1. INTRODUCTION

This chapter presents an overview of the Lung Screening Study and an introduction to this document, the Manual of Operations and Procedures.

1.1 Background of the Lung Screening Study

Lung cancer is the leading cause of cancer-related death in the United States among men and women, afflicting about 172,000 each year and killing about 157,000. Disagreement over spiral computed tomography's (CT) place in lung cancer screening continues. Considering results from the Early Lung Cancer Action Project, some proponents say that the technology could be the single most important advance in decades, claiming that it could increase lung cancer five-year survival to 80%. Others say that the exact benefits and risks have yet to be determined and are asking for better proof. The argument appears to reflect a much larger divide over what evidence is required and how it should be obtained before an emerging cancer early detection technology is adopted. While spiral CT represents one of the most exciting new imaging techniques, it needs to be studied appropriately if the technology is to be translated into an effective screening tool.

Uncertainty regarding the efficacy of spiral CT in reducing lung cancer mortality has resulted in conflicting positions in the medical community and confusion in the populations at risk. A multi-center randomized study is required to definitively assess the efficacy of spiral CT in reducing lung cancer mortality. At this point it is unknown and there is much debate regarding whether a trial investigating spiral CT screening for lung cancer with a mortality endpoint could recruit an adequate number of eligible participants at a suitable rate. The Division of Cancer Prevention (DCP) of the National Cancer Institute (NCI), in collaboration with six Screening Centers (SCs) throughout the United States, is seeking to obtain critical information necessary to design a long-term randomized controlled trial. That critical information will be obtained in the Lung Screening Study, a special project of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO). The Lung Screening Study will utilize six PLCO SCs to randomize a total of 3,000 men and women at high risk of lung cancer to either a one-time screening spiral CT or chest X-ray exam.

1.2 Objectives of the Lung Screening Study

The primary objective of the Lung Screening Study is to measure the lung cancer detection rates of single view (postero-anterior) X-ray and spiral CT. Randomization will be used to assign 3,000 individuals at elevated risk of lung cancer to one of the two screening modalities. Both groups will be followed to compare the spectrum of benign and malignant conditions identified with each screening exam; the medical burden of diagnostic work-up also will be determined. Follow-up will include ascertainment of adverse medical outcomes associated with diagnostic work-up. Additionally, the Lung Screening Study will obtain critical information necessary to inform the design of a future large randomized controlled clinical trial of spiral CT with lung cancer mortality as the primary endpoint. The Lung Screening Study will allow the NCI to:

- Determine whether an adequate number of eligible participants can be recruited at a suitable rate:
  - SCs will recruit, consent and randomize a modest number of individuals (3000) nationwide over a two-month period to measure recruitment yield and assess the potential to conduct a trial.
  - Randomized individuals will be screened to assess compliance.
- Determine the medical burden of diagnostic work-up following spiral CT screening and chest X-ray screening.
- Estimate contamination and compliance of randomized individuals in a randomized controlled trial involving spiral CT.

Additional information regarding the design and objectives of the Lung Screening Study is provided in the study protocol (see Appendix 1-1).

1.3 Organizational Structure

The NCI, the Coordinating Center, and the six Screening Centers are the groups involved in designing, conducting and monitoring the Lung Screening Study. The roles and responsibilities of each group are described below.

1.3.1 National Cancer Institute

The PLCO Project Officers, Drs. John Gohagan and Philip Prorok, are responsible for design and oversight of all aspects of the Lung Screening Study. They will work directly with the Coordinating Center (CC), which will provide support for the development and implementation of the study protocol; Drs. Gohagan and Prorok also will work with the Principal Investigators from each of the SCs to ensure that the technical aspects of the study are carried out under rigorous scientific standards. The NCI Project Officers are also responsible for coordinating the analysis of the data generated by the Lung Screening Study and the dissemination of the results of the special study for the purposes of designing a randomized controlled trial. As detailed in various sections of this manual, the SCs are required to submit certain documentation regarding their plans and procedures to the NCI Project Officers for review and approval.

The NCI Contracts Officer is responsible for all contractual matters between the NCI, the CC, and each of the SCs.

1.3.2 Coordinating Center

The Coordinating Center (CC), Westat, will work closely with NCI and other study investigators to ensure overall success of the Lung Screening Study. The CC will coordinate activities related to the development of the study protocol, arrange and document meetings, and produce standardized study materials, including this Manual of Operations and Procedures. The CC will also be responsible for training the SC Coordinators and medical record abstractors on study procedures. The CC will monitor the work completed at the SCs through receipt of reports and data and will establish regular telephone contact with the coordinators at each of the SCs. The CC will also disseminate weekly reports to NCI on the progress of activities, including the status of recruitment, randomization, screening and follow-up and will conduct site visits as necessary.

