AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK
ACRIN #6654
CONTEMPORARY SCREENING FOR THE DETECTION OF LUNG CANCER

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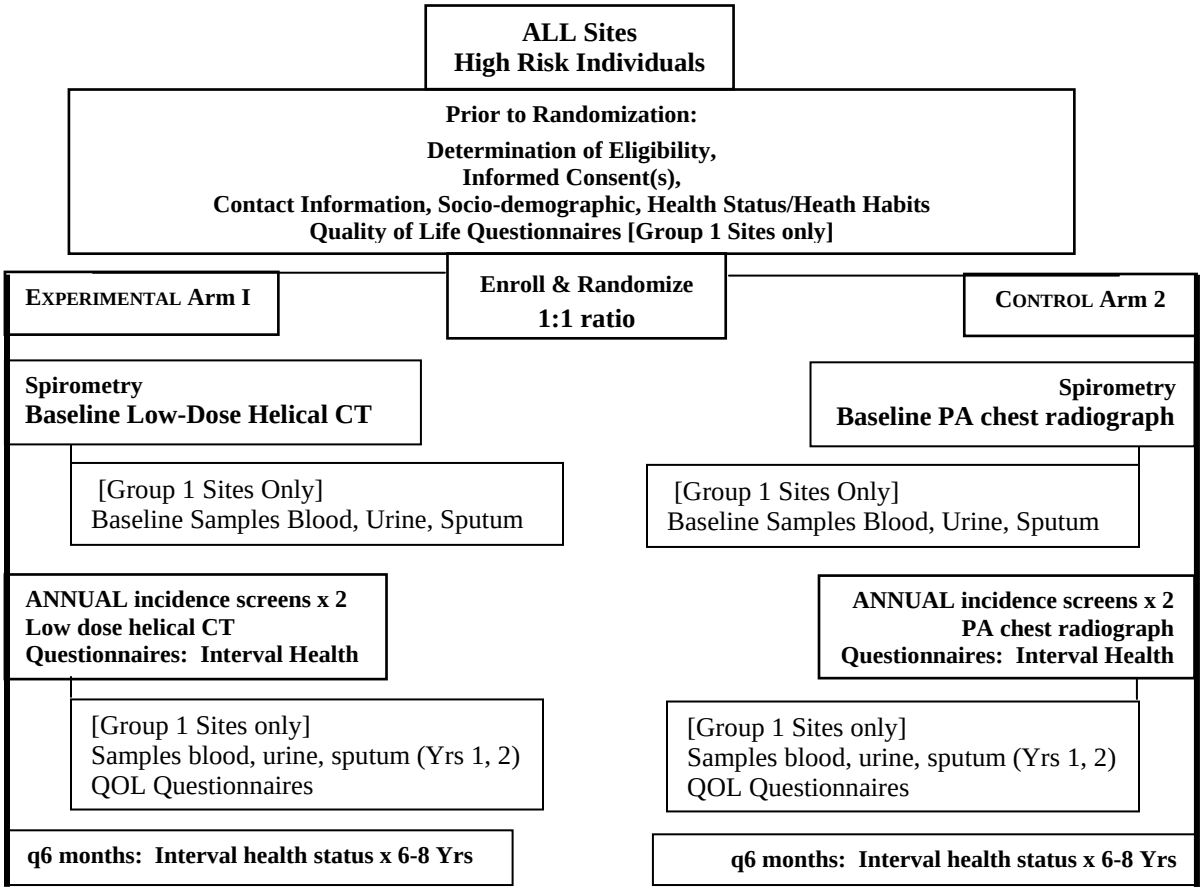
ACRIN 6654: CONTEMPORARY SCREENING FOR LUNG CANCER SCHEMA



Eligibility: *(see Section 4.0 for details)*

- Age 55-74 years and 364 days.
- Current or previous cumulative cigarette smoking history of ≥ 30 pack years *(packs per day x years smoked)*.
- Former smokers must have quit smoking within the previous 15 years.
- No medical or psychiatric condition precluding informed medical consent.
- Ability to lie on the back with arms raised over the head.
- No metallic implants or metallic devices in the chest or back *(pacemakers or Harrington fixation rods, etc.)* that would cause sufficient beam hardening artifact so as to degrade image quality in the lungs.
- No prior history of lung cancer.
- No treatment for, or advisement by a physician of evidence of *any* cancer within the past five years, with the exceptions of non-melanoma skin cancer and most in-situ carcinomas. (Treatment for, or evidence of, melanoma or in-situ bladder/transition cell carcinomas within the preceding five years renders the potential participant ineligible.)
- No prior removal of any portion of the lung, excluding percutaneous lung biopsy.
- No requirement for home oxygen supplementation for respiratory conditions.
- No participation in another cancer screening trial, [e.g., the PLCO, ELCAP, or single arm trials such as those of the Mayo Lung Trial, Jewish Heart and Lung Institute, or the Moffitt Lung Trial].
- No participation in a cancer prevention trial, other than smoking cessation programs.
- No present symptoms suggestive of current lung cancer, including: unexplained weight loss of over 15 pounds within the past 12 months or unexplained hemoptysis.
- No medical conditions that pose a significant risk of mortality during the trial period.
- No pneumonia or acute respiratory infection within 12 weeks of enrollment that was treated with antibiotics under physician supervision. *(These individuals would be eligible 12 weeks from the first dose of antibiotics.)*
- No individuals within 6 months of receipt of cytotoxic agents for any condition. *(These individuals would be eligible 6 months from the last dose of the drug from the final cycle.)*
- No chest CT scan within the preceding 18 months. *(These individuals would be eligible 18 months after chest CT.)*
- Signed study-specific informed consent prior to study entry.

Required Sample Size: Up to 25,000 participants

1.0 ABSTRACT

Lung cancer is now the most common cause of cancer death among women and men. Despite considerable clinical research in multi-modality cancer treatment, there has been no significant decrease in lung cancer-specific mortality over the past three decades. Approximately 80% of lung cancers are of non-small cell histology, for which prognosis depends primarily upon tumor stage at the time of diagnosis. Although overall survival rates with non-small cell carcinoma are dismal, patients with surgical stage I disease may have 10-year survivals of up to 70%. This has formed the rationale for early detection programs. Both chest radiographs and spiral computed tomography (CT) have been used to screen for lung cancer. Thus far, however, neither test has been shown to reduce lung cancer mortality. This project is a multicenter, randomized controlled trial involving 23 sites across the nation and will enroll up to 25,000 individuals at high risk of developing lung cancer. High risk will be defined by age 55-74 years with a current or previous heavy smoking history equaling at least 30 pack years; former smokers must have quit within the preceding 15 years. Prior to randomization, all sites will collect standardized eligibility data, including health histories, smoking behavior, and sociodemographic data, and will complete spirometry. The Experimental group at all sites will undergo screening with low dose helical CT. The Control group at all sites will undergo screening with chest radiographs. Experimental and Control arms will be screened annually for at least two incidence screens and will be followed thereafter for up to a total of eight years to determine outcomes. All participants will be contacted at six-month intervals to document interval health status and changes in smoking behaviors. The primary endpoint of the trial is to determine which screening test is better at reducing lung cancer-specific mortality. Secondary endpoints include: all cause mortality, differences in stage distribution at diagnosis, and differences in cost and medical resource utilization between the two arms. At some of the participating institutions, three additional study aims will include: [1] the creation of a bank of specimens from well-characterized high-risk cohorts that can be used to test future potential biomolecular markers of lung cancer; [2] evaluation of the influence of screening on smoking behaviors; and [3] the evaluation of screening on various issues of quality of life and anxiety.

2.0 BACKGROUND AND SIGNIFICANCE

Lung cancer is now the most common cause of cancer death in men and women in the United States.[1,2,3] Despite considerable research in treatment, mortality from primary lung cancer has risen over the past three decades, and approximately 85% of individuals who acquire lung cancer will die from it.[3,4] More Americans will die from lung cancer than colon, breast, and prostate cancers combined.

Small-cell lung cancer accounts for roughly 20% of lung cancers. Small-cell lung cancer behaves aggressively with early and wide dissemination and is not favorably influenced by existing screening or treatment methods. Non-small cell lung cancer *(NSCLC)* accounts for about 75% of all lung cancers. The prognosis in patients with NSCLC relates primarily to surgical stage at the time of diagnosis, although performance status, ethnicity, and histologic type are lesser determinants. Overall 5-year survival from lung cancer is less than 15%[3]; however, patients with surgical early stage NSCLC who undergo curative resection have 5-year survival rates of 40-70%. Survival in a cohort of 598 patients with surgically resected stage I tumors was recently reported.[5] The overall 5-year survival rate was 75%; however, when stratified by TNM tumor classification, patients with T1 tumors fared better than those with T2 tumors, with 5-year survival rates of 82% and 68%, respectively.[5,6] Tumor size also influenced survival, which was best in those with tumor diameters less than 1 cm and poorest in those with diameters greater than 5 cm. The improved survival seen with the early detection of NSCLC has formed the rationale for lung cancer screening.

2.1 Risk Factors for Lung Cancer

Cigarette smoking is the single most important risk factor for lung cancer; 85% of lung cancer deaths are attributable to smoking.[7-11] Three decades have passed since the first report by the United States Surgeon General on the causal relationship between smoking and lung cancer in men. Although smoking prevalence has considerably decreased over this period, annual cancer statistics of the American Cancer Society show a significant increased incidence in lung cancer owing to persistent risk among former smokers of advancing age. Indeed, lung cancer is increasingly a disease of former smokers. While primary prevention is rightfully an important focus for reducing lung cancer, it is an incomplete preventive solution for the population at risk. Former smokers have already achieved smoking cessation, but will continue to be the source of an increasing fraction of lung cancer in the future.

The relative risk of lung cancer is influenced by duration of smoking, intensity of exposure *(number of cigarettes smoked per day)*, and duration of smoking cessation in ex-smokers. Risk increases in rough proportion to the number of cigarettes smoked per day.[12,13] Duration-specific risks increase steadily, but are most significant beyond 20 years of smoking duration. Cancer risk remains elevated in former cigarette smokers, declining significantly beyond five years from cessation. The following table shows the calculated excess risk of lung cancer death in males due to smoking when stratified by age and smoking category. From these data, we can see that a 55 year old male who smokes 25 cigarettes or more per day has a 12.6% chance of dying from smoking-related lung cancer by age 75; and an 18.5% chance by age 85.

Table 1: Percent Probability of Dying from Lung Cancer Due to Smoking Based on Age and Smoking Status[14]

Age	Smoking Category	Percent Probability of Lung Cancer Death		
		Age 65	Age 75	Age 85
35	Former	1.9	4.4	6.5
	Current < 25 cigarettes/day	2.5	6.3	9.3
	Current > 25 cigarettes/day	6.3	13.0	17.9
45	Former	1.9	4.4	6.7
	Current < 25 cigarettes/day	2.5	6.4	9.5
	Current > 25 cigarettes/day	6.4	13.3	18.5
55	Former	1.6	4.3	6.6
	Current < 25 cigarettes/day	2.1	6.4	9.8
	Current > 25 cigarettes/day	4.6	12.6	18.5
65	Former		3.2	5.9
	Current < 25 cigarettes/day		5.2	9.4
	Current > 25 cigarettes/day		10.4	18.0

Lung cancer occurs primarily in patients between ages 50 and 80 years. The relative risk of lung cancer is also influenced by other host factors, including gender, ethnicity, socioeconomic status, family history, occupational exposures, and the presence of airflow obstruction.[15,16,17] Statistics from the Surveillance, Epidemiology, and End-Results *(SEER)* program show that the age-adjusted lung cancer incidence is higher among African-Americans than Caucasians of the same gender and is also greater in lower socioeconomic classes, relating to differences in access to medical care, smoking patterns, and diet. Lung cancer prevalence is particularly high among individuals smoking 30-40 pack years or more with airflow obstruction, defined by FEV1/FVC less than 70% and an FEV1 less than 70% predicted.[18] Indeed, airflow obstruction is associated with a 4-5-fold increase in lung cancer when all other risk factors are controlled.[15,16,17] In a recent study of 148 emphysema participants being evaluated for lung volume reduction, the prevalence of asymptomatic lung cancer was 5%.[19] Cancer risk presumably derives from poor clearance of carcinogens from the bronchial epithelium and peripheral airspaces. At the highest risk of lung cancer are individuals with previously surgically treated stage I NSCLC or supraglottic primary neoplasms.[5,20,21,22]

2.2 Historical Lung Cancer Screening Trials

At the present time, it is generally accepted that screening for lung cancer confers no mortality benefit. Several large randomized controlled trials, although differing in experimental design, concluded that screening did not reduce lung cancer-specific mortality. In four major prospective trials, screening was performed by some combination of chest radiography *(CXR)* and histologic sputum analysis at various frequencies as tabulated below.[23-27] The participants were all male smokers over 45 years of age at high risk of developing lung cancer *(smoking > 1 ppd):*

Table 2: Summary of Screening Protocols in Four Major Lung Cancer Screening Trials

GROUP	Johns Hopkins & Memorial Sloan-Kettering Lung Projects *(N = 10,000)*		Mayo Lung Project *(N = 10,000)*		Czech Study [1]	
	Screen	Frequency	Screen	Frequency	Screen	Frequency
Control	CXR	Annual	Recommendations: CXR[2] + Sputum Annually		None	
Experimental	CXR Sputum	Annual Q 4 months	CXR Sputum	Q 4 months	CXR Sputum	Q 6 months x 3 years

Note: [1] Both Czech groups underwent CXR + sputum at year 3; CXR at years 4,5,6
[2] Roughly half of Control subjects received annual chest radiographs

In the Johns Hopkins and Memorial Sloan-Kettering trials, both Experimental and Control participants underwent annual screening chest radiography.[23,24] The trials were designed to address the incremental benefit of sputum cytology analysis rather than chest radiographs per se. Although they found that sputum analysis did not favorably influence outcome, these studies achieved survival rates among all groups three times higher than predicted by epidemiological data, thus inviting the supposition that annual radiographic screen may indeed have improved outcome. The Mayo Lung and Czechoslovak trials showed advantages to the screened groups with respect to earlier stage at diagnosis, resectability, and survival. However, because the Experimental groups in both studies demonstrated *increases* in cumulative lung cancer incidence above that of Control groups *(p = 0.019)*, significant improvements in case fatality *(# cancer deaths / # individuals with cancer)* did not translate into significant reductions in lung cancer mortality *(# cancer deaths / # individuals screened)*.[25,26,27]

2.3 Early Detection Biases in Screening

The disparities in these trials between lung cancer mortality and the improvements realized in stage at diagnosis, resectability, and survival within the screened group have been ascribed to three biases peculiar to screening: lead-time, length, and overdiagnosis.[28,29,29b]

2.3.1 *Lead-Time Bias:* Lead-time bias pertains to comparisons between screening and non-screening cases that are not adjusted for the timing of diagnosis. If screening detects disease earlier, the patient will survive longer from the time of diagnosis even if death is not delayed. Although readily measurable, survival is an inadequate measure of the effectiveness of screening, and has no predictable relationship to mortality.

2.3.2 *Length Bias:* Length bias pertains to comparisons between screening and non-screening conditions that are not adjusted for the rate of cancer progression and the tendency of screening to detect slow-growing cancers. Screening ideally detects cancers in the detectable preclinical phase, that period in which the cancer is present but produces no symptoms. The likelihood of detection by screening is directly related to how quickly the cancer grows: the more slowly growing the neoplasm, the longer it is present without symptoms, and the greater the likelihood of detection. Fast-growing cancers have a commensurately shorter detectable preclinical period. Overall, screening tends to detect tumors of more indolent biology and growth potential.

2.3.3 *Overdiagnosis Bias:* Overdiagnosis bias refers to the phenomenon of detecting pseudodisease, e.g., a lung cancer that would otherwise have remained subclinical before death from other causes. There is contradictory evidence on the issue of pseudodisease. In small studies of individuals with clinical stage I lung cancer who have not been treated by surgical resection, mortality is 80% at ten years. However, high mortality does not imply that *all* lung cancers are lethal, only that *known* lesions are lethal.[30] Published reports have documented "surprise" lung cancers at autopsy/necropsy in individuals who have died of other conditions such as coronary

artery disease. Also, it is well known that small lung lesions less than 2 cm diameter may be easily overlooked at autopsy due to sampling error. The reported necropsy "surprise" detection rates suggest that there may be a significant reservoir of asymptomatic lung cancer.[31]

2.4 Analysis of the Influences of Screening Biases on the Mayo Lung Project

In the Mayo Lung Project *(MLP)*, the screened group demonstrated 46 excess lung cancers *(206 cases in screened group versus 160 cases in unscreened group)*. This excess was largely accounted for by a higher number of early stage lung cancers among screened participants. However, there was no proportionate *decrease* in late stage cancers[26] and ultimately, no decrease in lung cancer-specific mortality. The excess lung cancers in the screened participants have been explained by: [1] pseudodisease, e.g., overdiagnosis bias in the screened group, [2] underdiagnosis of lung cancer in the non-screened group; e.g., misclassification of cause of death; and [3] a fundamental flaw in the process of randomization whereby the Experimental group as a whole had a higher risk profile for lung cancer. These contentions are not supported by recent re-analysis of the risk-defining features of the two groups.[29b,32]

Ultimately, the results of the MLP do *not* prove that lung cancer screening with chest radiographs is futile. However, they *do* indicate that, as a matter of public policy, CXR screening cannot be endorsed without better demonstration of screening benefit. For this reason, the National Cancer Institute has initiated a large randomized controlled screening trial using chest radiographs for lung cancer screening as part of the Prostate-Lung-Colorectal-Ovarian *(PLCO)* trial, with one objective being the determination of whether screening reduces lung cancer-specific mortality by at least 10% relative to unscreened groups. It is hoped that this trial will resolve lingering questions about the utility of chest radiographic screening.[33]

2.5 Lung Cancer Screening with Helical CT

Although there is ongoing controversy regarding the utility of chest radiography in early lung cancer detection, it is generally acknowledged that helical CT represents an important advance in lung nodule detection and characterization.[34,35] Helical CT allows the whole chest to be surveyed in a single suspended breath-hold, reducing motion artifacts and eliminating respiratory misregistration and the potential to under sample the whole lung. Nodule detection increases in parallel with narrower slice thickness. The effective slice thickness, and therefore the in-plane resolution of axial reconstructions, is determined by the combination of beam collimation, table incrementation, and interpolation algorithm.[36,37,38] Because the resulting data set is volumetric, overlapping axial reconstructions can effectively increase z-axis resolution and the potential to detect small lung nodules *(between 5-10 mm diameter)*.[39]

In one recent retrospective review of missed lung cancers by incremental CT, the mean diameter of missed lesions was 1.2 cm *(range: 2-20 mm)*, whereas retrospective analysis on chest radiographs observed a mean diameter of missed lesions of 1.6 cm *(range 8-34 mm)*.[40,41] Although there is greater radiation exposure with CT than chest radiography, low dose techniques have achieved calculated exposure doses that are 17% that of conventional CT and 10 times that of chest radiograph.[42]

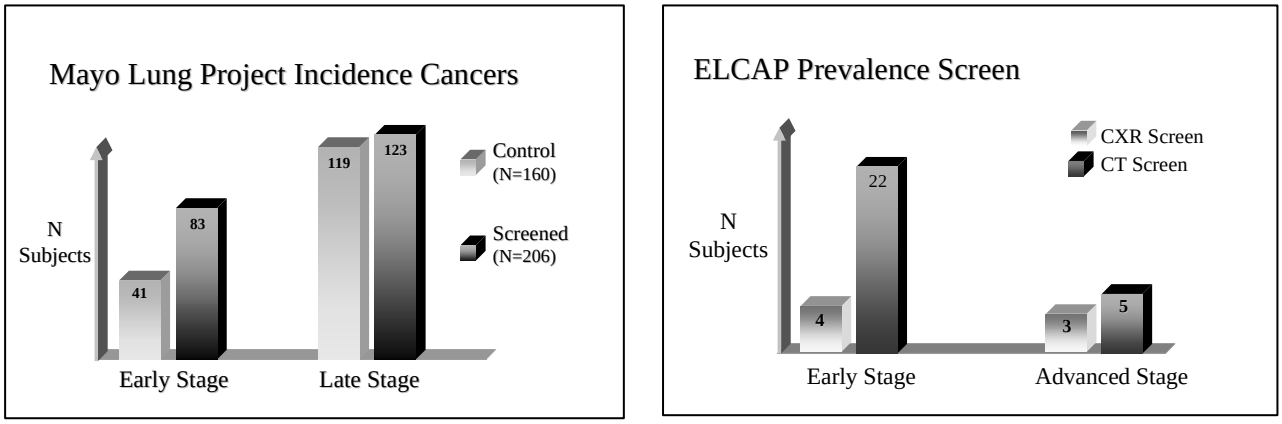
Screening trials using low-dose helical CT are in progress in both the United States and Japan.[42,43,44] These single-arm trials have demonstrated striking increases in the detection of early stage lung cancers. In Japan, where roughly 70% of lung cancers originate in the lung periphery[42,43] large trials in high-risk individuals have consisted of chest radiographs, low dose helical CT, and sputum cytology at six month intervals over a two year period.[42] Suspicious focal abnormalities detected on *any* screening modality were further characterized with high-resolution CT *(HRCT)*. Among 1,369 participants, 229 cases were referred for HRCT; of these, 19 were referred for tissue sampling. Overall, 18 lung cancers were found: 15 peripheral cancers by imaging *(CT alone or CT and chest radiography)* and 3 central lesions by sputum cytology alone. Low-dose helical CT depicted all peripheral lung cancers as well as one lung metastasis whereas only four of 15 peripheral cancers were seen on chest radiography; in no participant was chest radiography the sole method of detection. Fourteen of the 15 cancers were stage I at diagnosis with mean diameters on helical CT of 16 mm ± 7, versus 30 mm ± 14 on projectional radiography. These

findings confirm the sensitivity of CT over chest radiography in detecting smaller, early stage lung cancers.

The most heavily publicized CT screening trial in the United States, the Early Lung Cancer Action Project *(ELCAP)*, has reported its results of a prevalence screen of 1000 individuals at high risk of lung cancer who have been followed with annual low dose helical CT and chest radiographs.[44] In the ongoing ELCAP trial, the prevalence CT screen was positive in 233 participants, of whom 16 *(7%)* were lost to follow-up. Of the remaining 217 participants, 27 primary lung cancers were found *(2.7% prevalence of lung cancer)*. With low dose CT, 96% of cancers were resectable, and 81% were stage I at diagnosis. Relative to chest radiographs, prevalence CT screens detected three times more nodules, four times more cancers, six times more stage I lesions, but roughly equivalent numbers of advanced stage cancers. Incidence data show lower numbers of abnormal screening CT exams, a greater proportion of which reflect malignancies. These incidence screens, the stage distributions, and long-term follow-up will be important to observe.[44]

Figure 1: Distribution of Stage in the (a) MLP incidence screens and (b) ELCAP prevalence screen. In both trials, the primary screening intervention resulted in an increase in the number of cancers found, the excess cancers being mostly early stage tumors. In the MLP, screening conferred no mortality benefit. The effect of CT screening on mortality in ELCAP awaits follow-up.

(a) **(b)**



The ELCAP trial is a single-arm design; as such, it will be very difficult to determine whether CT screening will achieve a genuine decrease in lung cancer-specific mortality or merely an "improved survival" due to the screening biases of lead-time, length, and overdiagnosis. Unfortunately, the preponderance of early stage cancers found at screening CT, combined with optimistic survival predictions, have been promulgated in the lay press to predict *mortality* reductions of up to 80%. These conclusions are not supported by scientific data and overstate what is currently known about lung cancer screening with CT.

