National Cancer Institute
PLCO Etiologic and Early Marker Studies (EEMS)
Polices & Procedures
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1. Background

1.1. The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial is a large, randomized trial to determine if screening for these cancers reduces mortality. The Trial was carried out by the NCI under contract with investigators at ten clinical centers and a coordinating center in the United States.

The study enrolled 76,693 men and 78,217 women with no history of PLCO cancers, ages 55 to 74, and randomized them to an intervention arm, which received annual screening for 6 years, or control arm, which received usual care. Participants in the intervention arm received baseline (T0) and 5 subsequent annual screenings (T1-T5), and follow-up for cancer and death outcomes continued for at least 7 additional years (T6-T12). Participants in the control arm were also followed for at least 13 years after enrollment, but did not receive any screening examinations as part of the study. The ten PLCO Screening Centers began enrolling participants in 1993 and the final participants were enrolled in 2001. The screening phase of the trial concluded in 1999 for the first entrants and in 2006 for the last entrants to the trial. Extended follow-up through 2015 is on-going.

1.2. PLCO Etiologic and Early Marker Studies (EEMS)

The Etiologic and Early Marker Studies (EEMS) is a component of the PLCO Trial. By collecting biologic materials and risk factor information from trial participants, PLCO EEMS provides a rich resource for research on cancer etiology and early detection biomarkers, and by doing so adds substantial added value to the trial.

Etiologic studies investigate the environmental, biochemical and genetic risk factors for cancer. Early detection biomarker studies aim to develop reproducible, reliable biomarkers of early disease, ideally with high sensitivity and specificity, as potential screening tests. The PLCO EEMS directly addresses the following strategic priorities of the National Cancer Institute:

- Understand the causes and mechanisms of cancer
- Improve early detection and diagnosis

Data and specimens currently available for research in EEMS include:

- Demographic, dietary, and other risk factor information on all participants
- Information on all-cancer incidence and selected other medical conditions on all participants
- Fractionated blood specimens collected from the intervention arm participants at each of the 6 screening rounds
- Cryopreserved whole blood collected at T3 from intervention arm participants
- Buccal cell samples from control arm participants

Additional collections in support of EEMS research include:

- Updated risk factor information
- ER/PR status for breast cancer cases in the both arms
- Tumor tissue microarrays (TMA) and additional tissue cores for colorectal cancer, colorectal adenomas, and ovarian, prostate, lung and breast cancers.

Some unique advantages of the PLCO biospecimens include:

- Information on all-cancer incidence
- Samples were collected before cancer diagnosis
- Serial blood samples over a 6-year period
- Large participant pool without cancer for control group selection
- Initial treatment information for P, L, C, and O cancers
- Matching blood and tissue samples from the same subject

The PLCO Biorepository currently stores approximately 2.9 million biologic specimens collected from PLCO participants. These specimens and their associated data are available to all qualified researchers through a peer-review process. The scientific utilization of the PLCO Biorepository is actively managed by the NCI, with the goal of maximizing the scientific potential of the resource and meeting strategic priorities.

2. PLCO Biospecimens Resource Descriptions

2.1. Blood Specimens

At each of the six screening rounds, additional blood samples (not used for CA125 or PSA screening tests) were collected from consented screening arm participants under an IRB approved protocol. Amounts collected and fractionation protocols varied by study year (Table 1). Serum samples are available for all screening years except for T3[1]. Plasma, red blood cell, and Buffy coat fractions are available for all screening years except for the 2nd and 3rd year (T1 and T2). All blood samples were processed within 2 hours of collection following a uniform protocol and stored at -70°C or -157 °C.

Cryopreserved whole blood was collected at T3. These samples contain viable lymphocytes which can be used directly for *in vitro* functional studies and are suitable for EBV transformation to cell lines. Whole blood samples are stored in vapor phase liquid nitrogen freezers.

Table 1. Summary of blood specimens

Study Year	Specimen Type	Vacutainer	Vials/Pat.	Vol/Vial (ml)
T0	Buffy Coat	Green	1	1.8
T3	Buffy Coat	Green	1	1.8

[1] Remnant serum samples from CA-125 and PSA tests are stored for all screening participants for all study years. These samples have been thawed once, but otherwise collected and stored under the same condition as the biorepository samples. These samples are also available for research.

