Appendix 1-1

LUNG SCREENING STUDY
PROTOCOL

Purpose of this PLCO Special Study:

The PLCO trial is assessing the mortality impact of single view (PA) chest X-ray (XRY) for lung cancer screening. In a clinical series published by Henschke, et al. in 1999 [1], spiral CT (SCT) detected more benign, indeterminate, and malignant lung lesions among heavy smokers than did chest X-ray. The public health implications of this finding are not established. The National Cancer Institute (NCI) is contemplating a randomized controlled trial to determine if lung cancer screening with SCT will result in reduced lung cancer mortality compared with XRY screening. The findings of Henschke, et al. [1] are representative of a selected clinical series. Additional data contrasting SCT with XRY performance in a screening environment are required as a basis for further evaluation of SCT for lung cancer screening.

The NCI, through this PLCO Special Study, seeks to measure in two randomly assigned and comparable screening populations of age-eligible smokers the lung cancer detection rates of single view (PA) XRY compared to SCT. Both groups will be followed to compare the spectrum of benign and malignant conditions discovered in each, and the medical burden of diagnostic work-up will be determined. Follow-up will include ascertainment of adverse medical outcomes.

Scientific Background:

Lung cancer is the leading cause of cancer-related death in the United States [2]. It is estimated that 157,000 persons will die of lung cancer in 2000 [2]. Although the most straightforward way to reduce lung cancer risk is to stop smoking, smoking cessation programs have had limited success. Furthermore, an elevation in lung cancer risk is believed to remain, at least in the short-term, for persons who are recent quitters. Because symptoms of lung cancer often do not appear before disease is advanced, secondary prevention is an appealing option.

Attempts to evaluate lung cancer screening modalities began over 25 years ago. Early studies, including the Philadelphia Pulmonary Neoplasm Research Project [3], the Veterans Administration Study [4], the South London Lung Cancer Study [5], the North London Cancer Study [6] and the Kaiser Foundation Health Plan Multiphasic Screening Trial [7], observed no significant impact of screening. Many of these studies had serious design limitations and as such, the NCI sponsored, in the 1970's and 1980's, three randomized controlled trials to assess lung cancer screening modalities. Trials conducted at Johns Hopkins [8] and Memorial Sloan-Kettering [9] examined whether a regimen of chest X-ray and sputum cytology vs. chest X-ray alone reduced lung cancer mortality, and observed no reduction in lung cancer mortality for participants receiving chest X-ray and sputum cytology. The trial conducted at the Mayo Clinic [10] assessed whether an intense regimen of chest X-ray and sputum cytology (every 4 months) vs. usual care (recommendation to receive annual chest X-ray and sputum cytology) reduced lung cancer mortality. No reduction in lung cancer mortality was observed for the intensely screened arm.

Because the trial conducted at the Mayo Clinic (known as the Mayo Lung Project) [10] also had design limitations, the NCI is funding a study of chest X-ray versus usual care as part of the ongoing PLCO Cancer Screening Trial [11] to determine whether an annual screening chest X-ray can reduce lung cancer mortality. Randomization, screening, and follow-up of participants are still in progress.

Early results from another NCI sponsored project, the Early Lung Cancer Action Project (ELCAP) [1], indicated that spiral CT can identify many more lung lesions than can chest X-ray. ELCAP enrolled 1,000 volunteers (current or former heavy smokers) to receive both spiral CT and chest X-ray. There was no control group for this clinical series. Spiral CT identified non-calcified nodules in 233 participants while chest X-ray identified 68. Twenty-seven lung cancer lesions were detected. The public health significance of these findings is unknown.

Recent reanalysis of the Mayo Lung Project [12] data suggests that so-called "indolent" lesions exist in lung cancer – these are lesions with malignant morphology but little-to-no clinical relevance. These lesions would not have been detected in the absence of screening. Screening with spiral CT will likely identify indolent lesions and could result in many unnecessary diagnostic and treatment procedures. Diagnostic and treatment procedures for lung cancer are not without risk, and have been known to result in death.