2.6 Tumor Size Relative to Tumor Behavior

Lesion size is one of the defining features of anatomic staging with the TNM classification. The T status of a primary lung cancer stratifies tumors by size, with T1 lesions defined as 3 cm or less in diameter and T2 lesions being greater than 3 cm diameter.[45,46] Nodules detected on CT are consistently smaller than those detected on CXRs; as such, it is natural to assume that CT screening will affect a mortality benefit over non-screening because the average size of the detectable lung cancers is smaller. However compelling the logic, a linear relationship between tumor size and mortality has not been shown for lesions within the T1 designation. Simply stated, it is not known whether the detection and treatment of a 5 mm diameter T1 cancer will affect a better outcome than the detection of a 20 mm diameter T1 cancer. A recent retrospective study found no survival advantage among T1 cancers based upon size.[47] This observation is somewhat counter-intuitive. It is possible that ascertainment bias and small sample size may have obscured a predictable relationship between tumor size and outcome. Alternatively, as

intimated by the investigators, there may be confounding biological variables that influence tumor aggressiveness beyond size.[48]

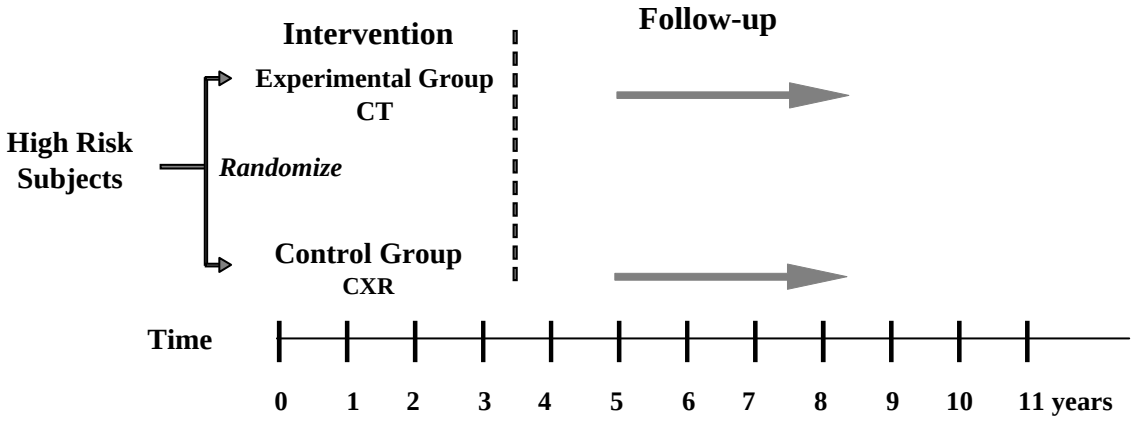
The latter contention is indirectly supported by other studies that show carcinocythemia and the potential for metastatic dissemination among T1 lung cancers. In patients with stage I lung cancer, peripheral blood samples taken before, during, and after curative surgical resection showed circulating cancer cells in some of the patients.[49] Patients in whom circulating tumor cells are seen following surgery have a significantly worse survival when compared with patients in whom carcinocythemia is not found. Similarly, other investigators have used specialized tissue processing and stains to detect microdissemination within regional lymph nodes in patients with T1 lung cancers undergoing curative surgery.[50] Again, some patients with T1 lesions demonstrate microdissemination and have significantly worse outcomes than patients in whom microdissemination has not occurred.

We are still very early in our understanding of tumor biology and the behavior of lung cancer. What we *do* understand is that lung cancers are biologically heterogeneous, and tumor size alone is not adequate to explain their behavior. This has significant implications for lung cancer screening with CT. A major impetus to migrate from chest-x-ray screening to CT screening for lung cancer is the promise of detecting smaller lung cancers. Yet, we do not currently know that outcomes are necessarily better when the cancer is 2 mm as opposed to 20 mm. As purveyors of public policy, we are obliged to avoid the premature endorsement of a screening process before its benefits and liabilities have been reconciled.

2.7 Measuring Screening Effectiveness

2.7.1 *Lung Cancer-Specific Mortality:* As we have seen, although survival from diagnosis is appropriate when measuring the effectiveness of treatment, survival is misleading as a measure of screening effectiveness due to the confounding effects of screening biases. The purpose of lung cancer screening is to prevent or delay lung cancer related death. As such, lung cancer-specific mortality is the most appropriate measure of screening effectiveness. Measurements of mortality are based upon following individuals from the time of the decision to screen, rather than from the time of diagnosis. *(As an aside, case fatality rate measures the number of deaths from the time of diagnosis of cancer but also does not take into account length and overdiagnosis biases).*

Figure 2: RCT Template for Lung Cancer Screening with CT



2.7.2 *The Randomized Controlled Trial (RCT)*: The RCT is particularly appropriate for determining the benefits of screening because it circumvents the limitations imposed by the screening biases of lead-time, length, and overdiagnosis. In the RCT, individuals are randomized to one or more groups in order to equally distribute the known and unknown variables that may influence outcome *(Figure 2)*. The outcome variable, disease-specific mortality, is measured from the time of randomization. As such, any differences seen between the groups may be ascribed to the intervention itself.

2.7.3 *Limitations of the RCT*: Despite the strengths of the RCT in determining screening effectiveness, there are a number of challenges associated with this design. First, the validity of the outcome measurement, lung cancer-specific mortality, depends upon the integrity of the different cohorts with respect to assigned interventions. All study participants must comply with the intervention to which they have been randomized. In practice, a proportion of Experimental participants will drop out of the study for reasons of inconvenience, discomfort associated with the intervention, or simply lack of interest. Similarly, a proportion of Control participants will undergo the Experimental intervention, contaminating the Control group, should the intervention become widely available. Noncompliance by either group may diminish any observed effect of the intervention. With lung cancer screening, this would reduce the potential mortality benefit of screening. Non-compliance must be carefully factored into the parameters of experimental design and accounted for in sample size calculations.

The sample size requirements of a screening RCT and the required duration of surveillance of the separate cohorts are considerable. This is due to the fact that despite targeting individuals at highest risk of lung cancer, few participants will develop lung cancer. Moreover, because of the effects of lead-time and length bias, individuals with early stage diagnoses may have longer survival. Estimates of the sample size that would be required to detect a 30% difference in mortality between cohorts screened for lung cancer with helical CT exceed 20,000 participants. Another limitation of the RCT is misclassification. In the MLP, the Experimental group demonstrated excess lung cancers. Some have ascribed this to overdiagnosis bias in the screened participants. Similarly, underdiagnosis of lung cancer in the Control group *(misclassification of cause of death)* may have been contributory. Such underestimates of lung cancer incidence and mortality in the Control group would lower the observed benefit of screening. Determining the outcomes *(lung cancer incidence, cause of death, diagnosis or treatment complications, etc.)* of all participants in the RCT requires aggressive, long- term surveillance of the cohorts and medical follow-up with chart reviews, physician communication, and review of the National Death Index, processes that are time and labor intensive.

Finally, as with any clinical research design, it is important that the methods can be generalized: they must reflect as much as possible the practices likely to be operative in the community at large, while also ensuring the best opportunity to detect mortality benefit.

2.8 Limitations of Helical CT Screening

The experiences of ELCAP and other CT screening trials also portend the potentially deleterious effects of CT screening due to the detection of large numbers of small, indeterminate nodules that will require additional evaluation. Small nodules in high-risk individuals may require biopsy or, at a minimum, repeated CT scans over 2-3 years to ensure the absence of growth.[44] In the ELCAP prevalence screen, 23% of all screening CT scans were abnormal, meaning that one or more nodules of indeterminate malignant potential were detected. Of these, the majority of nodules were benign. The ELCAP trial followed participants with positive screens with limited high-resolution sequences through abnormal nodules. The images were analyzed using a proprietary program to determine the growth rate over time. Using this method of surveillance, there were no lesions referred for thoracotomy that were not malignant, suggesting that the positive predictive value of follow-up CT is extremely high. Although the proportion of positive *(abnormal)* incidence screening scans in this cohort have been much smaller, the participants have been followed in a controlled fashion using the same scanners and readers over time, a luxury that may not be reproducible across the country.

It is not known whether this degree of success in preventing unnecessary instrumentation for benign disease would be generalized across the country if CT lung cancer screening were to become public policy at this early stage. The indeterminate solitary pulmonary nodule is a vexing problem, particularly in persons at high lung cancer risk. Previous studies have shown that primary lung cancers comprise roughly 30-40% of lung nodules on chest radiographs.[51,52,53] In some reports, half of all surgical

resections for indeterminate nodules yielded benign histologies.[54] The prevalence of indeterminate lung nodules *(e.g., positive screens)* on CT screens will necessarily be higher in regions of the country where certain granulomatous infections *(blastomycosis, coccidioidomycosis, and histoplasmosis)* are common. For example, the Mayo Clinic, where histoplasmosis is endemic, has also reported initial data using low dose helical CT, and observed positive CT screening exams in 51% of prevalence and roughly 15% of incidence scans, respectively.[55] Some investigators recommend that small nodules *(< 5 mm)* be followed with imaging at regular intervals to minimize unnecessary biopsy or surgery.[44]

Additional concerns regarding the utility of screening helical CT include the selection of optimal acquisition parameters, examination costs, and greater time requirements for study interpretation, a limitation for which computer-assisted analysis may be a partial solution.[56]

2.9 Assessing Quality of Life, Psychological Impact, and Economic Costs of Lung Cancer Screening

The traditional measure of cancer screening is a reduction in lung cancer-specific mortality with acceptable financial and medical risks. In recent years, increasing attention has been placed upon screening-related quality of life and psychological impact.[57-63] Such influences begin with the invitation to participate in screening and accrue at each step of the screening process.[57] Throughout the process, participants may experience increased anxiety, intrusive thinking, and depression in the context of screening for a life-threatening disease.

The psychological impact of lung cancer screening with low-dose helical CT merits study for several reasons. First, the baseline screening CT exam is associated with a relatively high false-positive rate, which has ranged from approximately 20% to 50% in two large series performed in the United States.[44,55] Second, the majority of individuals with false-positive studies will require close follow-up CT scans for a minimum of 2 years to confirm the benign nature of a nodule.[44] The unique combination of a high false-positive rate and the long period of observation to confirm a benign diagnosis suggests that lung cancer screening with CT may be associated with a higher psychological impact than traditional screening studies for other cancers.[64]

Positive screening results will trigger additional evaluation that can be expected to produce some degree of physical discomfort and anxiety. These psychological and physical effects will affect participants in whom cancer is established as well as participants with ultimately benign nodules. In both instances, screening may negatively impact quality of life. Although it is expected that the psychological impact of screening will vary among individuals, the psychological cost is likely to be highest in those with false-positive screens and in those determined to have untreatable disease.[57]

Despite these considerations, the earlier detection of lung cancer may be expected to lead to earlier treatment. To the extent that screening is successful, screened participants may realize less suffering from lung cancer. In a previously published cost-effectiveness analysis of mammographic screening, de Haes[65] found that adjustment for quality of life decreased the effectiveness of screening by about 8%, but not enough to eliminate the benefit derived from reduced breast cancer mortality. However, there is currently no data or hypothetical analysis available to indicate how adjustments for quality of life will affect quality associated life years due to lung cancer screening.

This trial provides the opportunity to assess the issues of screening-related quality of life and anxiety. As well, it will enable the benefits of screening to be weighed against the economic costs of a screening program. To our knowledge, no paper has summarized the economic costs for each year of life gained or each quality-adjusted year of life gained as the result of lung-cancer screening with helical CT. Beyond providing information about the psychological consequences of screening, this research may prove useful for influencing screening design, developing strategies to reduce screening-related anxiety, and enhancing compliance with the screening process.

2.10 Lung Cancer Screening with Biomolecular Markers

Lung cancer results from a complex interaction between genetic predisposition and environmental influences. According to the concept of multi-step carcinogenesis, malignant transformation results from the process of initiation, in which exposure of the respiratory epithelium to carcinogens affects mutations

in specific genes, proto-oncogenes, and tumor suppressor genes.[66,67,68] Once epithelial cells undergo initiation, cellular proliferation and monoclonal expansion of the malignant cells depends upon tumor promotion, which is affected by various environmental carcinogens and cellular growth factors such as epidermal growth factor *(EGF)* and gastrin-releasing peptide *(GRP)*. Although lung cancer typically occurs with exposure to carcinogens such as tobacco smoke, radon, etc., there are wide variations in individual susceptibility that relate to these molecular genetic factors. This accounts for the fact that some individuals with heavy tobacco consumption develop lung cancers while others do not.

Table 3: Oncogenes and Markers Associated with Lung Cancer

Oncogene	Mutation	Frequency*	Primary Histology
Dominant Oncogenes or Protooncogenes: Promote Cellular Deregulation			
K-ras	Point mutation	30%	Adenocarcinoma
erb B1 *(or EGFR gene)*	Overexpression	20%	Squamous cell
EGFR *(erb B1 gene product)*	"	90%	Squamous cell
	"	20-75%	Adenocarcinoma
erb-B2 (or *Her-2/neu*)	Overexpression	27-36%	Adenocarcinoma
Recessive Oncogenes or Tumor Suppressor Genes			
p53	Deletion or Point mutation	50-80%	All
3p	Deletion	50%	All
Tumor Associated Antigens Found on Sputum Epithelial Cells			
Hn-RNP *(31 KD glycoprotein)*		90%	NSCLC

* Frequency of occurrence in NSCLC

Several genetic abnormalities have been associated with lung premalignancy or overt lung cancers *(Table 3)*.[69,70,71,72] These gene mutations and their products can be identified in extremely small quantities from sputum and tissue samples using contemporary techniques in molecular biology such as polymerase chain reaction *(PCR)*, single strand conformation polymorphism *(SSCP)* analysis, differential nucleic acid hybridization, and nucleic acid sequencing. The probability of successfully sampling the sputum for epithelial molecular markers of carcinogenesis is enhanced by field carcinogenesis, the concept that exposure of the entire respiratory epithelium to inhaled carcinogens transforms cells throughout the lung. Sputum samples may not contain cells from the most advanced focus undergoing neoplastic transformation but may contain evidence of the proliferative stimuli affecting the epithelium. Moreover, these cells and cancer-associated gene products are shed into the blood stream and may also be found in urine and other body samples.

Tumor-associated antigens expressed on sputum epithelial cells have been identified in sputum samples up to two years prior to the development of non small-cell lung cancer using tumor-associated monoclonal antibodies *(Mab)*. The Mabs detect a 31-Kd glycoprotein cell surface antigen homologous to hnRNP. When the latter was used to examine archived sputum samples from the Johns Hopkins screening trial[23], antigen overexpression was demonstrated in over 90% of lung cancers and predicted NSCLC in individuals with moderate atypical metaplasia who later developed lung cancer with a sensitivity of 91% and a specificity of 88%.[73] Preliminary results of prospective trials by the Lung Cancer Early Detection Working Group *(LCEDWG)* using hnRNP to detect preclinical lung cancer have shown that hnRNP overexpression was predictive of outcome in 32 of 40 participants at risk of a second primary lung cancer within 12 months and was predictive of outcome in 69 of 94 miners at risk of primary lung cancer. Up regulation of hnRNP in sputum correctly predicted cancers in 67% and 69% of patients within these cohorts, respectively.

The classical cancer progression model suggests that cells progress from normal to hyperplasia *(regular metaplasia)*; to slight, moderate, and marked dysplasia; and finally to neoplasia. Overexpression of hnRNP predates morphologic abnormalities in 94% of LCEDWG cases and persists throughout carcinogenesis[74], whereas many of the other markers, such as K-ras and p53 mutations, are seen in half or

more cells with moderately atypical metaplasia.[75,76,77] It may prove that hnRNP expression is the earliest, most sensitive marker of carcinogenesis, while K-ras and p53 mutations and 3p or 9p losses of heterozygosity are late, more specific markers of neoplasia.

These data are optimistic; however, there is no existing panel of markers that will reliably identify pre-malignancy or early lung cancer. Moreover, the collection of sputum samples requires strict quality control mechanisms in order that cellular yields are genuinely representative of the lower respiratory tract rather than the oropharynx, which would be expected to influence epidemiologic results. The cohorts in this study participating in biomarker collection will undergo annual collection of blood (both serum and buffy coat), urine and sputum, which will provide a rich foundation for testing biomarkers found to be promising in preliminary tests conducted outside of the ACRIN trial. Participants will be fully characterized and followed for at least six years. The detection of biomarkers occurring regularly in the setting of pre-malignancy or very early malignancy would have profound implications for more precise selection and stratification of populations at risk for lung cancer and would influence diagnostic strategies to localize lesions using fluorescent bronchoscopy, volumetric CT, or PET. Moreover, the detection of pre-neoplasia would identify cohorts who may benefit from biomarker modulation through aggressive primary prevention with smoking cessation, chemoprevention, or new methods of gene therapy to enhance programmed cell death.

Urine also provides a potentially rich substrate for determining risk of lung cancer, prognosis, and potential methods of treatment. Urine is a rich source of secretory proteins *(natural occurring angiogenesis compounds including Endostatin and Angiostatin were discovered from the urine)*. With continuing rapid advances in proteinomics, urine represents a potentially invaluable source of biomarkers unique to cancer patients. For example, it has become possible to compare protein expression from urine in patients with malignancies to urine from normal individuals in an effort to determine differential expression, and thus create tumor protein profiles. These extremely powerful techniques are unlike genomic array analyses that examine known genes, as the entire spectrum of proteins *(known, unknown, or unsuspected)* could be evaluated. This discovery process could lead to molecular profiles that could then be correlated with clinical data to provide both prognostic and therapeutic information.

2.11 Ethical Considerations of Screening

Also at the heart of screening for lung cancer is the reality of differential health care access across the diverse socioeconomic strata of the United States. Lung cancer cuts across all such boundaries; any multicenter trial must incorporate these diverse strata, ensuring the participation of individuals who may be fully insured, underinsured, and uninsured.

By its very nature, the screening process will convert some ostensibly healthy individuals into patients, who will then be subject to medical interventions at some level of emotional, economic, and medical expense. One challenge of a screening trial is in the execution of a thoughtful, well-designed study with appropriate end-points. Equally important is the challenge of ensuring that outcomes relate to the intervention and are not obscured by differential health care access and treatment due to socioeconomic status.

For example, it is conceivable that a multi-racial screening trial could show mortality advantages for specific ethic groups solely on the basis of differential health care access following a positive screening test. The screening test itself is important only in so far as it advances the diagnosis of cancer such that early intervention is curative, prolongs life (beyond lead time bias), or improves the quality of life. If the evaluation of a positive screening test *(or its speedy treatment)* is delayed in economically disadvantaged persons for lack of financial or medical resources, it is likely that mortality benefit will be realized non-uniformly.

One of the ways in which this trial distinguishes itself is in the clear provision of standardized guidelines for the management of the positive screening test. It is the sincere belief of the study investigators that there is some obligation within the trial to provide medical assistance to the few participants who lack medical resources with which to undergo appropriate evaluation for positive screening tests. It is only

through these provisions that the trial will effectively represent all racial and economic interests as well as ensure that the trial outcomes relate to the screening intervention itself rather than to barriers to the underinsured, the uninsured, and the economically disadvantaged.

2.12 Summary

There is no data yet to show that low-dose helical CT screening will realize a decrease in lung cancer specific mortality. By analogy to the early lung cancer screening trials, a decrease in mortality cannot be inferred by prolonged survival. Moreover, none of the current screening trials has experimental controls, which precludes the determination of the single most valid measure of screening benefit: lung cancer-specific mortality.

The following things are apparent at this time:

- CT screening will detect more cancers, cancers of earlier stage and smaller cancers than are routinely detected by CXR or symptoms;
- Small tumor size, within the size range of early stage *(T1)* cancers, has not been shown to be predictive of the cancer's propensity to spread and cause death;
- Lead-time, length, and overdiagnosis obscure the significance of prolonged survival with screening;
- Prolonged survival does not confer a mortality reduction and does not validate screening effectiveness;
- Prevalence screening CT scans will be abnormal in roughly 20-50% of screened individuals, depending upon the prevalence of granulomatous disease and other respiratory conditions in the screened population. Although fewer incidence-screening tests will be abnormal, the percentage of abnormal incidence screens over time, and their significance, are not known;
- Although the vast majority of abnormal screening studies will be due to benign disease, individuals with abnormal screening CT will effectively become patients, subject to psychological consequences and additional unnecessary, potentially dangerous, procedures such as biopsy or extended follow-up to ensure that the nodules are not cancer.

Given the billions of dollars that would be required to implement annual lung cancer screening for high risk individuals nation-wide, a randomized controlled trial will be critically important to determine whether CT screening confers true societal benefit.

3.0 SPECIFIC AIMS

3.1 Primary Specific Aim

To determine whether lung cancer screening using low-dose helical CT reduces lung cancer-specific mortality relative to screening with chest radiographs in a high-risk cohort.

3.2 Secondary Specific Aims

3.2.1 To compare all cause mortality between screening with CT versus chest radiographs.

3.2.2 To compare differences in stage distribution between the two arms of the study.

3.2.3 To compare lung-cancer related medical resource utilization between the two arms of the study.

3.2.4 To compare issues of quality of life and psychological impact associated with annual screening and with a positive screening test between the two arms of the study.

3.2.5 To assess the economic consequences of screening with CT versus chest radiographs.

3.2.6 To develop a tissue bank from individuals at high risk of lung cancer both with and without pathologically proven lung cancers. This bank will be a rich resource for determining biomolecular markers of high predictive value in stratifying levels of lung cancer risk such as pre-malignancy *(risk of future development of lung cancer)*, subclinical lung cancer, and advanced disease.

3.2.7 To assess the impact of screening on smoking behaviors.

4.0 PATIENT RECRUITMENT AND SELECTION

4.1 Recruitment Strategies

Methods of recruiting high-risk current and former smokers will vary across sites, depending upon the specifics of the participant demographics and resources available.

4.1.1 All sites will base initial recruitment on a national launch coordinated by the NCI Office of Communication. This plan will include a video news release (VNR) for broadcast via satellite, to be promoted in advance to stations in markets of the participating sites. The NCI will also sponsor a teleconference for media outlets allowing for questions and answers with the principal investigators of the NLST or other representatives. The teleconference and VNR will occur on the same afternoon.

In-house resources of the NCI, specifically the Cancer Information Services (CIS), have developed a protocol specific for the NLST. The initial media launch will direct all interested individuals to a toll free number (1-800-4-CANCER) for information about the trial. Trained operators will provide an initial screening to determine eligibility by ascertaining the following data:

- Age 55-74 and 364 days
- Current or former (quit within the last 15 years) smoker
- No history of lung cancer
- No treatment for, or advisement by a physician of evidence of *any* cancer within the past five years, with the exceptions of non-melanoma skin cancer and most in-situ carcinomas. (Treatment for, or evidence of, melanoma or in-situ bladder/transition cell carcinomas within the preceding five years renders the potential participant ineligible.)
- Not enrolled in any other screening or cancer prevention trial
- No chest CT within the prior 18 months

Eligible individuals will be directed to the nearest screening site based on their calling area code. Ineligible individuals will be offered NLST brochures to share with others as well as the availability of referral to Smoking Cessation Call Centers across the country. Former smokers will be given reinforcement for their success at quitting smoking.

Printed materials, including a brochure describing the NLST trial, a question and answer (Q&A) fact sheet, and a web site with downloadable information, as well as pointers to the various NLST sites and other cancer information services, have been developed in conjunction with the joint ACRIN and LSS groups comprising the NLST.

Additional recruitment efforts will involve four primary strategies:

4.1.2 Recruitment by regional public service announcements. Many of the accrual institutions are located in urban areas with large minority populations. With this in mind, local radio and newspaper announcements will be distributed to establish cohorts that include both genders and that accurately represent the racial diversity of the communities. All such media announcements will be approved by the ACRIN Lung Committee and the NCI in advance of their use.

4.1.3 Recruitment through communication with individual physicians, primary physician groups, and lung health programs, and by educational promotion through existing medical clinics and community health programs, free health clinics, women's health centers, hospitals, imaging centers, and cardiovascular clinics.

4.1.4 Targeted mailings within the cities that span the regional ethnic demography. The infrastructure for this method of solicitation is already in place with the Lung Screening Study (LSS) of the PLCO, with which the ACRIN Lung Study has developed a common experimental methodology. The ACRIN and LSS recruitment sites are dissimilar, which will help to ensure that targeted mailings can be successful as a primary means of recruitment for the ACRIN Lung Study without compromising the LSS.

4.1.5 Existing high-risk cigarette smoking cohorts that are already established in conjunction with other trials, or that may be available through organizations that maintain such databases, may be eligible for inclusion pending approval of the respective funding agencies and investigators. For example, participants who satisfy eligibility criteria for this screening trial may be drawn from the following cohorts:

4.1.5.1 Participants screened or enrolled for the Lung Health Study *(LHS) (N = 6000)*. The LHS followed middle-aged cigarette smokers with mild COPD in whom two interventions *(smoking cessation and inhaled anticholinergic bronchodilator)* were compared with smokers receiving *no* intervention.

4.1.5.2 Participants who undergo pre-screening for participation in the National Emphysema Treatment Trial *(NETT)* or the retinoic acid treatment trials. Such individuals must undergo spirometry as part of the determination of eligibility, thus ensuring a means to confirm that they have sufficient pulmonary function to qualify for the ACRIN screening trial.

4.1.6 Potential participants who have been informed of the trial based on targeted mailings, information brochures, or public announcements will indicate interest by returning a reply card *(available with mailing and information brochures)* or by contacting the site by telephone. In the case of written reply cards, the site will contact the potential participant by telephone to administer the E1 Eligibility Form. With telephone reply, the form will be administered at the time that the interested individual calls the site.