Study Year	Specimen Type	Vacutainer	Vials/Pat.	Vol/Vial (ml)
T3	Buffy Coat	Lavender	1	1.8
T5	Buffy Coat	Lavender	2	1.8

Study Year	Specimen Type	Vacutainer	Vials/Pat.	Vol/Vial (ml)
T4	Buffy Coat/RBC	Lavender	1	3.6
T0	Plasma	Green	2	1.8
T3	Plasma	Green	2	1.8
T3	Plasma	Lavender	4	0.8
T4	Plasma	Lavender	1	3.6
T5	Plasma	Lavender	4	1.8
T0	RBC	Green	1	1.8
T3	RBC	Lavender	1	1.8
T5	RBC	Lavender	1	1.8
T0	Serum	Red	4	1.8
T1	Serum	Red	2	1.8
T2	Serum	Red	2	1.8
T4	Serum	Red	2	1.8
T5	Serum	Red	2	1.8
T0	Serum Zinc free	Royal blue	1	1.8
T3	Whole Blood	Yellow	12	1.8

2.2. Buccal Cells

Buccal cells were collected from participants in the control arm of the trial. Eligible control arm participants supplied a single saliva sample at home using a collection kit sent to them by mail. The kit contained all the supplies required to collect and return the sample to the Biorepository for processing. Participants collected buccal cells simply by rinsing with the provided mouthwash (Scope) for 45 seconds and then spitting the mouthwash into the sample vial included in the kit. The filled vial was then returned by mail for processing.

Buccal cells were spun down and resuspended in 3ml Tris-EDTA buffer and stored in 2 vials of 1.5 ml each at -70^{o}C. These samples serve primarily as a DNA source. Although originally envisioned purely as a source of human DNA, recent advances in non-human DNA methods have made these samples a unique and extremely valuable resource for microbial and viral studies.

2.3. Tumor Tissue Microarrays

The Pathology Specimen Collection (PSC) program was initiated in January 2006 to collect tumor tissue samples from PLCO participants. Formalin-fixed paraffin-embedded (FFPE) tissues blocks were collected from pathology departments for selected cases, and Tissue microarrays (TMA)

are constructed from them. Additional tissue cores were also collected for DNA, RNA, and protein sources. Table 2 shows the TMAs currently available.

The lung cancer TMA collection also includes cases from the LSS component of the National Lung Screening Trial (NLST). Cases from the ACRIN (American College of Radiology Imaging Network) component of NLST are managed by ACRIN.

A unique value of the PLCO Pathology Specimen Collection (PSC) is that nearly all tissue samples will have corresponding prediagnostic blood samples or buccal cells from the same patients. In addition, a wealth of epidemiological and clinical data are available for each pathology specimen. These resources can be used to 1) relate environmental, biochemical, and genetic risk factors to histological and molecular-pathologic sub-types, to better specify etiologic relationships and2) relate early marker profiles to specific histological and molecular-pathologic sub-types.

Table 2. Summary of Completed TMA blocks

	Total cases	Total cores (tumor + NL)	TMA blocks (set of dup.)	Core size
Colorectal tumor	486	2851	14	1.0 mm
Colorectal adenoma	658	2026	4	0.6 mm
Ovarian tumor	213	1504	8	1.0 mm
Prostate tumor	640	3360	16	1.0 mm
Prostate tumor (CGEMS)	418	2281	11	1.0 mm
Lung tumor- PLCO	435	3773	8	1.0 mm
Lung tumor - LSS	446	3951	9	1.0 mm
Breast tumor (Female)	807	5557	14	1.0 mm
Breast tumor (Male)	11	77	1	1.0 mm

3. Policies for Access to PLCO Biospecimens and Data

- The PLCO Biospecimens resource is available to the entire scientific community. Access to the biospecimens and associated data is based on a peer review process. Details of the application and review process are described in the next section (The EEMS Application and Review Procedures).

- Only the specimens from subjects who have signed the appropriate consent will be released.

- Once a study is approved, data will be released only as "restricted-use" datasets. No identifying information will be provided in the released data sets.

- Data are non-transferable unless prior authorization by NCI has been granted.

- Recipients of PLCO samples are required to sign and abide by a NCI Material Transfer Agreement (MTA).