Project Description:

Administrative Structure:

Because this project is a special study within the PLCO trial, administrative and functional components of the PLCO will be followed. A detailed description of the administrative and functional procedures of the PLCO trial appears in the PLCO Manual of Operations and Procedures. PLCO is directed by NCI Project Officers with advice from the Steering Committee and oversight by an independent data safety and monitoring panel (the Monitoring and Advisory Panel). The work is carried out at ten screening centers nationwide with coordination and data management provided by Westat.

Six existing PLCO screening centers serve as study sites. Each site is randomizing approximately 500 individuals over a 2-month period.

Screening center tasks include:

- Recruitment
- Assessment of eligibility
- Informed consent
- Randomization
- Screening
- Assessment of compliance and contamination
- Reporting of screening results to participants and physicians
- Ensuring diagnostic follow-up of positive screens
- Abstracting medical record information
- Shipping of depersonalized data forms to the Coordinating Center
- Maintenance of current, complete, and secure case files

Coordinating Center tasks will include:

- Coordination:
  - Weekly meetings with NCI personnel to review progress and resolve problems.
  - Provide minutes of all meetings
  - Maintaining close contact with screening centers
  - Monitoring progress and protocol adherence at screening centers
  - Preparation of a monthly status report for the Project Officer
  - Coordination of conference calls as needed
  - Review and approval of credentials of spiral CT and chest X-ray examiners and trainers.
  - Development of study-specific information to supplement PLCO Manual of Operations and Procedures (MOOP)
  - Maintaining of an indexed protocol decision log
  - Maintaining a central records file
  - Development and printing of all study forms
  - Training of staff on all study forms
  - Preparation of OMB package

- Data Management:
  - Receiving, keying, and editing enrollment, contamination, compliance, screening, and follow-up data
  - Development and maintenance of a centralized randomization system
  - Development and maintenance of a centralized receipt control and Study Management System
  - Development and maintenance of documentation
  - Centralized data processing, management and preparation of reports

Recruitment:

Methods:

Selected screening centers will primarily use mass mailings to recruit 500 participants each. Other potential recruitment methods include posters in medical facilities, recommendations from clinical practitioners, and advertisements in newspapers or magazines. The information package to be either mass-mailed or supplied to interested persons will contain a cover letter, a fact sheet, a toll-free phone number to call if the potential participant has questions, and a reply card for the participant to return if he or she is interested in participating. It is estimated that each screening center will need to mail roughly 166,000 packages to obtain 500 eligible and interested participants.

Once the screening center receives a call or a reply card from an interested person, the screening center will determine eligibility using the Eligibility Screener. The Eligibility Screener form will query the participant as to age, smoking history, and lung cancer history, as well as other eligibility criteria. The form also will ask the person to provide his name, address, and telephone number. If the person is deemed eligible and is still interested, an appointment will be made either for an orientation session or screening.

Eligibility criteria:

- Ages 55-74 on date of randomization
- Cigarette smoking history of at least 30 pack-years
  - Current smoker or former smoker who has quit within 10 years of randomization

Exclusion criteria:

- Spiral CT exam of the lungs or chest in the 24 months prior to randomization
- Known previous history of lung cancer
- Currently undergoing treatment for any cancer other than non-melanoma skin cancer
- Previous removal of any portion of the lungs
- Unwilling or unable to sign the consent form.
- Participating in another cancer screening trial, including PLCO
- Participating in a primary cancer prevention trial other than a trial of smoking cessation.

Informed Consent:
Interested participants will be asked to sign an informed consent prior to randomization. This may be in advance or at their first visit to the screening center. The informed consent describes the study, study procedures, potential benefits and risks, alternatives to participation, the randomization process, the person's rights, potential costs, and procedures to maintain confidentiality. The name of at least one person in the screening center to contact and a phone number to call will be provided in the informed consent. A screening center staff member will be available to answer questions regarding the informed consent while the interested person is reading it over.

Randomization:
Randomization will occur via Internet access to a secure Westat web site. Each screening center will therefore be able to perform randomization at any time of the day on their own. Randomization will be stratified by gender and age group within each screening center. Randomization procedures will result in roughly equal numbers of participants in each study arm (spiral CT and chest X-ray). Randomization will begin on September 1, 2000 and conclude on October 31, 2000.