4.1.7 Some sites may elect to allow potential participants to complete portions of the E1 Form by mail. The participant-completed questions will be faxed to a dedicated FAX line or mailed to the site upon completion. The site RA will review the form to confirm initial eligibility, contact the potential participant to complete any remaining eligibility questions, and advise individuals of their eligibility status.

4.2 Inclusion Criteria

Based on published relative risk factors for lung cancer development, the following criteria are designed to establish cohorts at highest risk of lung cancer.

4.2.1 Age 55-74 years and 364 days.

4.2.2 Current or previous cumulative cigarette smoking history of $\geq$ 30 pack years *(packs per day multiplied by the number of years smoked).*

4.2.3 Former smokers must have quit smoking within the previous 15 years.

4.2.4 No medical or psychiatric condition precluding informed medical consent.

4.3 Exclusion Criteria

Exclusion criteria are intended to eliminate from consideration individuals unable to give informed consent or who, by virtue of medical disability, would unlikely survive to the end of the trial period. Also excluded are individuals unlikely to complete curative lung cancer surgery *(e.g., thoracotomy with lobectomy or pneumonectomy)*, individuals presenting with symptoms suggestive of lung cancer; individuals who have had recent chest imaging; or those with physical conditions that would preclude high quality screening CT. The exclusion criteria are:

4.3.1 Inability to lie on the back with arms raised above the head. Supine positioning, with or without the support of pillows under the head or extremities, with arms briefly resting above the head, is required for purposes of acquiring helical CT scans.

4.3.2 Metallic implants or metallic devices in the chest or back *(pacemakers or Harrington fixation rods, etc.)* that would cause sufficient beam hardening artifact so as to degrade image quality in the lungs.

4.3.3 Prior history of lung cancer.

4.3.4 Treatment for, or advisement by a physician of evidence of *any* cancer within the past five years, with the exceptions of non-melanoma skin cancer and most in-situ carcinomas. (Treatment for, or evidence of, melanoma or in-situ bladder/transition cell carcinomas within the preceding five years renders the potential participant ineligible.)

4.3.5 Prior removal of any portion of the lung, excluding percutaneous lung biopsy.

4.3.6 Requirement for home oxygen supplementation for respiratory conditions.

4.3.7 Participation in another cancer screening trial (such as the PLCO, ELCAP, or single arm trials such as those of the Mayo Lung Trial, Jewish Heart and Lung Institute, or the Moffitt Lung Trial).

4.3.8 Participation in a cancer prevention trial other than smoking cessation programs.

4.3.9 Present symptoms suggestive of lung cancer, including unexplained weight loss of over 15 lbs within the past 12 months, or unexplained hemoptysis.

4.3.10 No medical condition that poses a significant risk of mortality during the 8-year trial period.

4.4 Criteria for Postponement of Eligibility

Eligibility to participate in the ACRIN Lung Study and randomization should be postponed until the period of time in question under the following conditions:

4.4.1 Individuals within 12 weeks of a pneumonia or acute respiratory infection treated with antibiotics by a physician. *(These individuals would be eligible 12 weeks from the first dose of antibiotics.)*

4.4.2 Individuals within 6 months of receipt of cytotoxic agents for any condition. *(These individuals would be eligible 6 months from the last dose of the agent from the final cycle.)*

4.4.3 Chest CT scan within the preceding 18 months of study enrollment. *(These individuals would be eligible 18 months after chest CT.)*

4.5 Informed Consent

The study specific informed consents must be signed prior to study enrollment.

5.0 CRITERIA FOR SITE PARTICIPATION

5.1 Requirements

5.1.1 Approved as an ACRIN Institution.

5.1.2 Submit a protocol-specific application to ACRIN, including specification of CT scanners and chest radiographic machines to be used, qualifications of participating radiologists, qualifications of participating technologists and medical physicists, and satisfaction of interpretation competence *(see Appendix VII).*

5.1.3 Provide to ACRIN IRB documentation, consisting of a copy of full IRB approval of the protocol and the sample institutional study-specific consent form.

5.1.4 Designate a physician who is willing and committed to participate and oversee the trial at the site.

5.1.5 Have the participation of a Research Associate *(RA).*

5.1.6 Have Internet access for entry and transfer of data.

6.0 STUDY DESCRIPTION AND RANDOMIZATION SYSTEM

6.1 Enrollment Visit and Registration

6.1.1 Participants determined to be eligible based on completion of the E1 Eligibility Form by telephone or live interview will be scheduled for the Enrollment Visit. Since there may be a delay between initial E1-eligibility determination and the enrollment visit, the E1 will be re-administered at the enrollment visit, prior to registration/randomization, to confirm current eligibility. At the Enrollment Visit, the following procedures will be completed:

6.1.1.1 Explanation of the study intention and design.

6.1.1.2 **Informed Consent:** Once eligibility has been established, the potential participant will be consented. The individual will be provided with background information about the study and its goals. The requirements of the study, the implications of randomization, and the necessity for completing the required procedures will be emphasized. Permission will be asked to review medical records (*see Medical Record Release Authorization, or MRRA Form*), store image data, or contact family members to determine medical outcomes. In addition, consent to collect and bank blood, sputum, and urine specimens (*amongst biomarkers participants, Group 1 sites)* and to collect and store tissue specimens that may be obtained subsequent to diagnostic work-up for a positive screen will be obtained *(specimen consent is not mandatory for participation in the ACRIN-NLST trial).*

The following consents will be requested:

[1] General Consent Group 1: Consent to participate in the randomized trial comparing screening CT with chest x-ray. The consent includes review of medical records, contacting participant family or friends to determine participant health or vital status, storage of image data, and completion of various quality of life questionnaires.

[2] General Consent Group 2: Consent to participate in the randomized trial comparing screening CT with chest x-ray. The consent includes review of medical records, contacting participant family or friends to determine participant health or vital status, and storage of image data

[3] Medical Records Release Authorization

[4] Consent to obtain and bank specimens of blood, urine, and sputum at a central specimen repository (Colorado Lung SPORE Tissue Bank)

[5] Consent to bank tissue obtained in the course of diagnostic evaluation of positive screens at a central specimen repository (Colorado Lung SPORE Tissue Bank)

SITES	**CONSENTS TO BE OBTAINED**
Group 1 (10,000 participants)	Consents [1] [3] [4] [5]
Group 2 (15,000 participants)	Consents [2] [3] [5]

Individuals will be advised that their participation is voluntary and that their decision to participate or not to participate will have no effect on their current or future medical care. Efforts will be made to match the ethnicity of the potential participant with that of the interviewer, enlisting the part-time assistance of specifically trained interviewers who can speak Spanish, Farsi, or appropriate Asian languages and dialects. Potential participants for whom English or other appropriate language translation is not available must submit to the NCI documentation of IRB approval to administer an English language ACRIN-NLST Lung Study consent to non-English speaking individuals. All participants will be reimbursed for time and travel at the completion of their screening examinations.

6.1.1.3 Completion of Questionnaires: Following informed consent, all potential participants will complete a detailed Contact Information Form, Sociodemographic/Health Status/Health Habit/Symptom Form (*DP Form*), and Tobacco Assessment Form *(SS Form)* as part of risk profile assessment. The contact information forms are a prerequisite to participation in the trial and are intended to ensure that participants can be reached throughout the course of the trial.

6.1.1.4 Quality of Life Instruments [Group 1 Participants only]: Individuals able to read or understand English or Spanish will complete a baseline quality of life questionnaire that includes both the SF-36v2 and EuroQuol EQ-5D instruments (*QP Form*). As inferred in Section 6.1.1.2 above, participant ethnicity or literacy in English does not influence overall eligibility for the NLST, as informed consent may be administered by translators fluent in the language of the potential participant. However, the quality of life instruments to be administered for the quality of life sub-studies have not been validated in all languages. As such, the NLST will solicit quality of life information only from participants who read or understand English (*American*) or Spanish to preserve the validity of the data collected.

6.1.1.5 Spirometry: Spirometry will be obtained as part of risk profile characterization using standardized procedures. The same hand-held device will be used across all sites. Forced vital capacity *(FVC)*, forced expiratory volume in one second (*FEV_1)*, and the ratio of FEV_1/FVC will be calculated and expressed in absolute terms and as a percentage of predicted values. This information will be recorded on the Pulmonary Function Data

Form *(PA Form)*. Spirometry may be performed before or after enrollment and randomization, according to the specific scheduling constraints of the individual sites.

6.1.1.6 Collection of Specimens for Banking [Group 1 Participants only]: Samples of blood and urine for the specimen banking portion of the study will be collected following randomization. Specimen containers and instructions for the collection of sputum samples at home will also be provided to participants at the time of blood and urine sample collection. Specimen collection kits with unique bar codes are provided to all sites by the Colorado Lung SPORE Tissue Bank. These kits are used at the individual sites to collect all specimens. Bar codes are linked with the NLST participant ID at the ACRIN site; the Colorado Lung SPORE Tissue Bank does not have access to participant identification. Participants may refuse to have samples collected and still participate in the ACRIN trial. Participants who have refused specimen collection at Baseline will *not* be asked to consent to specimen collection in Years 2 or 3. However, efforts *should* be made to obtain consent to procure remnant tissue from participants who undergo a screening–related tissue biopsy or lung resection**.**

6.1.1.7 Registration: The RA will register the participant by logging onto the ACRIN web site *(www.acrin.org)* and selecting the link for Data Center Login. The system triggers a program to verify that all regulatory requirements *(OHRP assurance, IRB approval)* have been met by the institution. The registration screen begins by asking for the date on which the eligibility checklist was completed, identification of the person who completed the checklist, whether the potential participant was found to be eligible on the basis of the checklist, and the date the study-specific informed consent form was signed.

Once the system has verified that the potential participant is eligible and that the institution has met regulatory requirements, it assigns a participant-specific case number. The system then moves to a screen, which confirms that the participant has been successfully enrolled/randomized. This screen can be printed so that the registering site will have a copy of the registration for the participant's record. Two e-mails are generated and sent to the registering site: the Confirmation of Eligibility and the participant-specific calendar. The system creates a case file in the study's database at the Data Management Center *(DMC)* and generates a data submission calendar listing all data forms, images, reports, and the dates on which they are due. To avoid duplicate randomizations, do not re-register or re-randomize a participant; contact the DMC regarding any questions or problems.

Participants will be randomized into Experimental and Control arms in equal proportions using the ACRIN web site. Randomization will be stratified by age, gender, and screening center and blocked, such that at each center each arm will have equal numbers of participants within each gender and age category. Only randomization requests made by personnel designated by the PI of the site and the ACR will be accepted. Randomization requests may be made 24 hours/day using the Internet Services Provider *(ISP)* of each site. Such a configuration employs current, proven Internet infrastructure and is the most economical solution for real-time, reliable access to a centralized computer server.

6.2 Unsuccessful Registrations

6.2.1 If the potential participant is ineligible or the institution has not met regulatory requirements, the system switches to a screen that includes a brief explanation for the failure to register the potential participant. This screen can be printed.

6.2.2 In the unlikely event that the ACR web registration site is not accessible, participating sites may still register a participant by faxing the completed eligibility checklist to the DMC at the ACR *(215-574-0300, ATTN: PARTICIPANT REGISTRATION)*. ACR staff will fax a response to the

registering site with the confirmation of registration and participant case number and randomization status as soon as possible.

6.2.3 Any problems or questions regarding registration or randomization of participants should be directed to the DMC. Never re-register or re-randomize a participant as this may lead to duplicate case randomization.

7.0 DATA COLLECTION AND MANAGEMENT

7.1 General

7.1.1 The ACRIN web address is *www.acrin.org*.

7.1.2 Data collection and management will be performed by the Biostatistics and Data Management Center *(BDMC)* of ACRIN under the direction of Dr. Constantine Gatsonis. The Biostatistics Center *(BC)* is located at the Center for Statistical Sciences in Providence, RI, and the Data Management Center *(DMC)* is located at the American College of Radiology's Data Management Department in Philadelphia, PA.

7.1.3 The BDMC uses screens on the ACRIN web site to register participants, collect participant data, and maintain calendars of data submissions for each participant. By using the World Wide Web, ACRIN has made participant registration, data entry, and updated calendar information available to clinical sites 24 hours a day.

7.2 Clinical Data Submission

7.2.1 As soon as a participant has been registered, the RA may download the participant's data submission calendar, which lists all forms and/or designated reports required by the protocol, along with the date that each form is due at the DMC. The form due dates refer to the data submission timeline and may or may not refer directly to the study activity timeline; all study activities should occur as specified by the protocol. These calendars will be updated as the study proceeds to reflect data that has been received, reply deadlines for queries about unclear data, deadlines for follow-up reports of adverse events, or revisions to the protocol which might change the data being collected or its timing. Updated calendars for each participant can be obtained 24 hours a day from the ACRIN web site.

7.2.2 An investigator is obliged to submit data according to protocol as detailed on each participant's calendar as long as the participant is alive and the case status is designated as open or until the study is terminated. The case is closed when all data has been received, reviewed, and no outstanding queries exist for the case.

7.2.3 To submit data via the ACRIN web site, the RA or investigator logs onto the web site and supplies the preassigned user name and password. Case report forms will be available on the web site through a series of links. The user selects the link to the appropriate form and enters data directly into the web-based form. As information is entered into the case report form, various logic checks will be performed. These logic checks look for missing data, data that is out of range, and data that is of the wrong type *(e.g. character data in a field requiring numeric responses)*. Such errors will be detected as soon as the user attempts to either submit the form or to move to the next page. Errors must be corrected before the form is transmitted to the DMC. The user will not be able to finalize form transmission to the DMC until all data entered passes these logic checks. Forms that are not completed in one sitting can still be submitted and completed at a later date. The data is transferred to the DMC and held.

7.2.4 Once a form is complete, the investigator presses the SUBMIT button on the participant calendar, and the data is transferred into the clinical database. No further direct revision of the submitted data is allowed after this point. An e-mail is generated and sent to the site listing all of the data just completed and submitted. Should a problem occur during transmission, this automated response supplies an explanation and instructions for resubmitting the data.

7.2.5 If a temporary problem prevents access to the Internet, investigators should wait until access is restored to submit data. Investigators should notify the DMC of the problem, and the DMC will give an estimated time when access is expected to be restored. If access will be unavailable for an extended period, sites must seek another Internet Service Provider *(ISP)*. On a short-term basis, the ACR can serve as an ISP.

7.3 Data Security

The registration system has built-in security features, which encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of identification codes and passwords.

7.4 Electronic Data Management

7.4.1 Data received from the web-based forms is electronically stamped with the date and time of receipt by the ACRIN server. The data is then entered into the database. A validation program is used to perform more extensive data checks for accuracy and completeness, etc. The logic checks performed on the data at this point are more comprehensive than those built into the web-based data entry screens. They include checking that answers are logical and based on data entered earlier in the current form. This validation program produces a log of errors, which is sent to the RA for resolution. This program is frequently updated to incorporate exceptions to rules so that subsequent, correctly entered data pass validity checks, minimizing the time the research associate at the DMC needs to spend resolving problems. Additional data review will take place once the data is transferred to the BC. The BC will run thorough cross-form validations and frequency distributions to look for unexpected patterns in data and other summaries needed for study monitoring. Any errors found at the BC will be reported to the DMC Coordinator for protocol 6654 for resolution.

7.4.2 If the program detects missing or problematic data, the DMC Coordinator will send a Request for Information *(Z1)* to the research associate at the institution specifying the problem and citing the case number, form type and specific elements in need of clarification/revision. The Z1 also provide a means of response from the institution. The DMC Coordinator then updates the participant's data submission calendar with the due date for the institution's response.

7.5 Missing and Delinquent Data Submission

In addition to providing the institution with a data collection calendar for each case, institutions are periodically prompted for timely submission of data through the use of a Forms Due Report. This is distributed at least quarterly via e-mail to both the RA and the PI at each site. The Forms Due Report is not a punitive report, but rather a tool to prompt submission of overdue data and serve as a tool to help reconcile data discrepancies between the DMC's case file and that of the institution.

7.6 Data Quality Monitoring

7.6.1 The BC at Brown University will maintain a study database at its site for monitoring data quality and for performing interim analyses. These data will be drawn directly from the DMC's permanent database using a Power Builder utility that allows BC staff to log onto the DMC computer and select needed data. This analysis database will be maintained in permanent SAS *(Statistical Analysis System software)* format on the BC's ACRIN server and updated on a scheduled basis, usually monthly, once the study is in its steady state. Any discrepancies and other data quality issues will be referred to DMC for resolution, since only the DMC can correct the data file. No changes to the data will be made at the BC.

7.6.2 A major goal of the monitoring of data in the BDMC is to assess compliance with the protocol and to look for unforeseen trends that may be indicative of procedural differences among clinical sites. If patterns are discovered in the data, which appear to arise from causes specific to an

institution, the BDMC will apprise the site of the problem and work with the site until the problem has been resolved. If the BDMC cannot find a solution, the problem will be brought to the Executive Committee for further discussion and resolution.

7.6.3 The BC, in conjunction with the DMC, will prepare frequent summaries of the accrued data to be presented to investigators. These summaries will report accrual rates *(overall and by sub-groups of interest to the investigators)*; assess the completeness and accuracy of the data; and discuss any trends that may impact the outcomes of the trial. These intermittent summaries will not include analyses of the study's endpoints.

8.0 DATA COLLECTION

8.1 Data Collection Forms

These are the various forms to be used for the ACRIN 6654 Lung Screening trial. Although many of the forms are completed by the RA directly, others may be completed on paper by participants, physicians, or other personnel and checked by the RA for completeness and legibility. All data are submitted electronically via the web by the RA. Any missing data elements are to be completed before proceeding to other data forms and/or questionnaires. Unless otherwise stated, the completed forms are kept in each participant's folder at the site and entered electronically into the ACRIN web site. All forms are completed at all sites unless otherwise specified.

1) **A0: Eligibility/Registration Form:** This form is the online registration form accessed via the ACRIN web site (www.acrin.org). The online registration provides the randomization for each participant. It also provides a unique case number for each participant. At the time of registration, informed consent is to be signed and dated. In the event of online registration failure, this form can be faxed to ACRIN headquarters.

2) **BL: Biomarker Collection Form:** [Participants of Group 1 sites only]: This form is completed by the RA at the time that samples are obtained from consenting participants. It documents the collection and labeling of the blood samples. A copy of the BL form accompanies the specimens, a copy is submitted to ACRIN via fax or mail, and a copy is retained at the site.

3) **C2: Screening CT Form:** This form is completed by the radiologist at the Baseline, Year 1, and Year 2 Annual Screening Visits. The form documents the technical quality of the helical CT scans, the radiologist's interpretation, and a final screening result. The form applies only to participants randomized to the Experimental Arm, Arm I. The form is submitted via the ACRIN web modules.

4) **Contact Information Form**: This form is completed at the Enrollment Visit. The form collects information used to maintain contact with the participant over the course of the trial as well as the name of a primary (*or other*) physician to whom results can be communicated. It also provides information about prior chest imaging studies and locations of those studies/reports. This form is retained at the site and is not submitted to the ACRIN master database.

5) **CS: Quality of Life Cover Sheet** [Participants of Group 1 sites only]: This form accompanies the Quality of Life Forms (QP, QL, and PQ Forms). It serves as the first page of those questionnaires, documents the time of completion of questionnaires, and notes whether the questionnaires were completed by the participant or with assistance. The form is completed by the RA and submitted by the site via the ACRIN web modules.

6) **CX: Cancer Progression Form:** This form is completed as part of the chart abstraction process and documents disease progression for participants in whom lung cancer is established during the trial. The form is completed by a medical abstractor using any necessary documents from the medical record(s), from the date of the positive screening test onward.

7) **DE: Diagnostic Evaluation and Staging Form:** This form is completed on participants in both Arms 1 and 2 who undergo any diagnostic procedures (*radiographic, medical, surgical*) in the course of

evaluating a positive screening test. The form is completed by a medical abstractor using any necessary documents from the medical record, from the date of the positive screening test onward. The form includes documentation of the source documents utilized, procedures performed, complications of those procedures, diagnoses (*clinical or pathologic*), and lung cancer stage, if applicable.

8) **DP: Demographic/Health Status/Health Habit/Symptom Form**: This form is completed by the participant (*or with assistance of the RA*) at the Enrollment Visit. The form records information on participant medical history, demographics and economic status, occupational exposures to potential carcinogens, respiratory symptoms, family history, and alcohol history. The form is submitted to ACRIN via the ACRIN web modules.

9) **DR: Screening Chest Radiograph Form:** This form is completed by the radiologist at the Baseline, Year 1, and Year 2 Annual Screening Visits. The form documents the technical quality of the CXR, the radiologist's interpretation, and a final screening result. The form applies only to participants randomized to the Control Arm, Arm II. The form is submitted via the ACRIN web modules.

10) **E1: Pre-Registration Eligibility Form:** The form is completed prior to informed consent and enrollment and determines eligibility for the ACRIN-NLST. The form may be completed by live or telephonic interview of participants, or by having participants complete site-specific web-based systems. For a participant to be eligible, the responses must reflect those indicated on the form as true or acceptable responses. Participants should not be advised what represents a qualifying response in order to minimize fraudulent answers. Since there may be a delay between initial E1 eligibility determination and the enrollment visit, the E1 will be re-administered at the enrollment visit, prior to registration/randomization, to confirm current eligibility. This worksheet is retained at the site and is not submitted to the ACRIN master database.

11) **ES: QF Coversheet** [Participants of Group 1 sites only]: This form accompanies the QF Quality of Life. It serves as the first page of the questionnaire, and is completed by the participant. The participant submits the completed paper form to the ACRIN Biostatistics Center (BC) by mail, along with the QF. The BC then submits the CS and QF forms to ACRIN Data Management Center for data entry (see Section 20).

12) **EX: Economic Assessments Form:** Data necessary to conduct comparative analyses of the costs of the two screening procedures will be collected throughout the study. The principal information will be units of utilization. Healthcare utilization will also be acquired for staging and treatment of disease recurrence in the two-year follow-up. Unit cost estimates will be based on Medicare reimbursement rates.

13) **F1 and F2: Follow-up Forms:** The F1 and its revision, the F2 Form, are completed by the participant at six month intervals to document changes in health status, interval medical encounters, medical interventions, (*with the names of facilities where performed*), changes in smoking behaviors, and changes in participation in other clinical trials. The forms will be used to determine cross-over between trial arms, medical resource utilization, and medical outcomes. All participants complete these forms. The forms are submitted by the site via the ACRIN web modules.

14) **FC: Vital Status Update and F1 Coversheet:** This form is completed by the RA at six month intervals or at the time of death of a participant. The form documents the vital status of participants and the source of information regarding vital status. For deceased participants, the cause of death, location of death, and date of request for death certificate are recorded. The form is submitted by the site via the ACRIN web modules.

15) **FS: Follow-Up Supplement:** This form is completed by the participant at 6-month intervals, as necessary, when participants indicate on F1 forms that they have had more provider visits or health care encounters than can be documented on the F1 form.

16) **I8: Historical Images –CXR Arm Form:** This form is completed by the radiologist at Baseline, Year 1, and Year 2 Screening Visits to record results of screening CXR *after* correlation with historical images. This form applies only to participants randomized to the Control Arm, Arm 2. The form is submitted via the ACRIN web modules.

17) **I9: Historical Images-CT Arm Form:** This form is completed by the radiologist at Baseline, Year 1, and Year 2 Screening Visits to record results of screening CT *after* correlation with historical images. This form applies only to participants randomized to the Experimental Arm, Arm 1. The form is submitted via the ACRIN web modules.

18) **IM: Screening Results Form**: This form is completed by the RA and documents the dates when participant and health care provider letters are sent describing results of screening examinations as well as any diagnostic recommendations for follow-up.

19) **MRRA: Medical Records Release Authorization:** This form is completed at the Enrollment Visit and updated annually. It authorizes the site to obtain medical records from sites where the participant will be *(or has been)* seen. The form allows ACRIN to maintain image data, cytology, or histologic materials for up to ten years for purposes of research and to contact next of kin to determine cause of death as needed. The form is retained at the study site and not submitted to ACRIN.

20) **PA: Pulmonary Function Test Form:** This form is completed during the enrollment process by the RA based on the results of forced expiratory maneuvers performed on a hand-held spirometry device. Information source: the pulmonary function test results from the SpiroPro device (SensorMedics Corp.; Yorba Linda, CA). The form is completed by the RA and submitted by the site via the ACRIN web modules.

21) **Participant Medical Diaries:** These are optional self-completed work sheets that are provided to participants in order to expedite later completion of the F1 Forms. The diaries allow for the recording of all medical encounters by date, type of visit, and whether or not any medical interventions/procedures were performed. These diaries are not collected by the sites or by ACRIN.

22) **PC: Specimen Packing Form:** [Participants of Group 1 sites only]: This form is used to document shipping and receipt of processed blood and urine specimens to the Colorado Lung SPORE Tissue Bank (CTB) for those individuals participating in biomarker collection. The form is completed by the CTB and submitted via mail/fax to ACRIN headquarters to document receipt of samples.