- Sample processing (DNA extraction, sample aliquoting, QC sample insertion and batching) shall be done at the PLCO central processing laboratories, unless otherwise negotiated during the review and approval process.

- Laboratory analyses shall be conducted in a blinded fashion. The linking of laboratory data with the corresponding individual data shall only be performed by the NCI PLCO team, and only after generation of the data. Analytic datasets will then be sent to the investigator who generated the data.
- Upon completion and publication of the study, laboratory data and final study results, with an accompanying data dictionary, shall be returned to the PLCO Trial by the investigator.

- PLCO EEMS adopts general NIH policies on data sharing, with adaptation to ensure participant privacy consistent with the informed consent. Raw and processed data as well as datasets used in a published and completed study will be made available for other appropriate research after investigators have completed their study aims. Raw and processed data will ultimately be incorporated into the study tracking system and linked to the original study and to the samples. Investigators may also be contacted by other investigators wishing to collaborate prior to completion of their study aims.

- Investigators are encouraged to develop proposals with realistic scope and focused aims, achievable within a reasonable period of time. Applications for multiple cancers/outcomes are not acceptable without strong scientific justification.

- Investigators have up to three years from the proposal approval time to request the shipment of samples and commence activities on the study. Reminders will be sent 2- and 2.5-years post approval reminding investigators of this provision. At 3 years the application will be withdrawn. A new application will need to be submitted and reviewed if the investigator wishes to conduct the study again.

- Investigators are required to complete annual progress reports. Failure to complete the progress report within 2 months will restrict an investigator's ability to submit EEMS applications and to proceed with approved applications.

- Investigators are expected to submit laboratory analysis results before they are provided with phenotype data for their population.

4. EEMS Research Priorities

This section describes the scientific objectives and priorities of the EEMS Program. Proposal applications that directly or indirectly address these objectives and priorities may be suitable for using the PLCO Biospecimens resource.

4.1. Etiologic Studies in PLCO

Risk factor characterization and association studies in epidemiologic cohorts are fundamental approaches to understanding the causes and mechanisms of cancer. The NCI Division of Cancer Epidemiology and Genetics (DCEG) coordinates investigations in PLCO of multiple inter-related environmental (including lifestyle), genetic, and biochemical risk factors for cancer and related diseases, through collaboration with a broad range of extramural scientists, the NCI Cohort Consortium and other interdisciplinary mechanisms.

To the extent possible, these investigations follow common study designs, taking full advantage of the extensive questionnaire and biologic sample base and the molecular /integrative epidemiology framework, to gain the greatest scientific benefit from proposed investigations. As a key feature of the coordination, studies in collaboration with investigators leading other large cohorts are carried out to study complex etiologic relationships and rare disease outcomes. Examples of these efforts include the Breast and Prostate Cancer Cohort Consortium (BPC3) and the Cancer Genetic Markers of Susceptibility (CGEMS) initiative. In addition to such large-scale efforts, the PLCO EEMS resource is also available for other important investigations on the etiology of cancer, and other selected diseases common to the age group of the trial participants.

In general, etiologic investigations of the effects of long-term exposure to lifestyle and environmental risk factors yield more information from specimens that are collected many years before cancer diagnosis, as opposed to specimens that are collected close to diagnosis.

However, PLCO welcomes creative and thoughtful proposals that wish to use specimens in any temporal relation to the disease outcome, as long as the use of such samples is appropriately justified.

Although serial samples may potentially be used for etiologic studies, such samples in PLCO are extremely precious and unique. Only exceptionally meritorious projects that justify the use of serial samples will be approved.

4.2. Early Marker Studies in PLCO

Biomarkers for early detection hold great potential for combating cancer. Screening and early detection has been proven to save lives from colorectal, cervical, breast and lung cancers. However, for most other cancers, there is currently no effective tool for screening or early detection. The NCI Division of Cancer Prevention (DCP) is committed to basic and clinical research in developing and evaluating early detection biomarkers.

The Early Detection Research Network (EDRN) and the Specialized Program of Research Excellence (SPORE) are the two NCI initiatives already in place to provide resources, infrastructure and scientific expertise for early marker research. Investigators from EDRN and SPORE, as well as other extramural research institutes have been using the PLCO specimens to further evaluate promising biomarkers.