The CC will design and manage the implementation of four centralized computer systems to support randomization, receipt control and study management, data entry and data editing. The majority of the data forms will be sent to the CC for central processing. The CC will perform quality assurance checks on all data received and will report results to both NCI and individual SCs. The central study management system will produce monitoring and progress reports to support SC recruitment, screening and followup. The CC will also provide a web-based remote randomization system. The CC will provide written documentation for all systems.

1.3.3 Screening Centers

Six PLCO SCs from different areas in the country will participate in the study. The SCs include the following:

- Georgetown University Medical Center, Lombardi Cancer Research Center
- Henry Ford Health System
- University of Minnesota School of Public Health, Virginia L. Piper Cancer Institute
- Washington University School of Medicine
- Marshfield Medical Research and Education Foundation
- The University of Alabama at Birmingham

SCs are responsible for designing procedures necessary to implement the Lung Screening Study at their particular institution and for carrying out all data collection activities as required by the study protocol. A list of the Principal Investigators from the SCs is provided in Appendix 1-2.

1.3.4 Information Management Systems (IMS)

Information Management Systems (IMS), located in Rockville, MD will provide support for statistical analysis for the Lung Screening Study. IMS staff will work closely with the senior statisticians from NCI to perform analyses and develop data reports using datasets provided by the CC. The NCI will use these reports primarily for endpoint monitoring and analysis.

1.4 Overview of Data Collection Activities

An overview of the activities of the Lung Screening Study is briefly described in Section 1.5. The remaining chapters of this manual provide detailed information on the standardized forms and procedures involved in each of these activities.

Initially, potential participants (men and women between the ages of 55 and 74) will be identified, and interest in the study and eligibility will be determined. Those who fulfill the eligibility criteria and are interested will be recruited into the study and must provide informed consent. Participants will be randomly assigned to one of two study groups: the intervention group will receive a single spiral CT screening, the control group will receive a single chest X-ray screening. Participant contact information will be collected for participants in both groups of the study.

Participants with positive screening results will be referred to the physician of their choice for further diagnostic evaluation. For those determined to have positive screens, the medical records will be reviewed and abstracted for diagnostic evaluation information.

1.5 Time Schedule of the Lung Screening Study

The Lung Screen Study will be conducted over one year. Study procedures will be tested during this time to provide input to the design of the future randomized trial. The time schedule for the study is as follows:

- Recruitment will start on September 1, 2000 and continue through October 31, 2000.
- Screening will be completed by January 31, 2001.
- Follow-up data collection will be completed by May 1, 2001.
- Contamination will be assessed from May 1, 2001 through June 30, 2001 (six months after randomization ends).
- Data analysis will be conducted from June, 2001 through August, 2001.
- The Lung Screening Study will be completed no later than August 31, 2001.

1.6 Study Policy Guidelines

1.6.1 Guidelines for Describing Study Sponsorship

Certain guidelines have been established that apply to materials produced for distribution to study participants, physicians, and others who may be contacted regarding the study. These materials include letters, brochures and similar items. Guidelines are as follows:

- The sponsorship of the special study should always be stated in such a way that the NCI is primary.
- The SCs should use SC stationery for all study materials.

1.6.2 Publication Policy

All data collected and stored according to the statements of work contained in contracts with the NCI for the Lung Screening Study are the property of the NCI. All Lung Screening Study publications must be approved by the NCI Project Officers and the NCI Contracts Officer.

1.7 Purpose and Organization of the Manual of Operations and Procedures

1.7.1 Purpose of the Manual

This Manual of Operations and Procedures has been developed for the Lung Screening Study by Westat, the CC, in conjunction with NCI. The purpose of this manual is to document the study procedures that will be implemented at all SCs. These procedures will enable each SC to carry out the study requirements as outlined in the protocol. It is expected that the Manual of Operations and Procedures will be used as a resource by the Principal Investigator, the SC Coordinator and their staff.

The Lung Screening Study Decision Log will be used in conjunction with the Manual of Operations and Procedures. This document presents NCI's decisions and resolutions regarding all protocol, procedural, and forms questions; suggestions for changes; and SC administrative and management issues. Often experts and or consultants are consulted for these resolutions. The final decisions are presented in a numbered and dated list (Lung Screening Study Decision Log) and distributed regularly to all study collaborators.

1.7.2 Organization of the Chapters of the Manual

Recruitment and eligibility determination of study participants, including obtaining informed consent and randomization and enrollment procedures, are covered in Chapter 2. Chapter 3 details the procedures for scheduling and conducting the screening visit. Chapters 4 and 5 detail the spiral CT and chest X-ray protocols. Chapter 6 provides procedures for reporting results to participants and physicians. Chapter 7 discusses the follow-up procedures for positive results from the screening exam. Chapter 8 discusses an assessment of contamination in both groups. Chapter 9 includes administrative procedures to be conducted at the SCs. It covers guidelines for SC management, including registration of staff, recordkeeping, data editing and other administrative functions. Data management procedures at the SCs are also included.

Appendices for Chapter 1

1-1 Lung Screening Study Protocol

1-2 List of Principal Investigators