23) **PQ: Participant Impact Questionnaire** [Participants of Group 1 sites only]: This form is completed by the RA on participants who require follow-up of a positive screening test. The form collects information on the subjective impact of the work-up on a participant resulting from the positive screen. The qualitative information includes time away from home or work and amount of discomfort the procedures may have caused. The form is administered to participants with a positive screening test *(Arms 1 and 2)* at the times specified in the protocol (see Section 20).

24) **PR: Protocol Variation Form:** This form is completed by the RA to document protocol deviations, when they occur.

25) **QC: Image Quality Form**: This form is completed by radiologists when reviewing subsets of screening exams for purposes of evaluating image quality.

26) **QF: Health Status/Anxiety Questionnaire (Screening SF-36v2™, EQ-5D, and STAI Y-1)** [Participants of Group 1 sites only]: This form combines two standardized, validated health status questionnaires (*SF-36v2™ and EQ-5D*) with the Spielberger State-Trait-Anxiety Inventory *(STAI-Form Y-1)*, which is used to measure anxiety. The form is administered to a subset of participants with a positive screening test *(Arm 1 and 2)* at the times specified in the protocol. The participant submits the

completed paper form to the ACRIN Biostatistics Center (BC) by mail. The BC then submits the QF form to ACRIN Data Management Center for data entry (see Section 20).

27) **QL: Annual Health Status Questionnaire (SF-36v2™ and EQ-5D)** [Participants of Group 1 sites only]: This form combines two standardized and validated health status questionnaires. The form is completed by a subset of participants who read or understand English or Spanish. The form is completed at each annual screening or follow-up visit, according to the methods of the quality of life sub-study (see Section 20) and is submitted by the site via the ACRIN web modules.

28) **QP: Baseline Health Status Questionnaire (SF-36v2™ and EQ Euroquol EQ-5D)** [Participants of Group 1 sites only]: This form combines two standardized and validated health status questionnaires. The form is completed by participants at the Enrollment Visit who read or understand English or Spanish. This form is submitted by the site via the ACRIN web modules.

29) **SS: Smoking Status Form:** This form is completed by the participant (*or with the assistance of the RA*) at the Enrollment Visit. The form records detailed information on smoking history, cigarette brands smoked, smoking cessation thoughts, and second hand smoke exposures. The form is submitted by the site via the ACRIN web modules.

30) **ST: Sputum Transmittal Form:** [Participants of Group 1 sites only]**:** This form documents shipping/receipt of sputum specimens by the Colorado Lung SPORE Tissue Bank (CTB). The form is enclosed in the sputum collection kits given to participants for home collection; the site telephone number is added to the form by the RA. Participants mail their specimens in a self-addressed envelope to the CTB. Upon arrival at the CTB, the form is submitted via mail/fax to ACRIN Data Management Center. A copy of the ST form accompanies the specimens, a copy is submitted to ACRIN via fax or mail, and a copy is retained at the site.

31) **TF: Treatment Form**: This form is completed as part of the chart abstraction process and documents all treatments received by a trial participant in whom lung cancer is established during the trial. The form is completed by a medical abstractor using any necessary documents from the medical record(s), from the date of the positive screening test onward.

8.2 Data Collection Table

Timetables for submission of annual screening studies will be provided at the time of study enrollment (*participant calendars*). Data forms to be completed for follow-up studies will be determined by the results of screening examinations and regular contacts at six-month intervals.

9.0 IMAGE SUBMISSION

9.1 Wherever possible, all images are requested to be provided in digital format. ACRIN has developed software that allows for electronic transmission to the ACRIN image archive of images that have been scrubbed of all patient identifiers. Individual PC computers with this software installed will be supplied to each participating site. ACRIN will be contacting each site individually to determine their readiness and ability to work with this system. If you have preliminary questions, you may contact either Rex Welsh or Fraser Wilton *(215-574-3215)* for information about this system. Once readiness has been determined, imaging personnel from ACRIN will coordinate the shipment and installation of the PC computers and train all operating staff on use of the system.

9.1.1 Annual Screening CT and CXR images will be collected for this study only. At this point in time, provisions are not available for the archiving of additional diagnostic images.

9.1.2 When direct transfer and electronic media *(CD, disk, tape)* of CXR images is not available, original images on film will be submitted via mail for digitization and subsequent entry to the image archive. For film acquisition, the identity of the participant will be reflected as follows: Institution ID, ACRIN Case #, study #. All media and film will be retained by the ACRIN

Headquarters unless otherwise requested and return packaging and postage is provided. Mailed film images or images on CD should be addressed and sent as follows:

ACRIN Image Archive
ACRIN 6654 Images
American College of Radiology
1818 Market Street, Suite 1600
Philadelphia, PA 19103
Attn: Anita Murray

9.1.3 Where required, images stored in the ACRIN Headquarters image archive may then be routed to other sites involved, using either FTP or CDROM where appropriate, for purposes of secondary review.

10.0 EXPERIMENTAL PROCEDURES

Both the Experimental and Control groups will undergo the following procedures at the time intervals specified. These procedures will be described in the following paragraphs.

Procedure	**Experimental *(Arm 1)***	**Control *(Arm 2)***
Spirometry	Baseline	Baseline
Low-dose helical CT chest	Baseline, Yr 1, Yr 2	None
Posteroanterior *(PA)* chest radiograph	None	Baseline, Yr 1, Yr 2
Interval health status and medical interventions (*F1 Form*)	6 month intervals	6 month intervals
Participants in Group 1 only Collect blood, sputum, and urine samples	Baseline, Yrs 1, 2	Baseline, Yrs 1, 2
Participants in Group 1 only QOL instruments: SF-36v2, EuroQol EQ-5D	Baseline and Annual*	Baseline and Annual*

*** Subsets of participants from the Experimental and Control Arms of Group 1 sites will complete QOL instruments according to algorithms. *(See Section 20.0)***

Baseline screening examinations should be performed within four (4) weeks of randomization (ideally within two (2) weeks of randomization).

For all cases exceeding the four (4) week window, participants should be questioned to ensure that they do not have an acute lower respiratory infection under treatment with antibiotics that would warrant rescheduling. Year 1 and Year 2 screening exams should be performed within one (1) month prior to three (3) months post the randomization anniversary dates. In cases where screen exams are performed outside these windows, sites should notify the DMC via the PR form.

11.0 LOW DOSE HELICAL CT TECHNIQUES AND PROCEDURES

Low-dose helical chest CT scans will be performed at baseline and annually at Years 1 and 2 (at times T1 and T2) on participants in the Experimental Arm. The scanners used to acquire the helical studies will be exclusively multi-channel helical CT scanners. The rationale for this is multifactorial. [1] The vast majority of positive screening CT scans will be for subcentimeter nodules in the range of 4-10 mm. Only multidetector CT scans effectively realize the spatial resolution mandatory for accurate and reproducible measures of nodule size and nodule attenuation at the level of subcentimeter micronodule that will dominate the positive screening CT. [2] Only MDCT platforms enable data acquisition within a single breath-hold at detector collimations and slice thicknesses of 0.5-2.5 mm. [3] Published and unpublished data from ongoing observational trials with screening CT indicate moderate degrees of reader variability as well as prospective failure to recognize lung nodules on screening CT. Multidetector scanners allow the retrospective reconstruction of image data into data sets of different spatial quality and image characteristics. Although not mandated by the protocol, these additional data sets and their permanent archive within ACRIN Headquarters will provide a resource for determining truth. Ultimately, the use of MDCT platforms will ensure that the screening CT, the primary test under consideration, is

of the highest quality, that the primary endpoint is not compromised by inferior image quality, and that the results will have significance beyond the period of this trial.

11.1 CT Acquisition Parameters

Radiation exposures will be as low as possible in keeping with good image quality. Because there is moderate variation in image quality across scanner platforms, a range of technical parameters will be accepted as follows:

- Primary scout performed in PA *projection* (tube at gantry bottom, patient supine) to minimize breast dose.
- kVp = 120
- mAs = 40-80 *(dependent upon participant body habitus and other factors).* Lower mAs will be accepted provided that excessive quantum mottle does not compromise image quality.
- Detector collimation= 0.5-2.5 mm *(for one data channel)*
- dFOV = smallest diameter of chest wall that will completely contain the lung parenchyma as measured from widest point of outer rib to outer rib
- Image reconstruction as follows:
  (a) Nominal reconstructed slice width: 2-3.2 mm
  (b) Reconstruction interval: 1.8-2 mm
- Reconstruction algorithm: Soft tissue/smoothing algorithm without high spatial frequency enhancement (e.g., GE Standard algorithm, Siemens B30f algorithm, etc.) for assessment of nodule attenuation
- Scan time (breath-hold duration): < 25 seconds if possible
- Table incrementation per rotation: variable according to scanner and participant
- Participants are imaged supine at suspended maximal inspiration with arms elevated over the head to minimize beam-hardening artifact.

The elements above describe the technical parameters for data sets used for primary interpretation. NLST sites may elect to reconstruct the volumetric data into additional data sets of different spatial quality, using different reconstruction algorithms, or with image processing methods such as maximum intensity projection reconstructions, according to their local practices.

All scan data acquired on trial participants will be archived and retained at the institution for the duration of the trial. Soft copy images will be sent to the ACRIN Image Archive for central storage *(see Section 9.0)*. This will enable permanent storage of image data as well as the ready distribution of images to other sites for purposes of image and interpretation quality control. Only annual screening examinations will be archived.

11.2 Screening CT Interpretation

All CT studies will be evaluated by a study radiologist according to the standard of practice at their institution. All studies will be viewed on soft copy workstations at lung windows *(width 1500-1700 HU, level -500 to -700HU) using a 1-up format*. Measurements will be obtained at view full or with magnification. The C2 Screening Data Form will be used to record the radiologist's interpretation of the screening study. Depending upon individual site policies, a separate formal interpretation may be incorporated into the participant's institutional medical record using reporting methods in accordance with the ACR Standard for Communication.[78]

Studies will be interpreted using a fixed sequential review format as follows:

- Isolated interpretation of screening examination
- Interpretation of screening examination in the context of historical images, as appropriate

The observations and conclusions of both the isolated study, followed by the study in the context of historical images, will be recorded. Although the isolated interpretation is not truly representative of screening test performance, both of these data points will be collected for modeling the benefit of screening under different conditions of time interval, etc.

In the event that an abnormality of potential relationship to lung cancer is detected, attempts will be made to procure historical imaging studies for comparison. If historical images become available at any time within four weeks of the screening CT examination, the I9 Form will be completed. Historical images submitted later than four weeks may be reviewed, and a revised I9 form with changes in the results and recommendations submitted, as appropriate.

11.3 Classification of Nodules on Helical CT

It is recommended that lung nodules detected on Screening CT will be evaluated based on the following classification:

Benign: Lesions with the following characteristics: calcification of central, rim, uniform, or other benign distribution; fat attenuation; linear morphology; and lesions documented to be stable for two or more years. The presence of micronodules < 4 mm diameter will be documented on screening CT but will not result in a positive screen.

Abnormal: Any new nodules > 10 mm diameter or enlarging nodules ≥ 7 mm diameter not satisfying criteria for benign or related to a clinically documented non-neoplastic process *(e.g., newly positive fungal serology, etc.).* Nodule characteristics such as longest axial perpendicular diameters, margin *(spiculated, smooth, poorly defined, other)* and attenuation *(soft tissue, ground glass, mixed, fluid, etc.)* will be recorded.

Indeterminate: New solitary or multiple micronodules 4-10 mm diameter or enlarging nodules < 7 mm diameter.

12.0 CATEGORIES OF CT SCREENING RESULT AND RECOMMENDED DIAGNOSTIC PATHWAYS

12.1 There are four *(4)* categories of screening results based upon nodule designations and other findings from screening CT. These screening results will drive subsequent management recommendations of the participant as described below:

Screening Result	Observation	Recommended Management
Negative	▪ No significant abnormalities ▪ Benign nodule*(s)* ▪ Noncalcified micronodule*(s)* < 4 mm ▪ Minor abnormalities, not suspicious for lung cancer	Continue annual screening CT
Negative	Significant abnormalities **not suggestive of cancer**	▪ Evaluation for condition unrelated to lung cancer *(Recommendations exceed the scope of trial)* ▪ Continue annual screening CT
Positive	▪ Nodule*(s)* 4 -10 mm diameter ▪ Enlarging nodules < 7 mm diameter ▪ Other suspicious change in nodule	▪ Repeat low dose helical CT or limited TSCT at 3, 6, (3 to 6), 12, or 24 months from the date of the [+] screening CT, depending upon lesion size and level of suspicion for lung cancer
Positive	▪ Nodule*(s)* >10 mm diameter ▪ Enlarging nodules ≥ 7 mm diameter ▪ Other suspicious change in nodule ▪ Mass ▪ Nonspecific findings suspicious for lung cancer	Additional diagnostic tests, which may include: ▪ Repeat low dose helical CT or limited thin-section CT of nodule*(s)* at 3, 6, (3 to 6), 12, or 24 months, depending upon lesion size and level of suspicion for lung cancer ▪ Diagnostic chest CT with nodule densitometry pre- and post-contrast administration ▪ FDG-PET or Technetium-99m depreotide scintigraphy ▪ Biopsy (percutaneous, bronchoscopic, thoracoscopic, open, etc.)

		▪ Other, specify
Inadequate Study	Not applicable	Reschedule Screening CT as soon as possible *(within one month of original screening CT)*

12.1.1 *Negative Screen, no significant abnormalities, benign nodules, non-calcified micronodules < 4 mm, or minor abnormalities not suggestive of lung cancer:* Participants with these screening results will continue with annual screening.

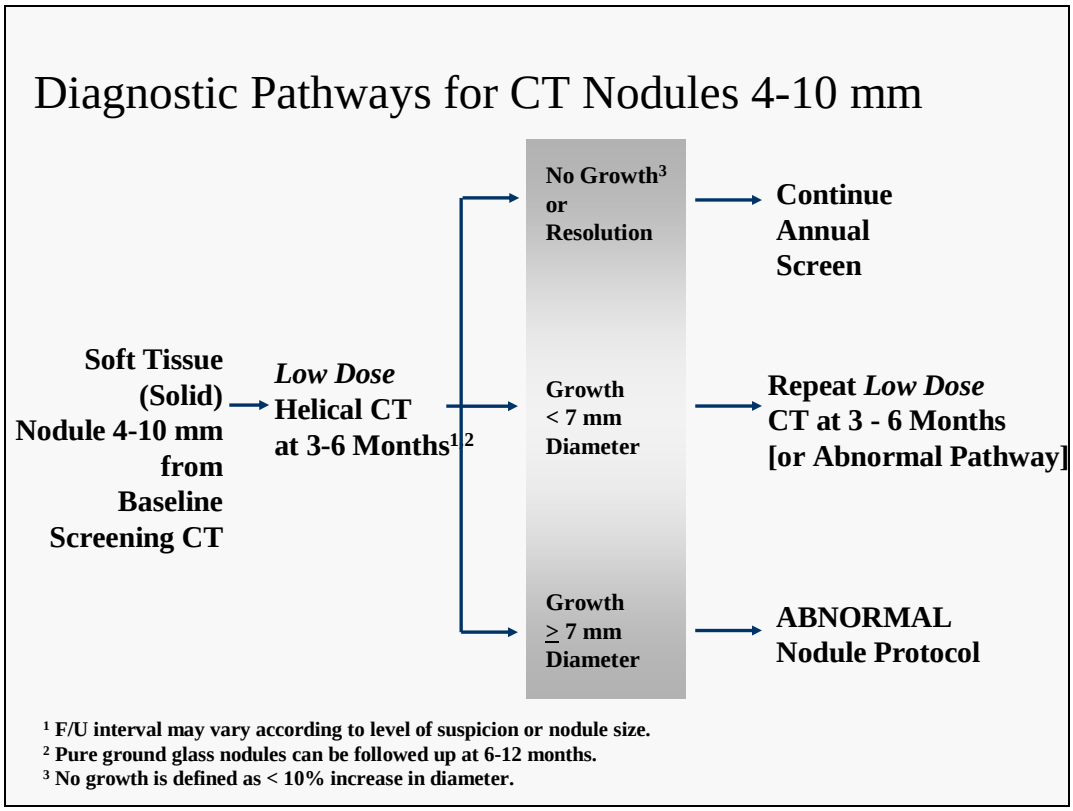
12.1.2 *Negative Screen, Significant Abnormalities Not Suggestive of Malignancy:* Participants found to have abnormalities of clinical significance unrelated to lung cancer will be referred to their physician for follow-up according to standard practices. Sites may or may not provide recommendations for further evaluation depending upon their local practice. The management of these participants is beyond the scope of this trial.

12.1.3 *Positive Screen; Indeterminate Nodules 4-10 mm diameter:* Participants with findings on screening CT suspicious for lung cancer will be advised to undergo additional evaluation designed to confirm a suspicion for lung cancer by documenting growth characteristics, morphology, or radionuclide uptake typical of neoplasm. In some instances, the initial level of suspicion may warrant immediate biopsy or open surgical procedure.

For nodules of 4-10 mm diameter, the standard practice that has been established will be to assess for interval change in size, morphology, or attenuation suggestive of malignancy. The ACRIN protocol will recommend a repeat low dose helical CT scan (or limited thin-section volumetric scan *(0.5-1.25 mm thick sections)* through the nodule at 3, 6, (3-6), 12, or 24 months from the time of the initial positive screening exam. The timing of follow-up is predicated on nodule size and the level of suspicion for lung cancer: smaller nodules or nodules of low suspicion for lung cancer are re-imaged at 4-6 months, while larger nodules or nodules of higher suspicion for lung cancer are usually imaged at 3-4 months. In the absence of change in character of the nodule, further evaluation is generally not required until the Year 1 (T1) screening.

Participants with nodules that show interval growth at follow-up of $\geq$ 7 mm will be referred for more definitive diagnostic testing. Opacities showing no growth or other change suggesting malignancy after 24 months on limited high-resolution CT follow-up will be considered benign. Participants being followed on the Repeat Low Dose Helical Protocol should continue to receive annual screening CT scans unless found to have lung cancer or other pathology that would preclude annual screening.

Figure 3: Recommended Pathway for Nodules of 4-10 mm Diameter on Screening CT



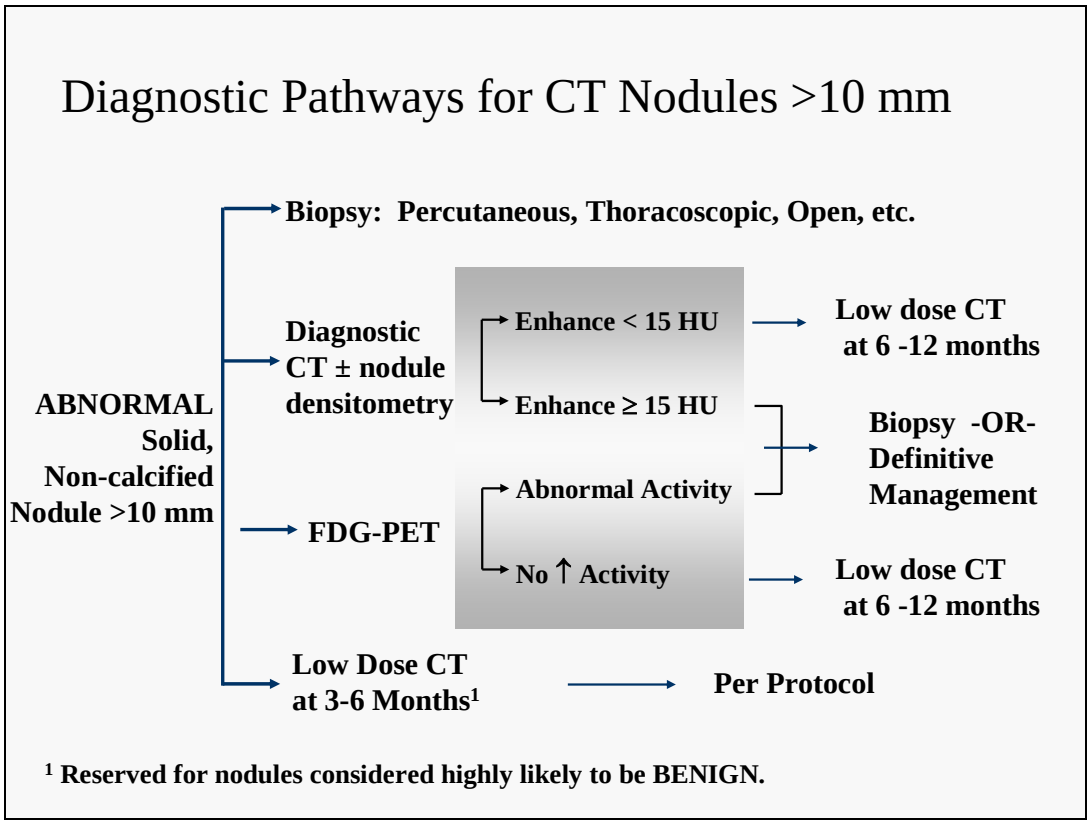
12.1.4 *Positive Screen; Nodule(s) > 10 mm Diameter or Lung Mass:* Participants in whom lung nodules > 10 mm diameter or masses are detected on CT screening will be encouraged to undergo further evaluation with the intent to confirm the presence or absence of malignancy based upon: (a) enhancement characteristics post-intravenous contrast administration, [79,80] (b) increased uptake on radionuclide tests, [81,82,83] or (c) histology, and to provide radiographic staging in preparation for definitive biopsy and treatment. At most sites, diagnostic and staging CT are normally performed as part of this process using relative generic acquisition protocols *(diagnostic CT protocols will not be specified by the ACRIN NLST protocol).*

The results of PET studies or other radionuclide scans will be recorded as part of the diagnostic evaluation of the participant on the DE Form. Excluded from contrast-enhanced nodule densitometry will be thin-walled cavitary or ground glass lesions, as these are known to be inadequately evaluated by this test.

12.1.5 *Positive Screen, Nonspecific Findings Suspicious for Lung Cancer:* Participants found to have nonspecific abnormalities of possible relationship to lung cancer will be considered to have a positive screen even in the absence of a discrete lung nodule or mass. Examples of such radiographic abnormalities are segmental or lobar atelectasis, a hilar or mediastinal mass, or pleural effusion. In such cases, additional evaluation may be advised, whether specifically in the form of diagnostic CT or simply "additional evaluation," depending upon the circumstances and local standard practices.

12.1.6 *Inadequate Study:* Participants with inadequate screening CT exams by virtue of technical limitations *(e.g., motion artifacts, excessive image noise, incomplete study, incorrect acquisition parameters, etc.)* will be rescheduled for a screening CT as soon as possible, but in all instances, within one month of the original screening test.

Figure 4: Recommended Pathway for Abnormal Nodule Seen on Screening CT



13.0 CHEST RADIOGRAPHIC TECHNIQUES AND PROCEDURES

13.1 Chest Radiographic Acquisition Parameters

Posteroanterior *(PA)* projection chest radiographs will be performed at baseline and annually thereafter on participants in the Control Arm *(Arm II)*. The acquisition devices will vary across sites and may include screen/film *(S:F)*, computed radiography *(CR)*, or digital radiography *(DR)* systems, providing that they have a speed of at least 200. The technical parameters vary slightly for the specific devices, with the following parameters applying:

The equipment used will include a rotating anode machine with a tube filtration sufficient to achieve a half value layer *(HVL)* greater than 3 mm of aluminum at 100 kVp. The recommended nominal focal spot size range is 0.6 -1.2 mm but shall not exceed 2.0 mm in any case. The system should provide a beam-limiting device for rectangular collimation. Automatic processing is required for film screen systems.

The technical parameters vary somewhat for the specific devices. The following parameters should serve as guidelines.

PARAMETER	Screen / Film	CR	DR
kV	120-150	100-140	110-150
Maximum* skin entrance exposure *(mGy)*	0.3	0.4	0.3
Maximum exposure time	40 msec	40 msec	40 msec
Source-image distance *(SID)**	≥ 72 inches	≥ 72 inches	≥ 72 inches
Anti-scatter device *(Grid)*	10:1 ratio or greater at 103 lines/inch (stationary), or 80 lines/inch (reciprocating)	Optimal for system	Optimal for system
Minimum collimation	To image receptor	To image receptor	To image receptor

* Skin entrance exposure may exceed these guidelines in large individuals.

Participants will be imaged upright at suspended maximal inspiration *(total lung capacity)* with scapulae positioned outside the lung fields if possible. The image should include both lung apices and both costophrenic angles. There must be adequate definition of the vertebral bodies, the left retrocardiac pulmonary vessels, lateral wall of descending aorta, and left hemidiaphragm. The technical parameters used should result in an image presenting the lung fields at a mid-gray level (i.e., optical density range of 1.4 - 1.8) for S/F systems, or with acceptable degrees of noise without overexposure to the participant in the case of CR or DR.