As illustrated in the text box below, a common process for developing biomarkers follows a series of phases, much like the drug development process. PLCO resources are most suitable for Phase III studies and in some cases for Phase II studies as well. Suitable studies should address questions including but not limited to: 1) how well can a biomarker distinguish sera collected from healthy individuals who later developed cancer, from those who did not; and 2) how early, before clinical diagnosis, a biomarker can detect cancer (commonly referred to as lead time).

In exceptional cases, PLCO specimens may be used for laboratory discovery of new biomarkers. Current biomarker research is severely limited by the lack of quality specimens. Clinical samples, typically used for biomarker discovery, are often biased in a systematic way that may lead to false discoveries or missed opportunities. Worse still, false discoveries lead to wasted downstream efforts and resources. Recognizing the critical role of high-quality specimens for discovery, PLCO will consider supporting discovery-based studies in special cases where there is compelling reason to do so. However, PLCO resources are limited, and they cannot meet the broad needs for all discovery-based research.

Phases of Biomarker Development in EDRN

(From M. Pepe et. al., *Journal of the National Cancer Institute*, Vol. 93, No.14, July 18, 2001)

Phase I: Preclinical exploratory studies to identify potential useful biomarkers.
Phase II: Clinical assay and validation studies to assess the capacity of biomarkers to distinguish between people with and without cancer.
Phase III: Retrospective longitudinal repository studies to determine if biomarkers can detect cancer before clinical diagnosis.
Phase IV: Prospective screening studies to determine the operating characteristics of the biomarker-based screening test.
Phase V: Randomized clinical trial to estimate the reduction of cancer mortality by the screening test.

4.3. Biospecimens Research

PLCO strives to adapt to the NCI Best Practices and to improve management practices to ensure quality control/quality assurance of the biospecimens.

Consistent with the goals for evidence-based best practices, PLCO will support limited pilot studies to assess quality of the PLCO specimens or suitability of certain assays (note that an EEMS application is required for all pilot studies). Specifically PLCO may consider the use of certain PLCO specimens (as specified in the Specimen Use Guidelines) to systematically evaluate the quality of the PLCO samples with regard to:

- Assay reproducibility
- Long-term intra-individual variation in analyte levels
- Effects of long-term storage on certain analytes or assays
- Effects of different sample processing methods on certain analytes or assays

5. PAR-25-248 Request for Specimen Verification and Policies

The NCI has issued a Notice of Funding Opportunity (NOFO) utilizing the PLCO Biospecimens Resource to Bridge Gaps in Cancer Etiology and Early Detection Research (PAR-25-248), for soliciting grant applications to utilize the PLCO Biorepository. This application requires a letter of support confirming the specimen availability, which can be obtained using the Request for Specimen Verification on CDAS. The full application instructions for this funding opportunity can be found here: https://grants.nih.gov/grants/guide/pa-files/PAR-25-248.html. If the study is approved for funding, the applicants are required to follow all EEMS policies and procedures listed in this document.

6. EEMS Application and Review Procedures

A goal of the EEMS application and review process is to ensure fair, equitable access to PLCO resources based on scientific merit and NCI priorities. Preliminary applications for access to the

PLCO biospecimens are accepted on a rolling basis. Upon receipt, proposals are reviewed for feasibility by NCI PLCO EEMS Staff. The purpose of this initial review is to ensure sample availability and concordance with PLCO EEMS scientific objectives and priorities. Please note, if you would like a letter confirming availability of specimens for a grant application, you must submit your request 1 month before you need it. Letter requests can be made through the discussion section of the preliminary application. Upon acceptance of the preliminary application, a final application may be submitted.

Final proposals are accepted on a twice yearly basis (June/July and January/February). They are reviewed by the PLCO EEMS Review Panel (see Section 7) for scientific merit. The EEMS Steering Committee (see Section 7) makes the final decisions based on the Panel review results and recommendations. Final decisions are communicated in writing to the applicants along with reviewers' written critiques. The current turnaround time is about 4-6 months.

If after the panel review the EEMS Steering committee requires clarifications to the final proposal the applicant has one year to respond to these clarifications. Failure to respond will result in the application being withdrawn. The applicant may apply again in a later round, but will be expected to respond to the clarifications at that time.