Screening:
Participants randomized to the spiral CT arm will receive one spiral CT scan; participants randomized to the chest X-ray arm will receive one PA chest X-ray. Screening tests are to be scheduled as soon after randomization as practical. Board certified radiologists will review the chest X-rays and the CT scans; findings will be noted on standard chest X-ray or spiral CT forms developed for this special project by Westat.

Positive Screens:
If a nodule that is suspicious for lung cancer is visualized on either chest X-ray or spiral CT, the screen will be considered positive. Other abnormalities not suspicious for lung cancer (for example, emphysema) also will be noted. Positive screens are defined in Chapters 4 and 5 of the Manual of Operations and Procedures.

Follow-up to Positive Screens:
Test results will be sent by mail to participants and their primary care physicians within three (3) weeks of exams. If a screening test is positive, i.e., is suspicious for lung cancer, the SC staff will notify the participant by telephone. If the participant is unavailable by telephone, results will be sent via certified mail. Positive screening results will be transmitted to physicians either via telephone, FAX or certified mail. The letters to the participant and his/her physician accompanying the screening results report will encourage appropriate diagnostic work-up. If the participant does not have a primary care physician, s/he will be offered a list from which to choose a referral physician. Work-up following a positive chest X-ray of the lungs is well established, and the standard of practice will be noted in the referral. Work-up following a positive spiral CT screening is not well established. Background information regarding appropriate work-up options for the spiral CT screen that are consistent with evolving opinion among experts will be provided to physicians who request such information, but specific recommendations on work-up will not be made.

When it has been determined that diagnostic work-up has been declined by a participant, this fact shall be recorded and dated, and any supporting information should be included in the participant's file.

Risks Associated With the Screening Procedures:
There may be certain risks and/or discomforts associated with the screening chest X-ray and spiral CT. A small amount of radiation is received as part of the chest X-ray; more radiation, but still a relatively small amount, is received as part of the spiral CT. This information is described in the informed consent.

Another issue is that it is possible that some of the cancers detected by the screening tests under investigation in this study may be very slow growing. It is possible that diagnosis (and treatment) of cancers detected in this study may not prolong life and may result in adverse outcomes. Additionally, it is possible that the screening tests may falsely suggest that a person has cancer. In this case, it is possible that some participants may suffer pain, anxiety, and expense that would never have occurred if the individuals had never undergone the screening tests. These factors are noted in the informed consent also.

Data Reporting:
Rapid reporting of data is essential. Each screening center shall ship to the Coordinating Center on a weekly schedule all pertinent data. Standard data forms designed for this Special Project will be used. All data sent to Westat shall be depersonalized and identifiable only by participant ID number before shipment by the screening center. Reported data shall include:

- participant study identification number,
- participant age, smoking history, and history of chest spiral CT,
- participant randomized group, initials, gender, date of birth, and date of randomization into the study,
- date and result of screening test for each participant,
- sufficient information regarding diagnostic procedures performed as a result of a positive screening test to allow determination of whether a cancer was or was not diagnosed as a result of screening,
- complete description of all procedures and medical or morbid events possibly associated with the test, and description of any diagnostic procedures subsequent to a positive test,
- for every lung cancer diagnosed during the special study in both randomized groups, date of and age at diagnosis, histology and stage at diagnosis,
- contamination data on a randomly selected sample of participants with negative screening results.

TIMELINE

Date	Activity	Responsible Party
September 1, 2000	Initiate recruitment, consenting, randomization, screening, and data reporting	Screening Centers
October 31, 2000	Complete recruitment of 400-500 participants (per screening center). Initiate medical record abstracting	Screening Centers
October and November, 2000	Analyze recruitment data	NCI and Westat
January 31, 2001	Conclude screening	Screening Centers
January through August, 2001	Analyze screening and follow-up data	NCI, Westat, and IMS
May through June 2001	Contamination Assessment	Screening Centers and Westat
June-August, 2001	Draft final report	NCI
August 31, 2001	Conclude project. Finish final report	NCI

References

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