All screening chest radiographs will be archived and retained at the institution for the duration of the trial. The original images *(or high quality duplicate images where original data cannot leave the institution)* will be mailed to the ACRIN Headquarters for archive. Soft copy images may be sent to the ACRIN Headquarters for central storage at those sites in which CR or DR systems and electronic projectional image transfer is in place. This will enable permanent storage of image data as well as the ready distribution of images to other sites for purposes of image and interpretation quality control. The stored image data will include annual screening chest-x-rays.

13.2 Chest Radiographic Interpretation

All screening chest radiographs will be evaluated by a study radiologist. Because of the transition to digital acquisition devices, there is great diversity in the practice of adult chest radiology. As such, screening chest radiographs will be viewed on film or soft copy workstations, depending upon local resources. Interpretation will use the DR Screening Chest Radiograph Form. Depending upon individual site policies, a separate formal interpretation may be incorporated into the participant's institutional medical record using reporting methods in accordance with the ACR Standard for Communication.[78]

As with the screening CT examinations, screening chest x-rays will be interpreted using a fixed sequential review format as follows:

- Isolated interpretation of screening examination
- Interpretation of screening examination in the context of historical images, as appropriate

The observations and conclusions of both the isolated study, followed by the study in the context of historical images, will be recorded. Although the isolated interpretation is not truly representative of screening test performance, both of these data points will be collected for modeling the benefit of screening under different conditions of time interval, etc.

If historical images become available at any time within four weeks of the screening CT examination, the I8 Form will be completed. Historical images submitted later than four weeks may be reviewed, and a revised I8 form with changes in the results and recommendations submitted, as appropriate.

13.3 Classification of Nodules on Screening Chest Radiographs

Chest radiographs are less sensitive for detecting lung nodules and provide less accuracy when measuring size. As such, the classification of lung nodules detected on screening chest radiographs is broader than that provided for screening CT. Similarly, the diagnostic options are not as well defined. The following definitions for nodules on chest radiographs are provided:

Benign: Focal opacities with the following characteristics: calcification of central, rim, uniform, or other benign distribution and lesions documented to be stable for two or more years.

Abnormal: Any visible new or enlarging nodules not satisfying criteria for benign or not clearly related to a clinically documented non-neoplastic process *(e.g., newly positive fungal serology, etc.)*.

14.0 CATEGORIES OF CHEST RADIOGRAPHIC SCREENING RESULT AND RECOMMENDED DIAGNOSTIC PATHWAYS

14.1 There are four *(4)* categories of screening results based upon nodule designations and other findings from screening chest radiographs. These screening results will drive subsequent management of the participant as described below:

Screening Result	**Observation**	**Recommended Management**
Negative	▪ No abnormalities ▪ Minor abnormality without need for follow-up	Continue annual screening CXR
Negative	Significant abnormalities not suggestive of cancer	▪ Evaluation for condition unrelated to lung cancer *(Recommendations exceed the scope of trial)* ▪ Continue annual screening CXR
Positive	▪ Lung nodule*(s)* ▪ Mass ▪ Other findings suspicious for lung cancer ▪ Abnormalities suspicious for lung cancer, no significant change	Additional diagnostic tests, which may include: ▪ Immediate follow-up CXR with or without additional views (specify: apical/lordotic, shallow obliques, with nipple markers, other views) to better determine whether the finding observed on screening is indeed a lung abnormality and its location *-or-* ▪ Repeat chest x-ray with fluoroscopy to better determine whether the finding observed on screening is indeed a lung abnormality and its location *-or-* ▪ Low kVp chest x-ray to determine whether the screening abnormality is calcified *-or-* ▪ Repeat two-view chest x-ray in three (3) months (may follow antibiotics) *-or-* ▪ Low-dose helical chest CT ▪ Diagnostic chest CT (with or without contrast-enhanced nodule densitometry) *-or-* ▪ Whole body [F-18]-fluorodeoxyglucose positron emission tomography (FDG-PET) scan to determine whether the abnormality observed on screening behaves like a cancer *-or-* ▪ Biopsy of the lesion
Inadequate Study	Not applicable	Reschedule screening chest radiograph as soon as possible *(within one month of original CXR)*

14.1.1 *Negative Screen, no abnormalities or minor abnormalities without need for follow-up:* Participants with no abnormalities or minor abnormalities without need for follow-up will continue with annual screening CXR.

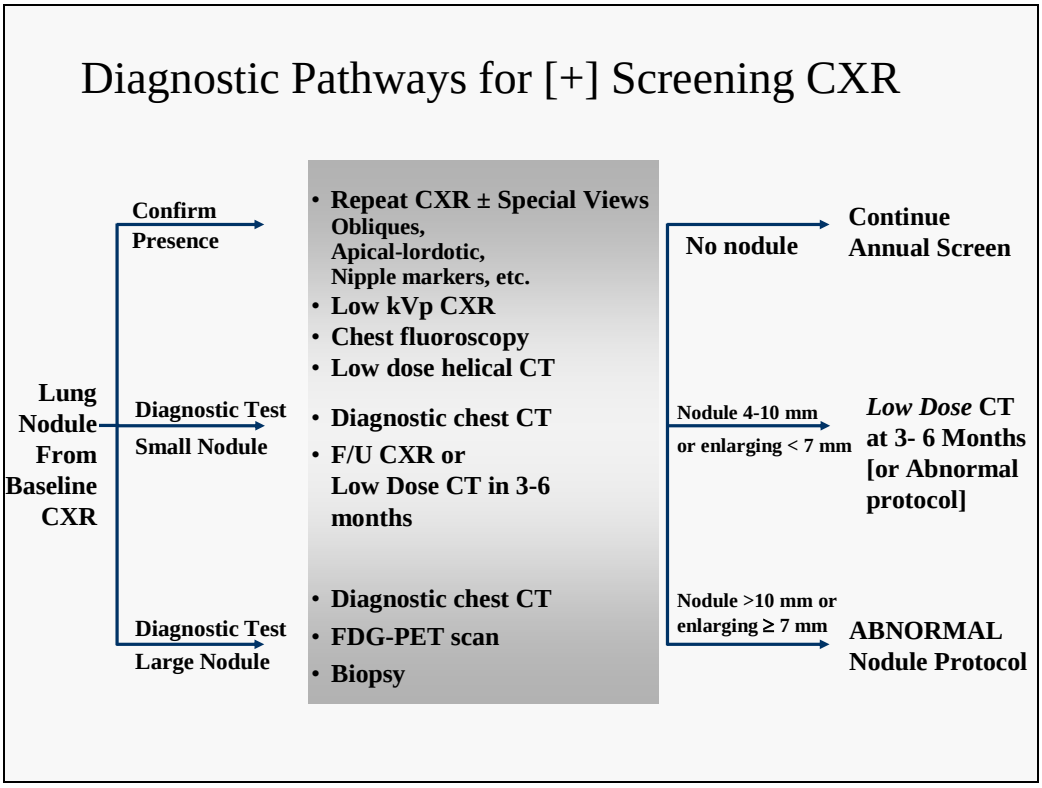
14.1.2 *Negative Screen, Significant Abnormalities Not Suggestive of Malignancy:* Participants found to have abnormalities of clinical significance unrelated to lung cancer will be referred to their physician according to standard practices. Sites may or may not provide recommendations for further evaluation depending upon their local practice. The management of these participants is beyond the scope of this trial.

14.1.3 *Positive Screen; Lung Nodules, Masses, or Other Findings suspicious for Lung Cancer:* Participants with findings on screening CXR suspicious for lung cancer will undergo additional evaluation designed to confirm the presence of the finding and the likelihood of lung cancer by documenting growth characteristics and morphology. In some instances, the initial high level of suspicion may warrant other diagnostic procedures, such as radionuclide imaging, CT, or biopsy procedures.

14.1.4 *Inadequate Study:* Participants with inadequate screening CXR by virtue of technical limitations *(e.g., motion, excessive noise, incorrect acquisition parameters, improper*

positioning, etc.) will be rescheduled for a repeat screening chest radiograph as soon as possible, but in all instances, within one month of the original screening exam.

Figure 5: Diagnostic Pathways for Positive CXR Screen



15.0 DEFINITIVE MANAGEMENT OF PARTICIPANTS WITH SUSPECTED LUNG CANCER

15.1 Given that the ACRIN trial will actively recruit participants across ethnic and economic boundaries, it is anticipated that up to 10% of participants will be under- or uninsured. Among these individuals, some will have positive screening tests and will be converted into patients, effectively ensuring that they will *remain* uninsured. Efforts must therefore be made wherever possible to ensure that diagnostic and therapeutic options are identified and financial assistance is made available to participants who are without other means to pay for the downstream consequences of the screening result. In the absence of this budgetary foresight, the study risks introducing bias in its outcome measures due to barriers imposed by inadequate health care access and financial resources.

The study coordinator will serve as a "case manager" for those participants identified as under- or uninsured with a positive screen. The study coordinator will ensure that each participant is referred to both appropriate financial assistance mechanisms and health care resources.

15.2 Abnormalities of malignant potential will be referred for definitive management under the direction of the primary physician. Local procedures and practice will vary across the accrual sites, but the intention of all subsequent management will be to confirm the presence of malignancy, establish clinical stage, establish surgical stage, and to attempt curative resection or other optimal treatment. These efforts may involve percutaneous lung *(or other organ)* needle aspiration biopsy, bronchoscopic sampling, thoracoscopic-directed or open biopsy, or nodal sampling with transcervical mediastinoscopy or thoracotomy. For invasive or minimally invasive procedures, the process of informed consent, technical standards, and procedures of the respective accrual sites will be observed, but are beyond the scope of this screening protocol. Cytologic or histologic tissue samples obtained from participants may be banked for

future biomolecular research; however, at no time will participants undergo procedures with additional risk solely to procure tissue for banking in this study (see Section below).

15.3 The surgical management of participants found to have lung cancer is not formally addressed by this screening protocol. Yet, the diligence and standardization of treatment is pivotal to ensuring the meaning and validity of collected data such as the outcome measures of mortality and surgical stage. The participating physicians and surgeons at the accrual sites will understand and follow published treatment recommendations, which include the following: [1] Pathologic Stage I lung cancer is early cancer and is best treated surgically; [2] Lobectomy is the procedure of choice; limited resections such as wedge-resection or segmentectomy do not achieve the same long-term survival and should be exclusively limited to patients with respiratory insufficiency or other medical condition that would preclude a safe lobectomy; [3] Pre-operative clinical staging with CT and FDG-PET provides valuable information, but cannot replace surgical staging. The accuracy of mortality data requires that patients undergo surgical staging with mediastinal lymph node evaluation using mediastinoscopy, limited thoracotomy, or lymph node dissection, before or at the time of thoracotomy. This should include a systematic *(usually radical)* dissection of lymph nodes to establish accurate surgical staging. Tissues resected at thoracotomy may include the primary tumor, lymph nodes, bone marrow samples from rib osteotomy, or metastatic lesions. In no instance, will specimen procurement for purposes of banking be associated with additional risk

16.0 SCREENING RESULTS COMMUNICATION AND PROCEDURES FOR PARTICIPANT FOLLOW-UP

16.1 The results of screening exams will be reported in writing to the participant and to their physician of record as indicated on Contact Information Forms completed at the time of participant enrollment. Letters of explanation will be issued within four *(4)* weeks of performance of the screening study. Participants with positive screens with no physician on record will be offered a list of physicians who could receive the results and oversee the management of the participant at the time of study enrollment. Under- or uninsured participants will be offered information on potential sources of financial assistance and access to health care services. Similarly, positive screening results will be reported to the physician of record by mail or fax, and telephone where appropriate. Depending upon individual site practices, formal reports may be issued with the explanatory letters.

Participants with a positive screen will be referred to their physician *(or assigned physician of their choosing)* for further diagnostic work-up and possible treatment according to the study recommendations *(see Sections 12.0 and 14.0)*. Any recommended diagnostic pathways will be described in detail to both the participant and physician of record. All participants, in both Experimental and Control arms, will be followed for the duration of the trial.

Participants may elect NOT to have results of NLST screening examinations sent to their referring physician(s). This must be formally documented in the participant's NLST chart by way of a progress note with participant signature or waiver. A specific waiver has been developed for use by sites that enables the participant to instruct the site NOT to send screening results letters until otherwise instructed by the participant in writing. The waiver provides space for participant signature and date of completion of waiver. Sites are encouraged, but not required, to use this form. The letters of explanation will be kept in the participant's file.

16.2 The participant letter of explanation must include the following information:

- A disclaimer stating that the examination is a screening examination, not a comprehensive examination;
- A statement providing the overall result of the screening examination with reference to any attached supplemental report for further details *(e.g., positive screen, indeterminate or abnormal opacities or masses, positive screen, non-specific finding(s) suspicious for lung cancer, etc.);*
- A statement advising the participant of any diagnostic recommendation(s) based on current practice that may be appropriate for the type of abnormality identified on a positive screening examination, preceded by a qualifier, "Among physicians, it is agreed that this abnormality requires a follow-up evaluation to distinguish between benign and cancerous lesions. The exact follow-up time interval

and method have not been scientifically established, but common methods may include: [list recommendations]."

- A statement that the screening test result as well as these recommendations for follow-up have been sent to the participant's health care provider, who may have alternative methods of evaluation within the range of current practice;
- A statement advising the participant to seek medical attention for a positive screening test result or negative screening test result with significant abnormalities unrelated to lung cancer;
- The site telephone number and the phone numbers of the site RA and PI for any questions or concerns the participant may have.

16.3 The physician letter of explanation must include the following:

- A statement that the ACRIN Lung Cancer Screening Trial is a NCI-sponsored scientific study designed to evaluate screening tests for lung cancer;
- The name of the participant whose results are being reported;
- A disclaimer stating that the examination is a screening examination, not a comprehensive examination;
- A statement providing the overall result of the screening examination with reference to any attached supplemental report for further details *(e.g., positive screen with lung nodules, findings possibly related to cancer, etc.);*
- A statement indicating that the participant has been advised to seek medical attention in the case of positive screening test results (or negative screening test results but with significant abnormal findings not suggestive of lung cancer);
- A statement advising the physician/health care provider of diagnostic recommendation(s) appropriate for the abnormality identified on screening, along with the following qualifier: "Among physicians, it is agreed that this abnormality requires a follow-up evaluation to distinguish between benign and cancerous lesions. The exact follow-up time interval and method have not been scientifically established, but common methods may include [*list recommendations*]."
- A statement that the results of this screening CT examination as well as these recommendations for follow-up have been sent to the participant, with the understanding that the physician/health care provider may have alternative methods of evaluation within the range of current practice;
- A statement encouraging the physician to proceed with diagnostic tests, whether those suggested, or others of his/her choosing, and indicating that all diagnostic follow-up could be performed at the NLST site;
- The site telephone number and the phone numbers of the site RA and PI for any questions or concerns the physician may have;
- A statement that the site RA will assist in scheduling any necessary diagnostic tests;

Sites may elect to follow-up specifically with participants in whom screening results were positive or in whom any recommendations for additional diagnostic testing were made in the screening results letters. The purpose of the follow-up call is to determine whether diagnostic tests were performed and to ensure that under- or uninsured participants are appropriately triaged to health care facilities in order to complete indicated diagnostic tests.

16.4 All Experimental and Control participants will be contacted at six *(6)* month intervals for purposes of determining all interval medical encounters *(hospitalizations, clinic visits, etc.)* over the preceding 6 months and any changes in contact information. The intentions of six-month follow-up are to:

- Maintain regular contact with all participants.
- Determine whether participants have undergone the screening interventions outside of trial.
- Determine interval lung cancers.
- Determine other major morbid medical conditions.
- Determine interval death of participants.
- Determine interval medical encounters (clinician visits, hospitalizations, etc.)

- Determine that under- or uninsured participants with positive screens receive referrals to facilitate access to health care services and financial assistance mechanisms.

The results of these interval follow-up contacts will be recorded on the F1 Follow-up Form and will determine whether additional data from medical facilities must be obtained for purposes of medical chart abstraction. The algorithm to be followed for determining chart abstraction follows *(Figure 5).*

16.4.1 Experimental participants for whom screening studies are positive due to (1) nodule(*s*) > 10 mm or masses, or (2) non-specific finding suspicious for lung cancer will undergo chart abstraction beginning from the time of the positive screening study. Similarly, 100% of CT screens documenting 4-10 mm diameter nodule*(s)* will undergo chart abstraction. All Experimental participants who undergo medical evaluation for significant screening findings unrelated to lung cancer will undergo chart review, given the moderate frequency with which additional evaluation may include thoracic or abdominal imaging procedures.

At six-month interval contact, all participants in whom lung-related encounters are documented *(e.g. imaging procedure, bronchoscopy, PET scan)* and 5% of participants in whom non-lung-related encounters occur will undergo chart abstraction. At the start of Year 2, the algorithms for chart abstraction may be revised depending upon estimated changes in the proportions of participants within each of the above categories and the information gained from chart abstraction.

16.4.2 Control participants with positive screening tests will undergo chart abstraction. At six-month interval contact, all control participants with lung-related encounters and 5% of those with non-lung related encounters will undergo chart abstraction.

16.5 Quality Assurance of Medical Abstraction will be ensured by documentation of the qualifications of the medical abstractors and nosologists as well as the procedures for monitoring the quality of abstraction.

16.5.1 Each abstractor and nosologist will be required to submit qualifications, training, and certification to the BDMC for review. The medical record abstractor should have knowledge of medical record terminology, anatomy, physiology and concepts of disease in addition to basic medical coding instruction. The abstractor should have a minimum of 2 years on-the-job experience abstracting medical records. The nosologist should also possess at least one of the following credentials:

- Certified Coding Specialist *(CSS)*
- Registered Health Information Technician *(RHIT)*
- Registered Health Information Administrator *(RHIA)*

For ICD-O-2 coding and TNM staging, individuals must be CTR or CTR-eligible, as evidenced by one of the following:

- Two years full-time equivalent experience in the cancer registry field
- Successful completion of a college level curriculum in cancer data management /cancer registry, and work experience of 120 hours in a CTR staffed computerized cancer registry or 240 hours in a non-CTR staffed computerized cancer registry.
- One-year full-time equivalent experience in the cancer registry field and successful completion of college level curriculum in medical records, nursing, or other allied health field.
- One year full-time equivalent experience in the cancer registry field and credentialed or licensed status in a recognized allied health field as determined by NBCR.

The BDMC will oversee medical abstraction and will facilitate regular communication with the sites on issues pertaining to medical record abstraction and problem resolution as well as to coordinate training. Depending upon site-specific internal review board policies, medical abstraction may be performed at the site or centrally at the BDMC using medical documents that have been scrubbed to replace all identifiers with trial-specific site and case numbers. The RA

and/or staff assisting with document procurement for medical abstraction and coding at each site will assist the BDMC in monitoring internal quality assurance at their site and providing input to resolve issues of medical abstraction that arise.

16.5.2 A 10% random sample of all participants for whom medical records were abstracted will be re-abstracted using different abstractors who are trained in the study protocol and who fulfill the background qualifications for medical abstraction, coding, and staging required by the ACRIN trial. All participant identifiers will be removed from medical documents and replaced with trial-specific site and case numbers. The results will be compared and reported to ACRIN or to the individual sites where the abstraction was performed.

Figure 5: Probabilities for Chart Abstraction of Participants Based on Study Arm, Screening Result, and Responses on F1 Data Form

Study Arm	Screening Result	Number with Screening Result per 12,500 Screened in Each Arm	Response on F1 Form	Anticipated Number Having Response of Interest on F1 Form (Source of Discovery)	Proportion for Chart Review	Number abstracted/12,500 participants/year
CT Screen Arm (12,500)	Positive Screening CT ▪ Abnormal nodule or mass ▪ Nonspecific findings suspicious of lung cancer	438 (3.5%)	All lung/chest related encounters	438 (Screening CT)	100%	438
	Positive Screen (~90%) ▪ Nodules 4-10 mm diameter (*Indeterminate)*	3937 (31.5%)	All lung/chest related encounters	3937 (Screening CT)	100%	3937
	Negative Screen ▪ No abnormalities ▪ Potentially significant findings not related to lung cancer	125 (1%)	▪ All encounters ▪ Capture non-lung cancer medical interventions prompted by screening CT	125 (Screening CT)	100%	125
	Negative Screen	8000 (64%)	▪ Lung/chest related examination or intervention ▪ Diagnosis of lung cancer	400 (F1 Form[1])	100%	400
			▪ Non-lung/chest related encounters	4000 (F1 Form[2])	5%	200
CXR Screen Arm (12,500)	Positive Screen ▪ Abnormal nodules or mass ▪ Nonspecific findings suspicious of lung cancer	1875 (15%)	All lung/chest related encounters	1875 (Screening CXR)	100%	1875
	Negative Screen ▪ No abnormalities ▪ Potentially significant findings not related to lung cancer	125 (1%)	All encounters	125 (Screening CXR)	100%	125
	Negative Screen	10,500 (84%)	▪ Lung/chest related examination or intervention ▪ Diagnosis of lung cancer	525 (F1 Form[1])	100%	525
			▪ Non-lung/chest related encounters	5250 (F1 Form[2])	5%	263

1: assumes 5% of participants in this category will have interval exams
2: assumes 50% of participants in this category will have interval exams

17.0 QUALIFICATIONS OF PERSONNEL AND QUALITY CONTROL MEASURES FOR IMAGING INSTRUMENTATION, IMAGE QUALITY, AND IMAGE INTERPRETATION

17.1 Qualifications of Personnel

17.1.1 *Qualifications of Radiologists*

Radiologists participating in the trial should meet the following qualifications:

- Certification by the American Board of Radiology, the American Osteopathic Board of Radiology, the Royal College of Physicians and Surgeons of Canada, United Kingdom, or equivalent accrediting board. Must have a valid, active medical license in the state in which screening is performed. Radiologists at federal sites must have an unrestricted license to practice medicine in their clinical specialty issued by one of the States, the District of Columbia, or a possession of the United States.
- Documented training in the physics of diagnostic radiology and radiation safety, as evidenced by completion of an accredited diagnostic radiology residency or 80 hours of documented, relevant classroom instruction. This training should include instruction in radiation monitoring requirements and the hazards of radiation exposure to both patients and radiologic personnel as well as the physical principles of CT and CT artifacts, technical parameters for CT examinations (*e.g. exposure factors, collimation, table speed, field of view, etc.*), screen-film radiography, digital or computed radiography, conventional image processing, and digital image processing.
- Involvement with the supervision and/or performance, review, and interpretation of at least 300 chest CT examinations in the past three (*3*) years -or- completion of an ACGME accredited radiology residency within the preceding 24 months.
- Involvement with the supervision and/or performance, review, and interpretation of at least 200 chest radiographic examinations per year
- Participation in continuing medical education in accordance with the American College of Radiology Standard for Continuing Medical Education (*CME*), which recommends 150 hours of Category 1 (*minimum of 60 hours*) or Category 2 (*maximum of 90 hours*) activities over three (*3*) years. This should include CME credits in chest CT and chest radiology.
- Completion of basic ACRIN certification before the time of site start-up.

In addition to the above, all physicians serving as readers for the screening tests and radiologic technologists will review a training set of images designed to ensure a common knowledge base for the interpretation of both chest radiographic and CT screening examinations. This training set (available on CD) will consist of screening examinations that demonstrate:

- Imaging findings ranging from normal to overtly abnormal, with the inclusion of focal opacities commonly observed in the course of low dose CT screening and chest radiographic screening
- Definitions of what constitutes a lung nodule and the nodule characteristics of attenuation and margin that are being recorded on the NLST data form as well as how to measure a nodule
- Deviations from the technical parameters specified by the protocol
- Suboptimal image quality for reasons of inspiratory volume, motion, beam hardening, etc.

The standard of truth for the training set was determined by consensus between three dedicated thoracic radiologists prior to distribution. The image data was reviewed at training sessions including both ACRIN and LSS physicians and is available for distribution electronically by CD to all readers at all sites. Readers will review the images independently, after which they can review the consensus opinions and explanations for the consensus opinions. Documented completion of this training session will be obtained prior to the reader's certification for the

NLST. Experimental designs to analyze observer variability within and between institutions will be formalized in ancillary projects in the future.