Application materials and all other relevant EEMS documents are posted on the Cancer Data Access System (CDAS) website https://cdas.cancer.gov/. Information on the specimens is also available on that website. Announcement of the upcoming open review cycle is emailed to prospective applicants on the EEMS mailing list about two months before the submission deadline; it is also posted on the above-mentioned PLCO website.

7. EEMS Proposal Evaluation Criteria and Considerations

Due to the exhaustible nature of the biospecimens, stringent evaluation criteria apply to the selection of proposal applications. In addition to the overall scientific and technical merits, a research proposal must demonstrate the need and suitability to use PLCO specimens. Parsimonious use of the samples is a must. Additional programmatic and resource management considerations will also be used to evaluate and prioritize research projects.

The below sections describe in more detail some of the specific requirements that are of particular importance.

7.1. Scientific and Technical Merit

7.1.1. Overall Study Design

Study design must be consistent with study aims, including appropriate choice of study subjects, assays, statistical methods, study power, and must address potential confounders and biases. Because of the importance of assay operating characteristics in the laboratory being used for a study, pilot studies may be needed to address inter- and intra-batch variability and inter- and intra-person variability, with the intraclass correlation coefficient (ICC) being a key parameter in determining the adequacy of approach. For high-dimensional data, a plan for independent validation should be included. Since some of the PLCO samples have been stored for many

years, potential analyte degradation needs to be considered. Multiplex assay approaches that minimize volume requirements are preferred.

For early marker studies, data from Phase II studies will be the basis for evaluation of a Phase III validation study. Performance indicators, i.e. sensitivity, specificity, and area under the ROC curve must justify the use of the irreplaceable PLCO samples. Performance requirement depends on the nature of the biomarker and the public health need, and will be evaluated on a case-by-case basis. Phase II studies may be considered for high priority public health needs, such as ovarian and pancreatic cancers, for which early detection tools are urgently needed. The proposed biomarker must show strong preliminary data with demonstrated reproducibility in independent sample sets. Preliminary data, ideally published in at least one peer-reviewed scientific journal, should be available to support the proposed research aims.

If the proposal is from an EDRN or SPORE investigator, the proposal may be evaluated in consultation with the EDRN or SPORE Program Official(s) overseeing the preliminary study.

Laboratory discovery of new biomarkers may be supported on a case-by-case basis. Additional criteria may include, but are not limited to:

- Public health needs
- No other suitable resources are available
- Research on rare cancers that requires pooling of samples from different sources
- Overall excellence in study design and data analysis plan
- Use of proven, matured technologies
- Parsimonious use of samples

In general, studies requesting serial samples (or longitudinal samples) are required to be conducted in a phased manner. In the first phase, the most proximate samples will be allocated to demonstrate assay performance. Serial samples may be used to determine temporal pattern, or lead time in a second phase, contingent upon promising results from the first phase. A new proposal that uses the initial results to convincingly justify the necessity of serial samples is required for the second phase.

7.1.2. Statistical Methods

Applications should include an analytic plan and a statistical methods section. It is also recommended that a biostatistician be included as a co-investigator. They should also include a proposed sample size and provide the estimated statistical power for the analysis. For studies with a large number of analytes, statistical adjustment for multiple comparisons must be used.

7.2. EEMS Programmatic Considerations

7.2.1. Collaboration & Coordination

Investigators not familiar with the PLCO trial and the PLCO biospecimens resource are particularly encouraged to seek collaborations or feedback. Duplicate or highly similar efforts are not supported in general. Investigators with similar ideas and approaches are usually asked to develop a collaborative project.

Programmatic and logistic coordination may be beneficial when multiple studies are ongoing and addressing related scientific questions. An example is studies that focus on the same cancer, and can use the same sampling plan and a core dataset. Use of a common sample and data set facilitates direct comparison or integration of data across studies. In addition, it is often necessary to coordinate among multiple studies so that the samples can be aliquoted at once, minimizing freeze/thaw cycles and saving labor cost. These considerations were key points in becoming involved in large consortial efforts to enlarge sample size.

Developing the most effective approaches for sample management is an on-going process and may evolve rapidly. EEMS does consider requests on a case-by-case basis, with application of the above-described principles.

