
Survey Instrument	**Total Annual Burden Hours**	**Hourly Wage Rate**	**Annualized Cost to Respondents by Year**
ASU	11,111.75	$19.29	$214,345.56
HSQ	111.08	$19.29	$ 2,142.80
PCRQ	177.83	$19.29	$ 3,430.40
Total			$219,918.76

The ICE number for PLCO is HN 3-012.

A.13. Estimate of Other Total Annual Cost Burden to Respondents or 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 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 $97,230 per); and non-NCI consultants to provide expertise relevant to the project and serve on the DSMB are estimated at $73,150, annually. The total annualized cost to the Federal Government for the proposed 3-year period is $12,599,193 (Table 14.1). These figures include direct and indirect costs.

Table 14.1 Annual Cost to the Federal Government			
	YEAR 16	YEAR 17	YEAR 18
Coordinating Center	$3,369,375	$3,537,843	$3,714,735
Screening Centers	7,731,148	7,884,040	8,020,527
Laboratory	575,427	599,414	0
TOTAL CONTRACTOR	11,675,950	12,021,297	11,735,262
NCI Staff	680,610	714,640	750,372
Non-NCI Consultants	73,150	73,150	73,150
TOTAL ANNUAL COST	$12,429,710	$12,809,087	$12,558,784

A.15. Explanation for Program Changes or Adjustments

Annualized burden is estimated at 11,401 hours per year for the proposed 3 years of data collection (Years 16, 17, and 18) of the PLCO trial. The annualized burden hours for the previous cycle (Years 13-15) was 23,086 hours. Estimated burden hours for this OMB cycle have dropped considerably this year because we are experiencing more deaths with study participants as they age. Additionally, a new instrument has been added, the Prostate Cancer Recurrence Questions (PCRQ) (Attachment 5) to complete information on prostate cancer in selected PLCO trial participants. The PCRQ will be administered twice: once at 5-years post-diagnosis and again at 10-years post-diagnosis.

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 and the laboratory. 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 (tenth 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.

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 1000 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.

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. After screening is completed, other modeling approaches to lead time estimation 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.

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 will be 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 will be conducted separately for each cancer site under investigation in the trial.

Complications of the screening and diagnostic procedures administered to trial participants will be recorded and monitored very closely. 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 will be examined for each cancer site at each SC for up to one year after a screening episode. Cancer incidence will also be 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 will also be 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, 140 PLCO papers have been published and 31 PLCO papers are in preparation (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.