17.1.2 *Qualifications of Radiologic Technologists*

The radiologic technologists involved in the performance of CT scanning or projectional imaging must have the following qualifications:

- Possess an unrestricted license in the appropriate state of practice. This requirement is waived in those states in which state licensure is not required or where there is a specific restricted license that grants privileges for radiologic work (i.e., Minnesota Limited Practice Technologists).
- Be certified by the American Registry of Radiological Technologists *(ARRT)* or by a state regulatory agency (i.e., Minnesota Limited Practice Technologists).
- (CT technologists) Have documented training and experience in CT, including training in the operation of CT equipment and knowledge in radiation physics. They are strongly encouraged to pass the advanced examination for CT certification
- Maintain compliance with ARRT requirement for CME of 24 credits per two (*2*) year period
- Complete a training program and sign a written attestation that they understand the materials describing the acquisition parameters and image quality requirements of the exams for which they will be responsible in the trial.

17.1.3 *Medical Physicists*

A medical physicist(s) will be available at each site to monitor and ensure the quality of equipment used to acquire screening examinations for the NLST. The medical physicist should have the following qualifications:

- Certification by the American Board of Radiology in one of the subfields of Diagnostic Radiological Physics or Radiological Physics.
- Participation in CME in accordance with the ACR Standard, which recommends 150 hours of Category 1 (*minimum of 60 hours*) or Category 2 (*maximum of 90 hours*) activities over three (*3*) years.
- Familiarity with the principles of imaging physics and of radiation protection; the guidelines of the National Council on Radiation Protection and Measurements; laws and regulations pertaining to the performance specifications of the imaging equipment; the function, clinical uses, and performance specifications of the equipment; and calibration processes and limitations of the instruments used for performance testing.
- Availability for questions or concerns regarding radiation dosimetry.

17.2 CT Equipment Certification and Qualifications

Any imaging equipment or scanner device used to acquire screening images for NLST will be certified for use at the time of site qualification.

17.2.1 *CT Equipment Certification*

The following tests and/or documentation will be required of all CT scanners at each site used to acquire screening studies:

- An NLST CT Equipment Certification and Annual Testing form will be submitted to ACRIN for every scanner used in the trial prior to NLST participant scanning.
- CT dosimetry index *(CTDI)* using the technique proposed in the Manual of Operations and using the recommended FDA-specified CTDI phantom
- Water phantom tests for purposes of water calibration, noise, and field uniformity

- Written documentation of the performance testing completed at the time of equipment installation (acceptance testing) is recommended in accordance with ACR standards, and records must be documented by the site, with copies available for review by NLST management.
- Subject dose as measured by an appropriate dosimetry method, such as optical stimulated luminescence *(OSL)* dosimetry or thermolucent dosimetry (TLD) is under consideration in conjunction with a commercial vendor.

Re-certification of the scanner with CTDI measurements and water phantom testing (as above) should be completed after any major changes to the CT instrument, such as a change in the x-ray tube, replacement of a detector, or replacement of the collimator.

The ACR has recently launched a voluntary CT accreditation program. The quality control measures in the NLST trial are based upon this accreditation program. However, formal site accreditation for CT by the ACR will not be required of the NLST sites.

17.2.2 *Ongoing CT Quality Control QC Measures*

A *QC* program will be established for all CT units with the assistance of a qualified medical physicist. The QC program will include at least the following QC measures at the stated frequencies:

- An ACRIN-NLST CT Equipment Certification and Annual Testing form will be submitted to ACRIN for every scanner used in the trial annually as long as scanner is used to scan NLST participants.
- Bimonthly: An ACRIN-NLST CT water data form for determination of water calibration, field uniformity, and noise is submitted to ACRIN bi-monthly for every scanner in the trial.
- Scanner performance surveys including assessment of: (a) alignment light accuracy, (b) slice thickness, (c) spatial resolution, (d) low contrast resolution, (e) image uniformity, (f) noise, (g) artifact evaluation, (h) CT number accuracy, and (i) display devices should be performed annually and documentation maintained on site with copies available for review by NLST management.
- At the regularly scheduled frequencies recommended by vendor: Preventive maintenance by a qualified service engineer with documentation of these maintenance checks.

The site medical physicist should be available to assist in prescribing corrective actions for unresolved problems. All test results, equipment deficiencies, corrective actions, and service records must be documented by the site, with copies available for review by NLST management.

17.3 Chest Radiographic Equipment Certification and Qualifications

Any equipment used to acquire chest radiographic screening images for NLST will be certified for use at the time of site qualification and ongoing quality control monitoring will continue throughout the period during which screening tests are acquired.

The medical physicist should conduct testing of the unit performance at the time of site certification and at least annually thereafter. The following tests are recommended for site certification:

- System assembly evaluation
- Collimation assessment
- Timer accuracy *(if applicable)*
- Linearity of air kerma *(exposure)* with mA and/or mAs *(if applicable)*
- kVp accuracy and reproducibility
- Exposure reproducibility
- Radiographic automatic exposure control *(AEC)* system performance assessment (if applicable)
- Beam quality assessment *(Half-value layer measurement)*
- Artifact evaluation
- Review of technologist QC program and QC tests

- An ACRIN-NLST CXR Equipment Certification and Annual testing form will be submitted to ACRIN for every CXR machine used in the trial prior to imaging NLST participants and annually thereafter as long as CXR unit is used to image NLST participants.

Routine QC procedures should be performed and documented as they apply for a given chest radiographic acquisition technology. Recommended QC procedures include (a) daily processor quality control, (b) weekly darkroom cleanliness, (c) monthly visual checklist, (d) quarterly review of repeat analysis, (e) annual screen cleanliness and screen-film contact, and (f) semi-annual analysis of fixer retention in film. Documentation of these and/or other site-specific quality control tests must be documented by the site, with copies available for review by NLST management.

17.4 CT Image Quality Control

Adherence to protocol technical parameters and maintenance of high image quality will be documented at start-up and ensured in two ways: [1] visual inspection of a continuous sample of at least 10% of screening CT scans from each site throughout the trial, and [2] reviewing of DICOM header information on scan data received at the ACRIN Headquarters.

Visual Inspection: The following elements will be visually reviewed by radiologist(s):

- Display field of view (reconstruction diameter)
- Reconstruction filter
- Appropriate site and anonymous participant ID
- Suspended maximal breath-hold
- Absence of motion
- Full extent of lung fields included on the exam
- Absence of significant beam hardening artifact

Review of DICOM headers at ACRIN Headquarters: Adherence to technical parameters will also be monitored by continuous review of DICOM headers on image data received at the ACRIN Headquarters. DICOM fields to be monitored include:

- No. images total
- kV and mA or mAs
- Slice thickness
- Table speed per rotation (*or pitch*)
- Reconstruction filter
- Participant NLST ID

Instances of protocol discrepancy will be documented and used to monitor trends or patterns of inconsistent use of the prescribed technical parameters that may warrant retraining or other intervention at the site.

17.5 Chest Radiographic Image Quality Control

Adherence to protocol acquisition parameters and image quality will be documented at start-up and throughout the trial, including the following:

- Collimation to include all essential structures
- Proper positioning
- Suspended deep inspiration
- Appropriate contrast and gray scale range
- Acceptable image sharpness and noise
- Absence of artifacts *(dust, lint, roller marks, film fogging, etc.)*
- Appropriate identification markers: site name, participant research ID, exam date, exam time, R/L marker, etc.

Image quality control problems will be logged and used to monitor trends that may warrant retraining or other intervention at the site.

18.0 ADVERSE EVENTS REPORTING

The objective of adverse event (AE) reporting is the documentation of all events occurring that may compromise the welfare and safety of trial participants. Through AE reporting, practice trends at an individual site or trial-wide resulting in unusual morbidity or mortality may be identified *more rapidly* than might be identified through data analyses of secondary outcomes such as medical resource utilization or complication rates. Adverse event reporting is to be distinguished from the collection of data for purposes of analyzing trial endpoints, which is achieved through the recording of specific data elements on case report forms and statistical analysis.

18.1 Definition of Adverse Event

An **Adverse Event (AE)** is any unfavorable and unintended sign, symptom, or disease *temporally* associated with the use of a medical treatment or procedure *regardless* of whether it is considered related to the medical treatment or procedures (attribution of unrelated, unlikely, possible, probable, or definite). (For example, hyperventilation and dizziness following pulmonary function testing)

18.2 Definition of Serious Adverse Event

A **Serious Adverse Event (SAE)** is any adverse event that results in any of the following:

- Death
- In-patient hospitalization (for reasons other than observation) or prolongation of an existing hospitalization
- A persistent or significant disability or incapacity
- Congenital anomaly/birth defects

18.3 Characterizing Adverse Events by Attribution and Severity

Once identified, the site PI should characterize the AE by **attribution** (whether it is related to a trial-related procedure) and **grade** of severity. The following guidelines apply:

The **attribution** of an AE or SAE characterizes its causal relationship to the trial-related procedure as follows:

- Unrelated – clearly **NOT** related to procedure
- Unlikely – doubtfully related to procedure
- Possible – may be related to procedure
- Probably – likely related to procedure
- Definite – clearly related to procedure

Grade denotes the severity of the AE and is graded according to the current version of the Common Terminology Criteria for Adverse Events (CTCAE v3.0), or the following categories (if the term does NOT appear in the CTCAE v3.0):

1 – Mild
2 – Moderate
3 – Severe
4 – Life-threatening or disabling
5 – Fatal

(For terms listed in the CTCAE v3.0, the grade is still recorded as 1, 2, 3, 4, or 5)

18.4 Direct and Indirect AEs in Screening Imaging Trials

- Complications associated with primary interventions are termed ***direct AEs***.
- Screening tests promote downstream, diagnostic interventions; complications associated with these diagnostic interventions are termed ***indirect AEs***.
- The primary interventions in this protocol are the screening helical CT or CXR examinations, phlebotomy for collection of biomarker specimens, and pulmonary function testing.

- In this protocol, **only direct adverse events associated with the primary trial interventions will be reported as adverse events.** Indirect adverse events will be documented as part of trial endpoints on case report forms.

18.5 Potential Expected and Unexpected Adverse Events in the NLST

Adverse events may be *expected* or *unexpected*.

- An ***expected* AE** is one that is described in the protocol, the consent form, or the investigator's manual of operations, such as bruising from phlebotomy.
- An ***unexpected* AE** is one that has not been described.

The adverse events listed below (Table 1) can be found in the Common Terminology Criteria for Adverse Events version 3.0 (CTCAEV3.0) and are relevant to the ACRIN-NLST.

Table 1: Expected Adverse Events within NLST: From Common Terminology Criteria for Adverse Events v3.0 (CTCAE)

Adverse Event	Likely Scenario	Severity Grades of AE				
		Severity 1	**2**	**3**	**4**	**5**
Direct Expected AE						
1. Drinking sputum preservative	Home sputum kit, inadvertent swallowing	1	2	3	___	___
2. Syncope	Phlebotomy, spirometry	___	___	Present	Life threatening consequences	Death
3. Dizziness	Phlebotomy, spirometry	Head movements or nystagmus only, not interfering with function	Interfering with function, but no interfering with ADL	Interfering with ADL	Disabling	Death
4. Hyperventilation	Phlebotomy, Spirometry	Not interfering with function	Interfering with function, but no interfering with ADL	Interfering with ADL	___	___
5. Bruising from needles	Phlebotomy	Localized or in a small, dependent area	Generalized	___	___	___
6. Bronchospasm, Wheezing	Spirometry	Asymptomatic	Symptomatic, not interfering with function	Symptomatic, interfering with function	Life-threatening	Death
7. Vasovagal reaction	Phlebotomy	___	Present without loss of consciousness	Present with loss of consciousness	Life-threatening consequences	Death
8. Cardiopulmonary arrest (non-fatal)	Spirometry	___	___	___	Life-threatening	___
9. Wound infection	Phlebotomy	*See CTAEv3.0*				

18.6 Regulatory and Reporting Requirements

Routine reporting is defined as documentation of adverse events on source documents and the AE CRF, and submission to ACRIN for preparation of a report for Data and Safety Monitoring Committee (DSMC) review, quarterly reports to CDUS, and the final study report.

Expedited reporting will be defined in the ACRIN-NLST as immediate notification of adverse event via telephone report within 24 hours of first knowledge of the AE and/or submission of the AdEERS report form to both the NCI-CIP and ACRIN. The AdEERS report must be submitted within ten (10) working days of first knowledge of the AE. Documentation by routine reporting also applies.

Grade 5 Adverse Events/deaths require (a) a telephone report to both NCI and ACRIN within 24 hours of knowledge of death, (b) expedited reporting as defined above, and (c) routine reporting, as defined above.

18.6.1 Adverse events in the ACRIN-NLST occurring within the timeframe identified below will be reported only during the T_0, T_1, and T_2 periods of time in which participants undergo primary interventions (screening, phlebotomy, pulmonary function tests). The reporting of AEs in this protocol will conform to the following:

1. Grade 3 Expected and Unexpected AEs with attribution of possible, probable, or definite and occurring within two (2) hours of the intervention (exception: 1 week for wound infections) will be reported by **routine reporting procedures** *(see ACRIN Adverse Event Reporting Manual).*

2. All unexpected hospitalizations (or prolongation of existing hospitalization) for adverse events with the severity (intensity) level of CTCAEv3.0 Grade 3, 4, 5 and attribution of possibly, probably, or definitely related to the primary trial intervention will be reported by **Expedited Written Report** within ten (10) working days of first knowledge of the event. Routine reporting procedures also apply.

3. Grade 4 Expected AEs with attribution of possible, probable, or definite and occurring within two (2) hours of the intervention (exception: 1 week for wound infections) will be reported by **routine reporting procedures**.

4. Grade 4 Unexpected AEs with attribution of possible, probable, or definite and occurring within two (2) hours (exception: 1 week for wound infections) will be reported within ten (10) working days of first knowledge of the event by **Expedited Written Report**.

5. Grade 5 AEs or **Deaths** with attribution of possible, probable, or definite relationship and occurring within 48 hours of the primary trial interventions will be reported within 24 hours of first knowledge of the death by Telephonic Report to ACRIN and NCI-CIP and followed by **Expedited Written Report** within ten (10) working days of first knowledge of the event. Documentation by routine reporting procedures also applies. All other deaths will also be reported by routine reporting procedures.

The following table summarizes the reporting requirements for AEs for the NLST:

DIRECT AE GRADE*	EXPECTED AE	UNEXPECTED AE
Grade 3	Routine Report	Routine Report
Grade 4	Routine Report	Routine and Expedited Reports
Hospitalization/Prolongation of hospitalization**	Routine Report	Routine and Expedited Reports
Grade 5***	1. Telephonic Report to NCI-CIP within 24 hours of first knowledge 2. Expedited Report 3. Routine Report	1. Telephonic Report to NCI-CIP within 24 hours of first knowledge 2. Expedited Report 3. Routine Report

* Direct AE considered *possibly, probably,* or *definitely related* and occurring within two (2) hours of the trial intervention (except for wound infection, occurring within one week).

** All unexpected hospitalization/prolongation of hospitalization for adverse events with the severity/intensity level of CTCAEv.3.0 Grade 3, 4, 5 and attribution of *possibly, probably,* or *definitely related* to the primary trial intervention

***Report only Grade 5 AEs (Deaths) considered *possibly, probably,* or *definitely related* that occur within 48 hours of the primary trial intervention.

18.6.1 Assignment of grade and attribution of each AE is the responsibility of the site Principal Investigator.

18.6.2 Events that are clearly reflective of the "main" adverse event (e.g., loss of consciousness, which is known to occur with vasovagal episode) should be noted in the Description of Event in the AdEERS - Single Agent Template report form, and should **not** be reported as separate events. See Section 18.8.2 for URL to obtain the AdEERS Form.

18.6.3 Prompt reporting of adverse events is the responsibility of each investigator, clinical research associate, and nurse engaged in clinical research. Anyone uncertain about whether a particular serious adverse event should be reported need to contact the ACRIN headquarters at 215-574-3150 for assistance. Any adverse event considered NOT directly related to the treatment or procedure should NOT be reported as a serious adverse event in this trial. General guidance can also be found in the ACRIN Adverse Event Reporting Manual.

18.6.4 All unresolved AEs should be followed by the principal site investigator until the AE is resolved, otherwise explained, or the site has documented due diligence in attempting to procure the requisite medical records without success.

18.7 Expedited Adverse Event Reporting Exclusions

For this protocol, the following AEs are specifically excluded from expedited AE reporting:
Complications of the following conditions, hospitalizations, prolonged hospitalizations, or surgeries should NOT be reported as an AE in this trial:

- Complication from diagnostic procedures performed because of the screening intervention
- Elective surgical or minimally invasive procedures for a pre-existing condition
- Hospitalization that is required to determine efficacy for the study
- Therapy for lung cancer
- Death from lung cancer
- Death from other cancer or pre-existing condition

These conditions will be recorded on study case report forms for purpose of endpoint analysis.

18.8 Directions for Reporting Adverse Events

18.8.1 Once the study site becomes aware of a serious adverse event with attribution of possibly, probably, and definitely related to the primary trial intervention, it should be reported using the AdEERS Report within ten (10) working days via fax to NCI and ACRIN, followed by a hard copy to NCI. All fatal (Grade 5) adverse events/deaths with attribution of possibly, probably, and definitely related to the primary trial intervention should also be reported via telephone to both ACRIN and NCI-CIP within 24-hours of first knowledge of the event.

18.8.2 An expedited adverse event written report requires submission of the paper template "Adverse Event Expedited Report—Single Agent" available on the CTEP home page, http://ctep.info.nih.gov. A copy of this form can also be found in the ACRIN Adverse Event Reporting Manual. Specific guidance on how to fill-out this form can be found on the website or obtained by contacting ACRIN at 215-574-3150.

NOTE: Do not send the form via the web site; it will not accept a form without the Course Information and Protocol Agent sections filled in. These sections are not relevant to imaging protocols.

18.8.3 All fatal (Grade 5) adverse events/deaths with attribution of possibly, probably, or definitely related to the primary intervention should be reported by telephone within 24 hours of first knowledge of the event. To make a telephone report, contact NCI-CIP at (301) 496-0737, available 24 hours a day (recorder after hours from 4:30 PM to 8:00 AM Eastern Time).

A copy of all AdEERS reports should be sent to NCI by fax at (301) 480-3507, followed by a hard copy via US Mail within ten (10) working days of first knowledge of the event. Completed expedited reports should be sent to:

Barbara Galen, MSN, CRNP, CNMT, Program Director
Re: Adverse Event Report
Cancer Imaging Program
6130 Executive Blvd., MSC 7412
Room 6050
Bethesda, MD 20892-7412

18.8.4 All fatal (Grade 5) adverse events/deaths with attribution of possibly, probably, or definitely related to the primary intervention should be reported by telephone within 24 hours of first knowledge of the event. To make a telephone report to ACRIN, call (215) 717-2763. This number is available 24 hours a day (recorder after hours from 5 PM to 8:00 AM Eastern Time). During business hours, ACRIN Data Managers for the protocol will be available. A copy of all AdEERS reports should be sent to ACRIN by fax at (215) 717-0936.

18.8.5 All reportable AdEERS reports should be sent to your local Institutional Review Board (IRB). Adverse events *not* requiring expedited reporting are normally reported to the local IRB in an annual report and/or continuing review. Please refer to your local institution's IRB policies regarding adverse events, serious adverse events, and safety reports.

19.0 INSTITUTIONAL AUDITS

19.1 Timing and Composition of Audits: Institutional on-site audits will be completed after the first 100 participants have been accrued or within 12 months of a site's enrolling its first ACRIN participant, whichever comes first. Auditors will follow procedures established by the Cancer Imaging Program (CIP) of the NCI. Instructions for preparing for the audit will be sent to sites in advance of the audit date. With these instructions, the auditors will specify which case records will be reviewed during the audit. Auditors will review 10% of the total number of cases accrued, with a minimum of 30 to a maximum of 40 announced cases per site, plus 6 unannounced cases (full review). The cases will be 2:1 in favor of positive screens. Auditors will review on-site records against the electronically completed case report forms (CRFs), and they will record their findings on specially prepared NLST audit forms. Major discrepancies will be forwarded to the appropriate oversight body within ACRIN. IRB procedures, approvals, and consent forms will also be reviewed at the audit. Subsequent audits will occur at 12 to 18 month intervals or will be scheduled based upon the outcome of the initial audit.

19.2 Site Preparation and Training: To help sites prepare for audits and assure that clinical RAs maintain records appropriately, ACRIN Headquarters and the trial leadership will offer training. This training will include basics of good clinical practice as well as special instructions for finding and filing the kinds of source documentation needed to verify the accuracy of submitted data for this trial.

19.3 Source Documentation: For purposes of the ACRIN-NLST, the screening results C2 or DR Forms will serve as source documents, but must be signed and dated by the interpreting radiologist to be valid. Participant self-completed CRFs will serve as source documents so long as they are signed and dated by the participant. The image interpretation data beyond that documented in the radiology report may be recorded on the CRF and is accepted as source documentation **if signed by the MD.** At the time of audit, the auditor will verify from the medical record the occurrence of the imaging examination, date of examination, the reader, and the date of interpretation. **Any use of an approved CRF as source documentation requires that the CRF be signed and dated and refer to the source of the information (participant questionnaire, CT, MR, etc.).** The medical records that contain data elements required for completion of specific forms (e.g., PA, DE, TF Forms) serve as source documents and should be retained in the participant chart. Section 19.6 includes a listing of study-specific forms, their due dates, and the acceptable source documentation. Any use of CRFs as source documentation when the protocol designates that the information must be audited against the medical record or other documents will be considered a deficiency.

19.4 Institutional Review Board: Sites must have on hand documentation of IRB approval prior to subject registration, including a copy of IRB approval of initial application, copies of IRB approvals of modifications, and copies of annual renewals. Please see Appendix XI for the contents of the NLST Regulatory Binder.

19.5 Conducting the Audit: Site audits for the ACRIN-NLST require the presence of the site principal investigator during the audit and for the exit interview. Whenever possible, the audit team will include a physician member, typically an ACRIN-NLST investigator, for educational purposes and interpretation of the protocol when necessary. The audit is usually conducted over 2-3 days, during which time the audit team must be provided a room with adequate space for the review of participant charts and records in private.

19.6 Audit/Source Documentation

The table below reflects the source documents and signatures required for the ACRN-NLST CRFs. The forms are listed in chronological order. Only forms listed on this table are reviewed at the time of audit.

Form	Data Collection / Timeline	Source Documentation
A0	Participant registration form Completed at registration via ACRIN web site	• A0: – RA signed, dated • E1: – PT signed, dated; RA signed • All Consent Forms: PT signed, dated; other signatures as required by local IRB
MRRA	Medical Records Release Authorization Completed at enrollment and annually with re-screen	• MRRA (Original): - PT signed, dated (copy not acceptable) • Annual MRRA renewal (Original)—PT signed, dated (copy not acceptable)
DP	Demographic/Health Status/Health Habit/Symptom Questionnaire Completed at enrollment	• DP: - PT signed, dated; RA signed to confirm review of data.
BL*	Biomarker Collection Form: Completed by RA to record collection of blood and urine collection. Specimen collection performed at registration or screening visit. Group 1 Biomarker participants sites only. Completed at baseline, Year 1, and Year 2	• Biomarker consent - PT signed, dated; other signature as required by local IRB • BL - RA completed, signed, dated
PA	Pulmonary Function Test Form: Completed by RA to record results of spirometry test, spirometry performed at registration or screening visit. Completed at enrollment	• PA: - RA completed, signed, and dated • Spirometry print-out • PA Questions # 9-13 verified against spirometry print-out
SS	Smoking Status Questionnaire: Completed at enrollment	• SS: - PT completed, signed, and dated; RA signed to confirm review of data.

C2 *Arm 1*	Baseline screen should occur within 4 weeks of randomization; annual re-screens should occur within 1 month prior to 3 months after the anniversary of randomization. Screening CT Form: Completed by radiologist and research associate to document findings and results of the screening CT exam.	• C2: - Reader Physician signed, dated; RA signed, dated to confirm review/completed form • Screening Results Letter: - Reader Physician signed, dated.** **The screening result and any recommendations should be consistent between the C2 Form (or I9 Form) and Screening Results Letter. If discrepant, refer to I9 Form to reconcile.
DR *Arm 2*	Screening Chest Radiograph Form: Completed by radiologist and research associate to document findings and results of the screening CXR exam. Baseline screen should occur within 4 weeks of randomization; annual re-screens should occur within 1 month prior to 3 months after the anniversary of randomization.	• DR: Physician - Reader signed, dated; RA signed and dated to confirm review/completed form. • Screening Results Letter: Physician - Reader signed, dated.** **The screening result and any recommendations should be consistent between the DR Form (or I8 Form) and Screening Results Letter. If discrepant, refer to I8 Form to reconcile.
IM	Screening Results Form: Completed by research associate to document participant and referring physician notification of screening exams. Screening Results letters should be sent within 4 weeks of the screening exam. Data Due: Year 1-within 8 weeks of registration via the ACRIN web site. Year 2, 3-within 4 weeks of screening exam.	• IM: - RA completed, signed, dated • Screening Results Letter: – Reader Physician signed, dated. • Results Withheld Letter or similar chart documentation, as appropriate based on IM. If IM reports that the results letter was not sent to the physician of record because the participant declined to identify a physician or notify his/her physician, either a Results Withheld Letter or other documentation must be in the study chart.
I8 *Arm 2*	Historical Images Form-CXR: Completed by radiologist and research associate to document comparison of screening exam with historical images. Historical images should be reviewed within 4 weeks of screening examination.	• I8: - Reader signed, dated; RA signed, dated; Physician completed, signed, and dated if historical images were reviewed to confirm review/completed form • Screening Results Letter: – Reader Physician signed, dated.