7.2.2. Balancing Current & Future Needs

Management of the biologic sample resources requires judicious balancing of the need to further the NCI goals in the short-term *versus* preserving samples for unforeseen future uses. The PLCO leadership takes stewardship of the resource most seriously, and decision rules, documented in the PLCO Biospecimens Use Guidelines, have been established to assure maintenance of critical levels of the samples for future studies for all study subjects.

Demands for samples will certainly increase with advances in the science, but time may also work in our favor, with advanced technologies tending to require less and less sample. For example, the DNA requirements for genome-wide association studies have fallen dramatically over the last few years. Whole genome amplification methods or EBV transformed cell lines generated from cryopreserved blood samples can be potentially used to enlarge the DNA base resource. Similar trends may occur for protein-based multiplex assays, such as Luminex. At this point, DNA resources from whole blood in the trial are quite adequate for most foreseen studies, while serum and plasma resources are more susceptible to depletion. However, the material from the buccal cell collection in the control arm is far more limited and thus more precious.

7.2.3. Proximate Samples vs. Distant Samples

A consideration in resource allocation is the somewhat different sample needs for etiologic and early marker research. For etiologic studies, samples collected too close to the date of diagnosis, or post-diagnosis, may be of limited use, because of concerns that putative disease risk markers may actually reflect disease state (so-called reverse causation bias). For this reason, it is a generally accepted practice to exclude from etiologic studies cases diagnosed within one year of blood draw. On the other hand, the 6-month to 3-year period prior to case diagnosis is probably of greatest interest with respect to early disease markers. Obviously, these are not invariable rules and there are overlapping demands, but this affords some flexibility in planning, particularly as the cohort follow-up extends, shifting the balance from short to longer-term follow-up times.

7.2.4. Serial Samples

While serial blood samples are available from the PLCO Biorepository, these are more limited in quantity (both sample volume and sample size) than single time point samples. For this reason,

investigators who propose to use serial samples must provide strong justification as to why serial samples are required in order to address the research questions. Applications requesting the use of serial samples will be subjected to additional scrutiny during scientific review and a higher bar for approval.

Serial samples are invaluable for etiologic and early detection studies. Both types of studies benefit from the ability to do small pilot studies to evaluate the intraclass correlation coefficients (ICC), because markers with poor ICC characteristics are unlikely to be informative in either type of investigation. In etiologic studies, measurements from samples collected at several time points could provide a better time-integrated estimate of "exposure," although so far this approach has been used only on small sub-samples, due to sample use burdens. For early detection studies, measurements at several time points can provide a picture of the time course of relevant marker levels prior to diagnosis, of critical interest in establishing screening frequency protocols and lead time. EEMS maintains that these time-related evaluations should occur only after PLCO studies demonstrate that the analysis from the disease-proximate samples shows adequate performance results.

7.2.5. Quality Control

Certain quality control measures should be incorporated into proposed assays. Pilot studies will be required for new assays to establish assay reproducibility. A pilot study typically involves a small number of samples, with the assays done laboratory-blinded and in repeat samples. Data from a pilot study must be evaluated and approved by NCI before full analytic samples can be released.

Systematic blinded QC sample insertion in the full analytic batch is necessary for monitoring assay quality. This is particularly important when samples are being assayed over an extended period of time. To minimize sample deterioration, thawing of samples will be coordinated to the extent possible at the PLCO processing lab. Aliquots of various sizes will be made at the first thawing of the samples to reduce freeze/thaw cycles.

7.2.6. Parsimonious use of samples

Regardless of study types, parsimonious use of the samples is a must, as PLCO samples are precious and depletable. To ensure that no amount of the biospecimens will be wasted, investigators must provide detailed justifications for the amount of samples requested. Investigators may be asked to list the exact amount of samples needed for each assay or laboratory method.

8. EEMS Management Infrastructure

The NCI Division of Cancer Epidemiology and Genetics (DCEG) and Division of Cancer Prevention (DCP) collaborate in the joint management of the EEMS program. Both Divisions are committed to supporting the PLCO EEMS infrastructure, providing extensive capabilities in biospecimens management and tracking, as well as scientific coordination, administration and strategic planning.