I9 *Arm 1*	Historical Images Form-CT: Completed by radiologist and research associate to document comparison of screening exam with historical images. Historical images should be reviewed within 4 weeks of screening examination.	• I9 - Reader signed, dated; RA signed, dated; Physician completed, signed, and dated if historical images were reviewed. • Screening Results Letter: – Reader Physician signed, dated.
F1/F2	Follow-Up Forms Completed by research associate every 6 months for the duration of the study.	• F1/F2: – PT and/or RA completed; RA signed, dated to confirm review/completed forms.
FS	F1 Form supplement Completed at 6 month intervals as necessary, when participants indicated on F1 forms that they have had more provider visits or health care encounters than can be documented on the F1 Form	• FS: – PT and/or RA completed; RA signed, dated to confirm review/completed form.
FC	Vital Status Form Completed at 6 month intervals or with change in vital status of participant	• RA signed and dated • If medical abstraction required, check for DE and/or TF and associated source medical documents –or– • Documentation of due diligence to obtain source documents for medical abstraction (separate worksheet)
DE	Diagnostic Evaluation Form Completed by Certified Medical Abstractors and Coders (Form is not ACRIN audited)	• If applies, form is in participant case record with abstractor's original signature and date. • Xerox copies of all medical documents that describe the methods, complications, and results of diagnostic tests that are performed as the consequence of an NLST screening result.
TF	Treatment Form Completed by Certified Medical Abstractors (Form is not ACRIN audited)	• If applies, form is in participant case record with abstractor's original signature and date. • Xerox copies of all medical documents that describe the treatments, complications, and responses to therapy for lung cancers diagnosed during the NLST.
CX	Cancer Progression Form Completed by Certified Medical Abstractors (Form is not ACRIN audited)	• If applies, form is in participant case record with abstractor's original signature and date. • Xerox copies of all medical documents that describe the cancer progression from the date of the positive screen forward.
	Medical Resource Guide for Un-insured or Under-insured Participants (Maintain copy of document in Regulatory Binder).	• Referral source for medical care (if A0 Question 15 = 7 or 8, then source documentation of information given to participant will be audited). • Progress note in participant file that the referral resources were provided, signed and dated by RA or PI.
	Smoking Cessation Materials (Maintain copy of document in Regulatory Binder).	• Referral source for smoking cessation for all participants who are current smokers. • Progress note in participant file that the smoking cessation resources were provided, signed and dated by RA or PI.

For participants in whom diagnostic evaluations are performed for suspected lung cancer, negative screens with significant findings not suspicious for lung cancer, symptoms, or other reason during the trial, formal medical abstraction will be performed by certified abstractors based upon source medical records documents procured from hospital or clinic charts. Similarly, all treatment records should be procured for source documentation on treatment evaluations and outcomes. These source documents should be maintained in the NLST participant chart to prevent a discrepancy or inability to document data collected by medical abstraction. Procedures for procuring medical records are detailed in the ACRIN-NLST Manual of Operations.

19.7 After the Audit

See the American College of Radiology Imaging Network AUDIT MANUAL (September 2002 v.8).

20.0 SECONDARY OUTCOMES: QUALITY OF LIFE [GROUP 1 SITES ONLY]

Important secondary end-points in this trial are the differential impact of CT versus CXR screening on quality of life (*QOL*) as well as the impact of a positive screening result on QOL and anxiety. To address these respective endpoints, QOL assessment instruments will be administered to participants according to the schema below *(Figure 6)*.

- **Impact of Screening on QOL *(Study 1)***
  A random sample of 1100 Experimental arm and 1100 Control arm participants will be asked to complete annual QOL questionnaires, from among those study participants who read or understand English or Spanish.
- **Impact of a Positive Screening Result on Quality of Life and Anxiety *(Study 2)***
  Among experimental arm participants, an estimated 30-35% *(approximately 1,500-1,750 participants)* will have positive screening results *(either abnormal or indeterminate nodules)* at the initial prevalence screen. In addition, we anticipate that at least 1% of those participants who screen negative for lung cancer will have potentially significant findings that are not related to lung cancer (approximately 10 participants). We will administer QOL and STAI instruments (*QF Form*) to 825 of the experimental arm participants with a prevalence screening CT positive for lung cancer or other potentially significant findings within one month of the positive screening test and at 6, 12, 18, 24, 30, 36 months following the positive screening test. Similarly, an estimated 10-15% of control arm participants *(500-750 participants)* will have positive screening results at the prevalence screen. As in the CT arm, we expect that at least 1% (approximately 10 participants) will screen negative for lung cancer but have potentially significant findings that are not related to lung cancer. 500 of the control participants with positive radiographic screens positive for lung cancer or other potentially significant findings will complete QOL and STAI instruments at the same time intervals. To serve as controls, equal numbers of participants from the Experimental and Control arms, respectively, with negative screening studies will be matched to the positive screened participants for accrual site, age, and sex. For those patients in the sub-study who are true positives (approximately 75 participants), diagnosed with lung cancer, and their matched controls, we will continue to collect these instruments every six months for the trial duration. In all instances, participants must be able to read or understand English or Spanish, as only these versions if the QOL instruments have been validated. Thus, in this sub-study, we anticipate approximately 2,500 participants. *(See Figure 6.)*

20.1 Tools For Quality of Life Data Collection

The instruments used to assess QOL include the EuroQol EQ-5D and the SF-36v2 instruments.[84-88] Both questionnaires have been demonstrated to be internally consistent, to be acceptable to participants, and to take a total of 12-15 minutes to complete. These questionnaires will be administered at study entry to all study participants who can read or understand English or Spanish. For participants who indicate at the time of enrollment into the study that English is their preferred language, the standard tools will be self-administered. For study participants who indicate that Spanish is their preferred language, translated and validated Spanish versions of the SF-36v2 will be used.[89] Because of the potential for misinterpretation or bias, other translations of these instruments, or translators to administer the instruments, will not be used in the trial. A 5-item Mental Health Index, the MHI-5, will be computed from elements of the SF-36v2 to

augment information about the participants' mental health. This can be computed separately without additional response burden on the individuals.

We will use the Beaver Dam algorithm[90] to convert the SF-36v2 scores into Quality of Well Being *(QWB)* scores, which classifies individuals according to symptoms and functional status. We will use QWB scores to quality-adjust the life years in the cost-effectiveness analysis. Each year of life *(or shorter interval of time)* will be assigned a value between 0 and 1.0 QALYS.

To measure certain effects of screening that may be short-lived, such as anxiety, we will use the Spielberger State-Trait-Anxiety Inventory *(STAI Form Y-1)*. The STAI Form Y-1 is a one-page 20-item questionnaire that can be completed in a few minutes.[91] Translation of the STAI form Y-1 into Spanish has also recently become available.

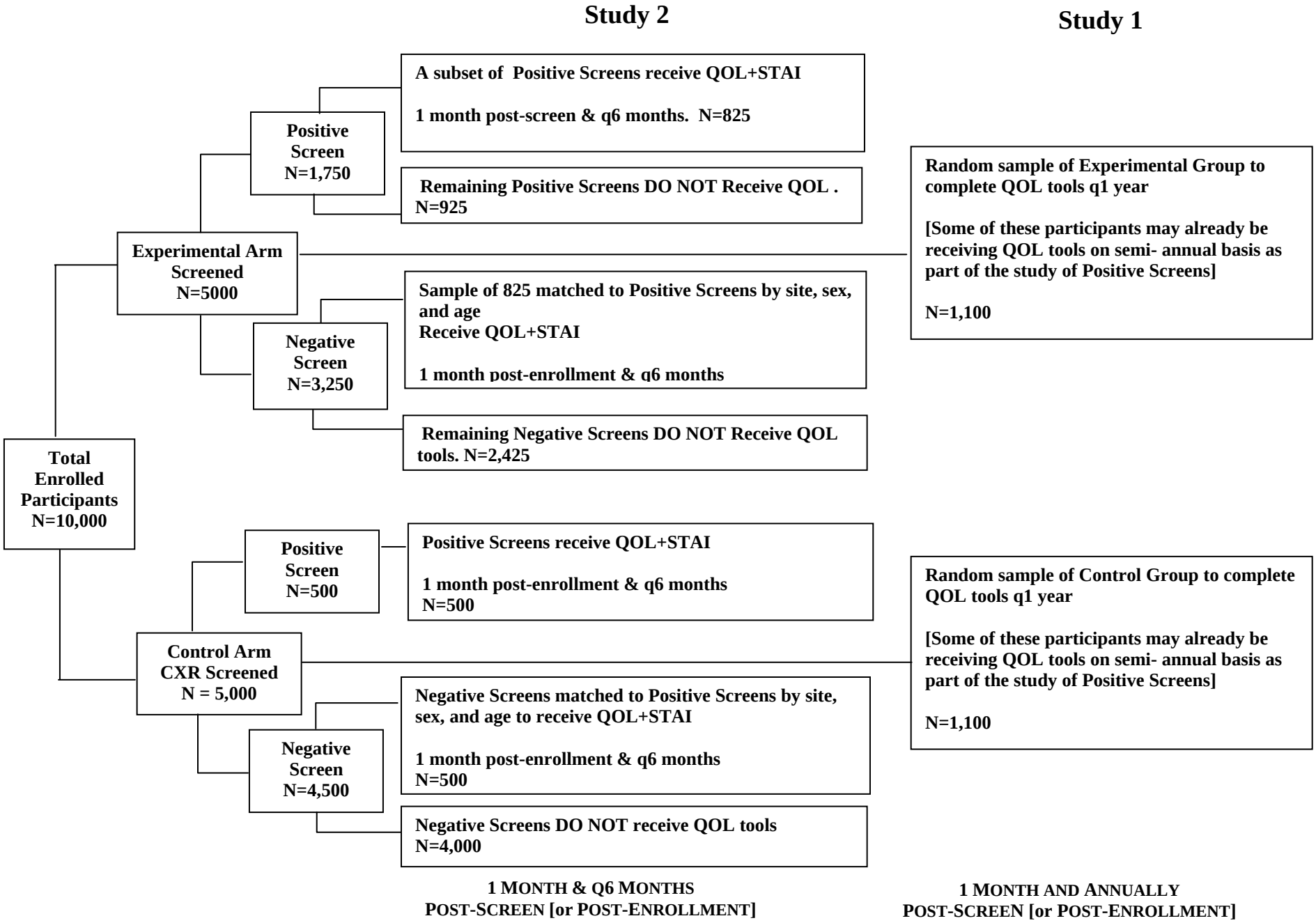


Figure 6: ACRIN NLST: Schema for Administration of the Quality of Life and Anxiety Instruments To be Performed Only at Group 1 ACRIN sites

20.2 Collection of Baseline Information on Quality of Life

To establish a baseline for the quality of life measurements, Experimental and Control arm participants who read or understand English or Spanish will be asked to independently complete the SF-36v2 and EuroQol-EQ5D questionnaires at the Enrollment *(first)* visit prior to randomization.
As necessary, the RA will encourage participants, but will not attempt to interpret the meaning of questions. During the trial-specific training sessions and during routine conference calls devoted to operational aspects of the trial, all RAs will receive training as to the manner in which they may assist participants.

20.3 Overview of General Impact of Screening on Quality of Life *(Study 1)*

A random sample of 1,100 experimental and control arm participants will be asked to complete the QOL instruments. During the portion of the trial in which participants are being screened, QOL instruments may be completed at the time of screening. If participants fail to complete the questionnaire when they return for screening or fail to return for screening, mailing of the quality of life tools will be coordinated from the ACRIN Biostatistics Center *(BC)*, located at the Center for Statistical Sciences, Brown University. BC personnel will mail participants copies of the SF-36v2 and EuroQol-EQ5D instruments (*QL Form*) as well as pre-addressed, stamped envelopes for return mailing to the Biostatistics Center. Participants will be provided with a toll-free number (which is answered by the RA at the BC) should they require assistance with reading questionnaires. If these questionnaires are not returned within 10 working days, the BC RA will telephone the study participants to ensure that the questionnaires were received and to encourage participants to complete and return them. If questionnaires are not returned within 20 working days, the BC RA will attempt to complete the questionnaires in a telephone interview. Telephone interviews will be conducted only as a final measure to avoid any biases introduced by differences in the method of administration of the questionnaires. The RA will make note on the cover sheet that the form was administered orally to the study participant. The RA will not attempt to interpret a question.

20.4 Impact of Positive Screen Result on QOL and Anxiety *(Study 2)*

20.4.1 *CT Screens:* An estimated 30-35% of experimental participants will have positive screening CT studies at baseline. 825 experimental arm participants with screens positive for lung cancer or other potentially significant findings not related to lung cancer will complete QOL and STAI instruments within one month of the positive test result and thereafter at six-month intervals from the time of the screening visit. To provide comparable controls, an equal number of experimental arm participants with negative screening CT exams matched by site of accrual, sex, and age, will complete the QOL and STAI instruments (*QF form*) in the same time intervals.

Chest Radiograph Screens: Based on published reports, we anticipate that only 10-15% of control participants will have positive screening chest radiographs. 500 control participants with screens positive for lung cancer or other potentially significant findings not related to lung cancer will complete QOL and STAI instruments (*QF form*) within one month of the positive test result and thereafter at six-month intervals from the time of the Screening Visit. An equal number of comparable controls will be drawn from control arm participants with negative screening chest radiographs, matched by site of accrual, sex, and age.

20.4.2 After selection into this sub-study, within one month of receiving the positive screening test result, the BC personnel will mail participants SF-36v2, EuroQol-EQ5D, and STAI questionnaires (*QF form*), along with pre-addressed, stamped envelopes for return mailing to the Biostatistics Center.

After the initial set of questionnaires, the four groups of participants will receive the three questionnaires semi-annually for 36 months from the initial date of the index screen. For this substudy, all questionnaires will be mailed from the BC using the approach described in Section 20.3. If these participants are among those already selected to receive annual questionnaires, they will no longer receive questionnaires on the annual schedule, but will be

"upgraded" to receive questionnaires on every six-month anniversary of their intake into the study.

20.5 Administration and Processing of QOL Instruments

A database will be maintained at the BC to monitor selection of study participants for each of the QOL studies and the receipt of mailed questionnaires and telephone contacts. If the questionnaires are not received at the BC within 10 working days of the date of the mailing, a BC RA will telephone the participant to determine whether the questionnaires were received and completed. Participants who did not receive the questionnaires will have additional questionnaires sent by mail after confirming the correct mailing address. If questionnaires were received but never completed, the BC RA will urge the study participant to complete and return the questionnaire. If the questionnaires are not received at BC within 20 working days of receipt of the mailing, the BC RA will telephone the participant and volunteer to assist in questionnaire completion. If necessary, the forms will be administered by telephone; the mode of administration of all such questionnaires will be documented in the trial database.

21.0 DETERMINATION OF SECONDARY OUTCOMES: HEALTH AND MEDICAL RESOURCE UTILIZATION

The impact of lung cancer screening on medical resource utilization will be studied. Among the outcome variables to be measured are:

- Medical resource utilization for positive screening tests resulting from both true positive *(malignant)* and false positive *(benign)* conditions.
- The impact of lung cancer screening on the occurrence of iatrogenic complication/illness requiring medical care.
- The proportion of the Control group that seeks CT screening independently of this clinical trial.

21.1 Methods of Collection of the Health and Health-Care Use Data

To ascertain the frequency and types of medical encounters of potential relationship to lung cancer and lung cancer screening, participants will be contacted at six-month intervals. At this contact, participants will be asked to answer a series of questions regarding interval medical visits, hospitalizations, or interventions that have occurred since the prior contact. Participants in both the Experimental and Control Arms will provide this information via interview (live or telephonic) or self-completed questionnaires. Particular emphasis will be placed on ascertaining whether any lung-related medical visits or hospitalizations have occurred or whether any of a number of specific lung-related diagnostic or therapeutic interventions has been performed.

If participants have had medical contact of potential relationship to lung cancer or lung cancer screening in the past six months, permission to contact the physician/facility of record will be obtained by the site RA for the appropriate facility, as provided for in the informed consent process. Copies of all pertinent medical records will be obtained for purposes of medical abstraction to detail procedures performed, therapies administered, and iatrogenic effects of any procedures or therapies related to lung cancer or lung cancer screening. The source documents from which these data are collected will be retained for purposes of documentation, as allowed by the individual institutions. At those sites in which copies of scrubbed medical documents cannot be released, chart abstraction will occur on site and the necessary data entry completed without retention of source documents.

If a participant cannot be contacted directly, sites will try to establish their vital status and update the contact information for that participant by contacting individuals and personal physicians listed on the Contact Information Sheet completed at enrollment and updated annually.

At the end of the study, the names and social security numbers of any participants reportedly deceased or lost to follow-up will be submitted to the National Death Index to determine whether they have died during the course of the study. For participants that match with the National Death Index, the death certificate will be obtained and the cause of death ascertained. In addition, the participant's

physician and next of kin will be interviewed. In cases for which the cause of death is uncertain, a truth panel consisting of physicians not participating in the trial itself will be used to determine the relationship of the cause of death to lung cancer.

For all participant deaths in the NLST, every effort will be made to procure the death certificate and any available medical record data detailing the terminal events. All lung cancer deaths will be reviewed by an independent Truth Panel of physicians not participating in the NLST to determine the relationships between cause of death, lung cancer, and screening interventions.

All participants will be required at the time of study enrollment to agree to a review of their medical records as well as notification of next of kin or close personal contact in the event of their death. Informed consent for medical record review and notification of next of kin will be renewed annually.

22.0 COST-EFFECTIVENESS ASSESSMENT

22.1 We will collect cost information on those participants to whom we administer the quality of life instruments to assess the impact of positive screening results on QOL and anxiety. In addition, we will obtain billing records from selected sites, such as Dartmouth-Hitchcock Medical Center, to help refine estimates of direct medical costs, direct non-medical costs, and opportunity costs for various alternative screening strategies *(including no screening)*. Direct medical costs will include those related to the screening tests and subsequent diagnostic evaluations, treatment for lung cancer *(and other conditions first detected through the screening process)*, and complications from testing, treatment, and morbidity. Non-medical and opportunity costs will include lost wages, traveling and lodging costs for the original screening tests and all subsequent evaluations and treatment for the screenee *(and caregiver)*. Pain and suffering will not be considered as a cost, but as a disutility measured in QALYS. The cost questionnaires will collect information on non-medical and opportunity costs and help in the collection of direct medical costs. Information to compute direct medical costs will also be abstracted from medical charts. The cost questionnaires will be administered at the same time as the quality of life questionnaires. Cost data will be collected on both Experimental and Control arms to determine whether some of the increased costs of CT screening are offset by lower costs of earlier treatment. We will assess the costs from the societal perspective of Gold.[92] All costs will be adjusted for inflation by using either the most recent general medical care component of the Consumer Price Index-Urban or the Medicare Economic Index as appropriate.[93,94] Future costs beyond the period of the study will be predicted, adjusted for inflation, and annually discounted at different rates in the 0% to 7% range.[92]

22.2 Medical

For many of the procedures and treatments in common use, such as full chest CT, bronchoscopy, and lobectomy, cost estimates will be derived from the existing literature and from Medicare cost data. In choosing among published estimates, estimates of actual costs rather than charges will be used.[92] For some of the procedures whose costs have not been published, Health Care Financing Administration *(HFCA)* cost data will be used to estimate the costs of inpatient hospitalization, physicians' services, and outpatient testing *(http://www.hcfa.gov/stats/pufiles.htm)*.

The costs of some newer procedures, such as screening helical CT and limited helical CT, have neither been published nor estimated by HCFA. For these procedures, we will estimate their costs using the approach of Medicare RBRVS, which divides the costs of radiologic procedures into professional and technical components.[95,96] The professional component is further divided into work, practice cost, and liability RVUs. To estimate the work RVUs, we will collect data on the radiologist's time required for planning and interpreting the examinations. In addition, we may survey a sample of radiologists to estimate a procedure's work RVUs *(by comparing the procedure to one with an established RVU, such as a PA and LAT chest radiograph [RVU of 1.00], or full chest CT exam)*. We will multiply the work RVU by 1.36 to account for the practice and liability RVUs, which together comprise 26.2% of total professional RVUs in radiology (Medicare RBRVS 1995). *(We will also multiply by the radiology conversion factor but not the geographical factor)*. To estimate the technical components, we will collect data regarding resource utilization, including CT examination time, technologist's time, contrast material, film, etc. In addition, we may survey technologists to

estimate the technical RVUs, which do not include a physician work component. We also will look at additional sources to estimate costs based on discharge diagnosis of lung cancer from the Healthcare Cost and Utilization Project.[97]

22.3 Non-medical

We will assess the non-medical costs to the screenee *(and caregiver)* by means of a questionnaire *(PQ Form)*. These costs will include out-of-pocket expenses for travel, food, and lodging related to the screening test and subsequent diagnostic tests and treatments related to screening. In addition, we will collect data on the time *(hours)* spent on all the above activities and hours of missed employment and volunteer activities. Similarly, we will collect data on the non-medical costs of lung cancer diagnosis and treatment in the Control arm. No standard questionnaires for this purpose exist to our knowledge. We will develop this questionnaire after examination of other ad hoc questionnaires and after assessment of ACRIN experience with a previously developed questionnaire in use for ACRIN Protocol 6651: Role of Radiology in the Pretreatment Evaluation of Invasive Cervical Cancer.

We will calculate cost-effectiveness with and without the inclusion of some, but not all, future "non-lung cancer" medical costs as recommended by Gold.[92] These issues are currently unresolved. Uncertainty in the analysis will be assessed through sensitivity analysis in which the assumptions about future costs and health states are varied and outcomes are assessed under these different assumptions.

23.0 STATISTICAL CONSIDERATIONS

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25.0 CORRELATIVE STUDY: BIOMOLECULAR MARKER BANK AND DISCOVERY NETWORK

Our knowledge of the molecular events heralding lung cancer and the specific markers associated with the evolution from initiation to invasion is only partial. This trial represents a tremendous opportunity to collect samples with which to better characterize the molecular events coincident with multi-step carcinogenesis because the participants are a high-risk cohort that will be well characterized and followed longitudinally.

25.1 Specific Aim

To implement a tissue/specimen bank of serum, sputum and urine samples from participants that will be optimally preserved and prepared for future state-of-the-art molecular assays, including but not limited to polymerase chain reaction (*PCR*), proteomics, and oligonucleotide microassays.

25.2 Overview of Blood, Urine, and Sputum Collection [Group 1 Sites Only]

Our hypothesis is that biomolecular markers may be identified in the blood, sputum, or urine that can enhance our understanding of the genetic events proceeding and associated with lung cancer. This can be achieved through an efficient biomarker discovery process. With input from the NCI and appropriate internal review boards of the current lung cancer SPORES *(University of Colorado, Johns Hopkins University, University of Texas, including UT Southwestern and the MD Anderson Cancer Center, and UCLA School of Medicine)*, we propose to develop a specimen bank of blood, sputum, and urine specimens for archiving. Although blood and sputum samples are currently used for most biomarker assays, we believe this trial presents a unique opportunity to also collect urine, which is a rich source of secretory proteins, is "non-invasive" and is easy to obtain. Participants of both the Experimental and Control Arms randomized into the study at sites collecting biomarkers [Group 1 sites only], will undergo collection of these samples at the time of enrollment and at the first and second incidence screens. This will provide a rich foundation for testing biomarkers found to be promising in preliminary tests conducted outside of the ACRIN-NLST trial.

Potential biomarker*(s)* for testing would be identified based upon preliminary data provided by studies performed *outside* of this trial. Request for use of banked specimens for biomarker studies and any associated data collected on NLST participants requires formal application to the ACRIN Biomarker Oversight Committee, comprised of molecular biologists, radiologists, and other scientists. Following approval by this committee, proposals are submitted for final approval to the NCI. The application process involves a description of study hypothesis, specific aims, types of samples requested, types of associated clinical data requested, statistical justification of sample size, assay descriptions, and quality control procedures to be implemented. Importantly, any additional specimens obtained from NLST participants *must also* go through this approval process to ensure that the primary biomarker collection is not compromised.