8.1. EEMS Steering Committee

NCI guidance and oversight of the management of the PLCO EEMS is carried out by the EEMS Steering Committee (SC), comprised of NCI scientists. The SC develops management policies and procedures, provides oversight and direction to the day-to-day management of the studies, and resolves conflicts over management and policy issues. The SC is composed of NCI staff from the Division of Cancer Prevention (DCP) and the Division of Cancer Epidemiology and Genetics (DCEG). All decisions of the SC are subject to review and approval by the DCP and DCEG directors.

8.2. EEMS Review Panel

The PLCO EEMS Review Panel is responsible for the peer-review of proposals submitted to the PLCO EEMS program. The panel is comprised of two NCI scientists from the extramural divisions (DCP and DCCPS), two NCI scientists from the intramural division (DCEG), two scientists from the PLCO screening centers, two biostatisticians (academic or NCI) and two academic scientists not associated with the PLCO Trial who have expertise in biologically based epidemiologic cohort studies. If needed, *ad hoc* reviewers may also be chosen for specialized areas of expertise. The Panel makes recommendations to the PLCO EEMS Steering Committee based on scientific and technical merits of each proposal.

Each panel member serves a 3-year term, with some exceptions. Although panel members are allowed to submit an EEMS application, or to be a co-investigator on an EEMS application during their term, they must recuse themselves from evaluating or discussing these applications. They are required to acknowledge any potential conflict of interest as soon as they are aware of such.

8.3. Contract Support

Contract support coordinates the EEMS application and review processes including the EEMS panel review meeting, and monitors progress and tracks status of all approved studies. Contractor also provides support for day-to-day biospecimens management actives, and the post-approval sample requisition process.

8.4. Study Management and Tracking

The Cancer Data Access System (CDAS) is developed and maintained by a contractor. All completed and on-going studies are stored in the database, including proposal abstracts and annual progress status. Prospective investigators can search for past and current research activities that may be related to proposed studies, thereby avoiding duplicate effort. The EEMS proposal review process is also managed and tracked by this database system.

8.5. Biospecimens Use Guidelines

A separate document entitled “Biospecimens Use Guidelines” has been developed to provide specific guidelines for each material type. The goal of the guidelines is to prevent sample depletion, and to ensure appropriate use of the samples, including quality controls. Sample selection must be based on the guidelines. Sample requests that violate the guidelines must be approved by the NCI.

9. EEMS Appeal Process

If an applicant has concerns about an EEMS Panel review and wishes to appeal the review outcome, he/she must submit a formal appeal letter within 30 days of the date on the final decision letter. An appeal letter must describe specific issues with the review. Appeals based solely on differences of scientific opinion will not be accepted. The EEMS Steering Committee will conduct the initial review of the appeal and make recommendations to the NCI Division Directors (Division of Cancer Prevention and Division of Cancer Epidemiology and Genetics). The Division Directors will make the final decision. There are three possible outcomes: 1) the appeal has merit and the application is approved, with or without certain conditions; 2) the appeal has merit and the application will be re-reviewed in the next round; and 3) the appeal has no merit and is rejected. The outcome of an appeal is final and cannot be appealed again.

10. EEMS Policy Regarding PLCO Genome-Wide Association Studies (GWAS) Data Access

Data from GWAS studies done with PLCO samples is available through the NIH and NCI established data policies that enhance access, maximize scientific use, adhere to ethical guidelines, insure fair play, and protect stakeholders. Clear guidelines can also avoid duplicative studies and enhance collaborative opportunities through a transparent process for approval and making available information on existing studies.

PLCO specimens have been used in multiple GWAS studies. Upon completion and publication of a GWAS study, the genetic data may become available through the database of Genotypes and Phenotypes (dbGaP) website (http://www.ncbi.nlm.nih.gov/gap/?term=plco). If you are considering using PLCO specimens to conduct Single Nucleotide Polymorphism (SNP) analyses for cancers where GWAS studies have been conducted, you will need to consult with the SNP list used for those studies.

Any bona fide research group may apply through dbGaP (http://dbgap.ncbi.nlm.nih.gov/aa/wga.cgi?login=&page=login) for access to PLCO GWAS data from published studies. This application includes verification by the institution that the investigators are full time employees, the IT system meets specific standards for the protection of sensitive data, any posted embargo will be respected, and the research will conform to standard protections of privacy and confidentiality. The investigator must also describe appropriate research goals.

All posted PLCO GWAS data have limited covariates associated with the genotypes. Individuals who receive GWAS data do not automatically receive access to other covariate data. Additional covariates are available only through the CDAS website (https://cdas.cancer.gov/learn/plco/instructions/). Approval can be gained through the PLCO data only application process, or through the EEMS process if biospecimens are also requested. Investigators may request and receive data from a more comprehensive set of covariates. After approval is obtained, a dataset will be created for the investigator containing requested covariates and ID linkage to GWAS data. Attempts to identify individuals for other linkage to preexisting PLCO datasets will be considered a violation of the Data Use Certification that is agreed upon for the release of genotype data. These violations are taken very seriously by NCI and NIH and may lead to censure and removal of funding.

11. EEMS Policy on Addenda

Certain circumstances may merit an addendum request to an approved on-going EEMS study. The addendum process is intended, in general, for small scale extension of an existing EEMS project. Requests of no more than 10% of the original request, either sample size or amount of the materials, are considered suitable for an addendum. Requests larger than 10% of the original approved requests, or limited expansion of scientific scope or aims, may be considered on a case-by-case basis by the EEMS Steering Committee. In general, no more than 3 addenda should be submitted per study (an addendum that does not involve new biospecimens, such as adding a PI or changing PI institution, is not counted toward the allowance).

Addenda that substantially expand the scope of the project—for example, examining a different class of markers, a different technology of assessment, or a different endpoint, will not be approved. These require a new application. NCI will make final decisions to accept or deny addendum requests.

12. EEMS Data Return and Data Sharing Policy

PLCO adopts NIH policies on data sharing, adapted as needed to ensure privacy protections consistent with the informed consent. When investigators generate new biomarker data using PLCO biospecimens, these data must be shared with PLCO and, ultimately, with the broader research community. To help ensure this occurs, PLCO ships only blinded specimens for biomarker analyses. To unblind specimens (and receive other participant data), investigators must submit their biomarker data (and relevant data dictionaries) to PLCO. These data are kept confidential by PLCO until the investigators publish their results or 18 months have passed since unblinding—whichever occurs first. After this period, other qualified researchers may request access by submitting a proposal to PLCO and receiving approval. If investigators wish to extend the 18-month confidentiality period, they must submit a strong written justification and obtain approval from PLCO.

For some especially large datasets (e.g. whole genome sequencing datasets), transfer of data to PLCO may pose a non-trivial technical challenge. If necessary, upon consultation and determination by the PLCO staff, datasets can be submitted to PLCO through NCI's Cancer Research Data Commons (CRDC) (https://datacommons.cancer.gov/explore/data-commons), or other appropriate repository listed here (https://www.nlm.nih.gov/NIHbmic/domain_specific_repositories.html). Investigators who wish to deposit data in a different repository must provide a strong written justification and obtain PLCO approval. Data and documentation provided to these other repositories should align at minimum with expectations required for submission to the NCI's CRDC.

In publications, there must be a statement informing the community of the name(s) of the data repository where the data has been deposited into (e.g PLCO CDAS or CDRC) and the associated accession number for data retrieval (e.g. EEMS ID).

Below is the list of data elements and other information that must be submitted to PLCO.

Assay Data: for each sample provide the following:

1. Sample ID (provided by PLCO)
2. Marker name(s) (include full protein name, gene symbol and aliases so that there is no ambiguity in the marker identity)
3. Marker measurement(s) (specify unit of measurement, assay batch number)
4. Name of the assay platform
5. Date and time assay performed
6. Reagent lot/batch number
7. Instrument(s) and calibration
8. Any QC data on the PLCO samples (as an example, PH level)
9. All other QC data
10. Missing value indicator and reason(s) for the missing value
11. If applicable, case/control predictions

Descriptive information

1. Name of the laboratory that performed the assay measurements
2. Name of the Principal Investigator responsible for the data submitted/Owner of the data
3. Study ID (EEMS XXXX-XXXXX) and title
4. Technical description of the assay platform(s)
5. Detailed assay protocol, including specimen preparation method
6. Description of method for normalization of marker measurements if applicable