Biomarker tests could be conducted in one or more laboratories housing the appropriate technology and methods to automate sample preparation as well as documented expertise in the performance of the particular assay. Attention will focus on the development of integrated biomarker sets to analyze multiple markers concurrently. Given considerations of hardware, the requirements of comprehensive database software, and analysis software capable of complex multivariate modeling, these biomolecular assays may be best performed in collaboration with industry. Tests for a particular marker will be conducted at one site for quality control purposes.

25.3 Biomarker Specimen Collection and Banking

Participants at selected sites (Group 1 sites only) who consent to collection of specimens will provide blood, urine, and sputum specimens for banking at the Colorado Lung SPORE Tissue Bank. These Specimens will be collected on both Experimental and Control participants at the Baseline, Year 1, and Year 2 screening examinations. This prospective sequential collection may enable the determination of the sequential genetic changes that precede or herald invasive cancer. To encourage the maximum number of specimens, participants who have refused specimens collection at Baseline, should *not* be asked to consent to specimen collection in Years 2 or 3. However, efforts *should* be made to obtain consent to procure remnant tissue from all participants who undergo a screening–related tissue biopsy or lung resection.

25.4 Tissue Specimen Collection for Banking

At all sites, we propose to collect leftover (remnant) tissue specimens and blood samples from participants who, during this trial, undergo biopsy procedures or surgery to remove tissues based upon a positive screening test or a suspicion of lung cancer. These tissues might include lung tissue, tumor tissue, lymph nodes, muscle, or tissue from organs such as liver or adrenal that are biopsied or removed as part of standard diagnosis or treatment. The tissue specimens may be benign or cancerous. Only tissues that would ordinarily be discarded after analysis for clinical purposes would be used for banking. The sample(s) of tumor taken for research will be taken from the tissue after it has been removed. Therefore, the use of this tissue for research will not result in any additional pain or side effects. No tissues will be removed solely for the purposes of this study. At the time of tissue collection, we would also request a blood sample of approximately 40 ml by routine phlebotomy.

The tissue and blood samples will be processed for banking at the Colorado Lung SPORE Tissue Bank, where the biomarker specimens from participants at the Group 1 sites are also being banked. Those sites that will not permit banking at distant facilities will bank their specimens, given the appropriate storage facilities and Certificate of Confidentiality, at their respective institutions. These specimens will be stored for purposes of future research, which may include genetic tests.

25. 5 Specimen Database

All participant information will be entered into the ACRIN Lung Cancer Screening database. This will include information about participant sociodemographic, health, cigarette smoking, and occupational histories as well as information relevant to cancer diagnosis, cancer therapy, and treatment response. All information will be coded with a study specific identification number and all personal identification information removed in order to maintain confidentiality. Only the tissue and participant study ID number will be retained at the Colorado Lung SPORE Tissue Bank. The Tissue Bank will have no method of associating any specimen with an individual or her/his confidential data.

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Appendix I

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK
ACRIN 6654
NATIONAL LUNG SCREENING TRIAL

SAMPLE CONSENT FOR RESEARCH STUDY
(Includes Biomarker Specimens and QOL)

This is a clinical trial, a type of research study. Clinical trials include only participants who choose to take part. Please take your time to make your decision. You may want to discuss this with your friends, family, or doctor.

The American College of Radiology Imaging Network (ACRIN) and the National Cancer Institute (NCI) sponsor this trial.

You are being asked to take part in this study because you are at increased risk of lung cancer due to your age and smoking history.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine whether screening people at high risk for lung cancer using spiral computed tomography (CT) of the chest will reduce the number of lung cancer deaths in comparison to screening with chest x-ray (CXR). Although it is known that spiral CT can detect smaller lung cancers than can CXR, it is not known whether screening with this new test will prevent lung cancer deaths. In addition, screening with spiral CT is expected to have more side effects than screening with CXR (risks listed below). The only reliable method of determining the benefits of screening with spiral CT versus CXR is a randomized clinical trial, where some participants will be screened with spiral CT and some will be screened with CXR. The value of screening with CXR compared to no screening is currently being assessed in another trial sponsored by the NCI.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

ACRIN is part of a larger trial called the National Lung Screening Trial, NLST, in which a total of 50,000 individuals will be enrolled. About 25,000 people will participate in the ACRIN-sponsored component of the trial. Approximately 1,000 participants will be enrolled at this institution.

WHAT IS INVOLVED IN THE STUDY?

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. You will be assigned to a group by a computer. Neither you nor the study team will choose the group into which you are placed. You will have an equal chance of being placed in either group.

About one-half of the study participants will be screened annually with a low-dose spiral CT; the other half will be screened with CXR.

If you are randomized to the spiral CT group, the exam will require that you lie still on your back on a table that moves slowly through a doughnut-shaped machine. The machine takes a series of

x-rays to create a three-dimensional picture of your lungs. It will be necessary for you to hold your breath for 20-25 seconds while you are being scanned.

If you are randomized to the CXR group, you will receive a single-view chest x-ray. This type of x-ray is commonly used to view the organs inside the chest. It will be necessary that you hold your breath for a few seconds while the x-ray is taken.

As a participant in this study, you will also be asked to give specimens of your blood, urine and sputum (spit). In addition, if you undergo a biopsy or have surgery in which tissue is removed for testing, we would like to keep any leftover tissue that might otherwise be discarded. These specimens and leftover tissues will be kept to help researchers in the future understand what causes cancer, how to prevent it, and how to treat it. The specimens of blood, urine, and sputum will be stored at a central storage facility at the University of Colorado Lung SPORE Tissue Bank. Leftover tissues may also be stored centrally at the Colorado Lung SPORE Tissue Bank or at the facility where you had the procedure(s) to remove the tissue. Participating in the collection of specimens or allowing us to keep any leftover tissues will not benefit you, but may benefit other people with lung cancer. We will ask you to sign separate consents to allow us: [1] to collect specimens of blood, urine and sputum and [2] to store leftover tissue samples. Some of the institutions participating in this trial across the country are not collecting specimens of blood, urine or sputum. However, all institutions will ask to collect leftover tissues for storage. You may decide not to provide blood, urine, and sputum specimens or leftover tissues and still participate in the screening portion of the trial. No matter what you decide to do, it will not affect your care.

<u>If you take part in this study, you will have the following tests and procedures:</u>
All participants will undergo:

- An interview to determine general information about your smoking habits, general health, work history, and personal contact information (address, telephone number, friends and family contacts).
- A simple breathing test through a mouthpiece.
- Every (6) six months you will receive a questionnaire or telephone call to ask about your health status.
- Questionnaires about your quality of life (QOL) at baseline (beginning of the study), at year one (1) and year two (2) follow-up.

<u>Arm 1: Experimental Arm</u>

- A screening spiral CT at the beginning of the study and at the next two annual screening visits.
- You may be asked to complete additional questionnaires about your QOL and anxiety one (1) month after the spiral CT and every six (6) months for up to six (6) to eight (8) years.

<u>Arm 2: Control Arm</u>

- A screening CXR at the beginning of the study and at the next two (2) annual screening visits.
- You may be asked to complete additional questionnaires about your QOL and anxiety (1) one month after the CXR and every six (6) months for up to six (6) to eight (8) years.

You and your physician will be notified of the results of these screening tests. If they show any abnormalities you may be advised to have additional diagnostic tests or procedures. These tests

might include additional CT scans, CXRs, a biopsy or surgery. These procedures are not part of the ACRIN-NLST trial itself. Although it may be in the best interests of your health to have these tests completed, you are not obliged to have them performed as part of this trial.

If you are asked to complete the QOL and anxiety questionnaires, sometimes you will complete them during the annual visit to have the screening test or you may have the questionnaires mailed to you from a central location at ACRIN. Also, you may be contacted on the telephone by an ACRIN representative to help you fill out the questionnaires or to remind you to send it back. Your address, phone number, and contact information for a close friend or family member will be provided to ACRIN for this purpose.

When you have your CXR or spiral CT, it will take approximately 30 minutes to 1 hour of your time. The QOL questionnaires will take approximately 20-30 minutes to complete.

HOW LONG WILL I BE IN THE STUDY?

You are being asked to actively participate in the study for six to eight years, depending on when you were first enrolled in the study. However, the study investigator has the right to take you off this study if you become too ill to have surgery for suspected lung cancer.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study investigator or a member of the ACRIN-NLST staff and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk of the following side effects. You should discuss these with the study investigator and/or your regular doctor. Risks and side effects related to screening for lung cancer include the following:

Very Likely

- Radiation dose from a screening spiral CT (100-300 mrem), which is less than or equal to the average annual dose from natural sources of radiation (300 mrem).
- Radiation dose from screening chest x-ray (8-12 mrem), which is much less than the average annual dose from natural sources of radiation (300 mrem).
- False positive screening spiral CT requiring a limited CT Scan test in 3 months (20-50%). The term "false positive" refers to a screening test in which findings initially of concern for cancer are later found *not* to be cancer.
- False positive screening CXR requiring a non-contrast CT Scan (5-10%).
- Anxiety about evaluation of false positive screening spiral CT or CXR results.
- Detection of abnormalities unrelated to lung cancer that could lead to unnecessary testing or treatment from screening with either spiral CT (10-15%) or CXR (1%).

Less Likely, but Serious

- False positive screening spiral CT requiring a full CT scan with intravenous contrast or other potentially invasive procedures (2-7%).
- False positive screening CXR requiring a full CT scan with intravenous contrast or other potentially invasive procedures (1-5%).
- Earlier diagnosis and treatment of lung cancer that is ineffective or unnecessary (< 2%) from screening with either spiral CT or CXR.
- Failure to detect a lung cancer that is present, and possibly miss an opportunity for cure.
- Death from biopsy (less than 1% of all biopsies); death from surgery (2-4% of all having surgery).

- Death from reaction to contrast material used in diagnostic CT scans (less than 1 in 40,000 of all receiving intravenous contrast).

There also may be other side effects that we cannot predict. Most side effects go away shortly after the screening is completed, but in some cases side effects can be serious or long lasting or permanent. You should also be aware that these screening tests are not a replacement for a physical examination or a substitute for a visit to your doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you during the course of the study. The possible benefits of taking part in the study are the same as being screened with a spiral CT of the chest without being in the study. These include:

- Prevention or delay of death from lung cancer.
- Prevention of, or reduction in, symptoms from lung cancer.
- Milder treatment, leading to fewer side effects, from treatment for lung cancer.

We hope the information learned from this study will eventually benefit you and others who are at risk for lung cancer.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other screening options that you might consider because of your risk factors may include the following: *(1)* to be screened with a spiral CT of the chest at your own expense, *(2)* to be screened with a CXR at your own expense, or *(3)* not to be screened for lung cancer at all.

Please talk with your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Throughout the course of the study we will collect information from you and your medical records that is relevant to lung cancer screening, including your screening test results, and, if applicable, follow-up tests or treatments related to lung cancer. We will keep this data in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN and the Center for Statistical Sciences at Brown University). The screening exams performed in this study and any pathological specimens that are obtained will also be retained for at least 10 years, but without any identifying information on them. If you choose to withdraw from the study, you may revoke your approval for the use of your future medical information. To do so, you must contact Principal Investigator in writing. However, to maintain the integrity of the study, we will maintain the information you had already provided for the duration of the study.

Medical abstractors contracted by ACRIN will review your medical records after they have signed a confidentiality agreement. These records would include all lung related visits to a health care provider and all hospitalizations. If you are concerned about the confidentiality of your medical records, the institution's protocol team will de-identify your records before they are sent to the abstractors.

Other individuals or organizations that may inspect and/or copy your research records for quality assurance and data analysis include the NLST protocol team at *institution* (principal investigator, study coordinator, and project assistant[s]), the Institutional Review Board at *institution*, the American College of Radiology Imaging Network (ACRIN), the National Cancer Institute (NCI), and other groups or organizations that have a role in this study.

Information gained from this study may be used in the future for secondary studies and research. No individual names or results that could identify you personally will be used.

Although all efforts will be made to keep your personal information confidential, we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

WHAT ARE THE COSTS?

The annual screening spiral CT and CXR will be paid for by ACRIN, the study sponsor. You may also be reimbursed for part of your travel expenses necessary for your participation at the time of your screening examinations.

You and your insurance company are responsible for all costs associated with diagnostic tests or treatments that result from screening. If you do not have adequate insurance coverage to pay for these procedures, we will try to find additional resources to help you.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

For information about your screening or participation, and research-related injury, you may contact:

Name_____ Telephone Number_____

For information about this study, you may contact:

Name_____ Telephone Number_____

For information about your rights as a research participant, you may contact:
(OHRP suggests that this person not be the investigator or anyone else directly involved with the research)

Name_____ Telephone Number_____

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at:
1–800–4–CANCER (1–800–422–6237) OR **TTY: 1–800–332–8615**

Visit the NCI's Websites for accurate cancer information at: http://cancer.gov/cancer_information or for comprehensive clinical trials information at: http://www.cancer.gov/clinical_trials. Information about NLST is posted at: http://cancer.gov/NLST. Visit ACRIN's Website for group information at: www.acrin.org.

PERMISSION TO REVIEW MEDICAL RECORDS:

By agreeing to participate, I give permission for my health care providers and hospitals where I have been seen to release my medical records to the study investigators.

SIGNATURE:

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form, I will receive a copy. I may also request a copy of the protocol *(full study plan)*.

_____ _____

Participant Signature *(or Legal Representative)* Date

Appendix II

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK
ACRIN 6654
National Lung Screening Trial

SAMPLE CONSENT FOR RESEARCH STUDY

(No Biomarker Specimen Collection or QOL)

This is a clinical trial, a type of research study. Clinical trials include only participants who choose to take part. Please take your time to make your decision. You may want to discuss this with your friends, family, or doctor.

The American College of Radiology Imaging Network (ACRIN) and the National Cancer Institute (NCI) sponsor this trial.

You are being asked to take part in this study because you are at increased risk of lung cancer due to your age and smoking history.

WHY IS THIS STUDY BEING DONE?

The purpose of this study is to determine whether screening people at high risk for lung cancer using spiral computed tomography (CT) of the chest will reduce the number of lung cancer deaths in comparison to screening with chest x-ray (CXR). Although it is known that spiral CT can detect smaller lung cancers than can CXR, it is not known whether screening with this new test will prevent lung cancer deaths. In addition, screening with spiral CT is expected to have more side effects than screening with CXR (risks listed below). The only reliable method of determining the benefits of screening with spiral CT versus CXR is a randomized clinical trial, where some participants will be screened with spiral CT and some will be screened with CXR. The value of screening with CXR compared to no screening is currently being assessed in another trial sponsored by the NCI.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

ACRIN is part of a larger trial called the National Lung Screening Trial, NLST, in which a total of 50,000 individuals will be enrolled. About 25,000 people will participate in the ACRIN-sponsored component of the trial. Approximately 1,500 participants will be enrolled at this institution.

WHAT IS INVOLVED IN THE STUDY?

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. It is like flipping a coin. You will be assigned to a group by a computer. Neither you nor the study team will choose the group into which you are placed. You will have an equal chance of being placed in either group.

About one-half of the study participants will be screened annually with a low-dose spiral CT; the other half will be screened with CXR.

If you are randomized to the spiral CT group, the exam will require that you lie still on your back on a table that moves slowly through a doughnut-shaped machine. The machine takes a series of

x-rays to create a three-dimensional picture of your lungs. It will be necessary for you to hold your breath for 20-25 seconds while you are being scanned.

If you are randomized to the CXR group, you will receive a single-view chest x-ray. This type of x-ray is commonly used to view the organs inside the chest. It will be necessary that you hold your breath for a few seconds while the x-ray is taken.

As a participant in this study, we will ask to keep and store any leftover tissue(s) obtained from you at the time of biopsy procedures or surgery for possible lung cancer. These tissues are removed for testing to make decisions about your care, after which there may be some leftover (remnant) tissue. Leftover tissues will be kept to help researchers in the future understand what causes cancer, how to prevent it, and how to treat it. The leftover tissues will be stored centrally at the Colorado Lung SPORE Tissue Bank or at the facility where you had the procedure(s) to remove the tissue. Allowing us keep your leftover tissues will not benefit you, but may benefit other people with lung cancer. We will ask you to sign a separate consent to allow us to collect leftover tissues for storage. **No tissues are ever removed from your body solely for purposes of this research**. You may decide not to provide leftover tissues and still participate in the screening portion of the trial. No matter what you decide to do, it will not affect your care.

<u>If you take part in this study, you will have the following tests and procedures:</u>

All participants will undergo:

- An interview to determine general information about your smoking habits, general health, work history, and personal contact information (address, telephone number, friends and family contacts).
- A simple breathing test through a mouthpiece.
- Every (6) six months you will receive a questionnaire or telephone call to ask about your health status.

<u>Arm 1: Experimental Arm</u>

- A screening spiral CT at the beginning of the study and at the next two annual screening visits.

<u>Arm 2: Control Arm</u>

- A screening CXR at the beginning of the study and at the next two (2) annual screening visits.

You and your physician will be notified of the results of these screening tests. If they show any abnormalities you may be advised to have additional diagnostic tests or procedures. These tests might include additional CT scans, CXRs, a biopsy or surgery. These procedures are not part of the ACRIN-NLST trial itself. Although it may be in the best interests of your health to have these tests completed, you are not obliged to have them performed as part of this trial.

When you have your CXR or spiral CT, it will take approximately 30 minutes to 1 hour of your time.

HOW LONG WILL I BE IN THE STUDY?

You are being asked to actively participate in the study for six to eight years, depending on when you were first enrolled in the study. However, the study investigator has the right to take you off this study if you become too ill to have surgery for suspected lung cancer.

You can stop participating at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study investigator or a member of the ACRIN-NLST staff and your regular doctor first.

WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk of the following side effects. You should discuss these with the study investigator and/or your regular doctor.

Very Likely:

- Radiation dose from a screening spiral CT (100-300 mrem), which is less than or equal to the average annual dose from natural sources of radiation (300 mrem).
- Radiation dose from screening chest x-ray (8-12 mrem), which is much less than the average annual dose from natural sources of radiation (300 mrem).
- False positive screening spiral CT requiring a limited CT Scan test in 3 months (20-50%). The term "false positive" refers to a screening test in which findings initially of concern for cancer are later found *not* to be cancer.
- False positive screening CXR requiring a non-contrast CT Scan (5-10%).
- Anxiety about evaluation of false positive screening spiral CT or CXR results.
- Detection of abnormalities unrelated to lung cancer that could lead to unnecessary testing or treatment from screening with either spiral CT (10-15%) or CXR (1%).

Less Likely, but Serious:

- False positive screening spiral CT requiring a full CT scan with intravenous contrast or other potentially invasive procedures (2-7%).
- False positive screening CXR requiring a full CT scan with intravenous contrast or other potentially invasive procedures (1-5%).
- Earlier diagnosis and treatment of lung cancer that is ineffective or unnecessary (< 2%) from screening with either spiral CT or CXR.
- Failure to detect a lung cancer that is present, and possibly miss an opportunity for cure.
- Death from biopsy (less than 1% of all biopsies); death from surgery (2-4% of all having surgery).
- Death from reaction to contrast material used in diagnostic CT scans (less than 1 in 40,000 of all receiving intravenous contrast).

There also may be other side effects that we cannot predict. Most side effects go away shortly after the screening is completed, but in some cases side effects can be serious, long lasting or permanent. You should also be aware that these screening tests are not a replacement for a physical examination or a substitute for a visit to your doctor.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you during the course of the study. The possible benefits of taking part in the study are the same as being screened with a spiral CT of the chest or chest x-ray without being in the study. These include:

- Prevention or delay of death from lung cancer.
- Prevention of, or reduction in, symptoms from lung cancer.
- Milder treatment, leading to fewer side effects, from treatment for lung cancer.

We hope the information learned from this study will eventually benefit you and others who are at risk for lung cancer.

WHAT OTHER OPTIONS ARE THERE?

You may choose to not participate in this study. Other screening options that you might consider because of your risk factors may include the following: *(1)* to be screened with a spiral CT of the chest at your own expense, *(2)* to be screened with a CXR at your own expense, or *(3)* not to be screened for lung cancer at all.

Please talk with your regular doctor about these and other options.

WHAT ABOUT CONFIDENTIALITY?

Throughout the course of the study we will collect information from you and your medical records that is relevant to lung cancer screening, including your screening test results, and, if applicable, follow-up tests or treatments related to lung cancer. We will keep this data in a confidential form at this institution and in a computer file at the headquarters of the American College of Radiology Imaging Network (ACRIN and the Center for Statistical Sciences at Brown University). The screening exams performed in this study and any pathological specimens that are obtained will also be retained for at least 10 years, but without any identifying information on them. If you choose to withdraw from the study, you may revoke your approval for the use of your future medical information. To do so, you must contact Principal Investigator in writing. However, to maintain the integrity of the study, we will maintain the information you had already provided for the duration of the study.

Medical abstractors contracted by ACRIN will review your medical records after they have signed a confidentiality agreement. These records would include all lung related visits to a health care provider and all hospitalizations. If you are concerned about the confidentiality of your medical records, the institution's protocol team will de-identify your records before they are sent to the abstractors.

Other individuals or organizations that may inspect and/or copy your research records for quality assurance and data analysis include the NLST protocol team at *institution* (principal investigator, study coordinator, and project assistant[s]), the Institutional Review Board at *institution*, the American College of Radiology Imaging Network (ACRIN), the National Cancer Institute (NCI), and other groups or organizations that have a role in this study.

Information gained from this study may be used in the future for secondary studies and research. No individual names or results that could identify you personally will be used.

Although all efforts will be made to keep your personal information confidential, we cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

WHAT ARE THE COSTS?

The annual screening spiral CT and CXR will be paid for by ACRIN, the study sponsor. You may also be reimbursed for part of your travel expenses necessary for your participation at the time of your screening examinations.

You and your insurance company are responsible for all costs associated with diagnostic tests or treatments that result from screening. If you do not have adequate insurance coverage to pay for these procedures, we will try to find additional resources to help you.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

A Data Safety and Monitoring Board, an independent group of experts, may be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed)

For information about your screening or participation, and research-related injury, you may contact:

_____ _____

Name Telephone Number

For information about this study, you may contact:

_____ _____

Name Telephone Number

For information about your rights as a research participant, you may contact:

(OHRP suggests that this person not be the investigator or anyone else directly involved with the research)

_____ _____

Name Telephone Number

WHERE CAN I GET MORE INFORMATION?

You may call the NCI's Cancer Information Service at:

1–800–4–CANCER (1–800–422–6237) OR **TTY: 1–800–332–8615**

Visit the NCI's Websites for accurate cancer information at:

http://cancer.gov/cancer_information or for comprehensive clinical trials information at: http://www.cancer.gov/clinical_trials. Information about NLST is posted at: http://cancer.gov/NLST.

Visit ACRIN's Website for group information at: www.acrin.org.

PERMISSION TO REVIEW MEDICAL RECORDS

By agreeing to participate, I give permission for my health care providers and hospitals where I have been seen to release my medical records to the study investigators.

SIGNATURE:

I have read all the above, asked questions, and received answers concerning areas I did not understand. I have had the opportunity to take this consent form home for review or discussion.

I willingly give my consent to participate in this program. Upon signing this form I will receive a copy. I may also request a copy of the protocol *(full study plan).*

_____ _____

Participant Signature *(or Legal Representative)* Date

Appendix III

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK ACRIN 6654

NATIONAL LUNG SCREENING TRIAL

SAMPLE CONSENT FOR RESEARCH STUDY

Blood, Urine, and Sputum Specimens for Banking

WHY IS THIS STUDY BEING DONE?

This portion of the study seeks to collect and store specimens of blood, urine, and sputum that may later be used to look for genetic causes and signs of lung cancer. If you agree, the specimens will be kept and may be used in future research to learn more about cancer and other diseases. The exact studies that will be performed are not all known at this time, but they will likely include biologic factors and inherited traits (genes that can be passed on in families) that may influence whether people develop lung cancer and related conditions. The samples will be given only to researchers approved by the American College or Radiology (ACRIN) and the National Cancer Institute (NCI). Any research using these samples must also be approved by an internal review board (IRB).

Participants in clinical trials include only those who choose to take part. Please take you time making your decisions. We encourage you to discuss your decision with your doctor, family, and friends.

WHAT IS INVOLVED IN THE STUDY?

If you would like to participate in this part of the study, samples of blood, urine, and sputum (spit) will be collected at your initial visit. You will also be asked to provide these same samples when you return for your next (2) two annual screening visits.

We would ask you to do the following:

1. **Blood Collection.** A blood sample will be drawn through a needle from a vein in your arm. The blood sample may amount to about 30 cc (1-2 tablespoons). Blood donation of this type is not mandatory and you may decline to provide blood at any time without jeopardizing your participation in this research or your access to health care.
2. **Urine Collection:** You will provide a urine sample in a urine cup.
3. **Sputum (phlegm) Collection:** You will be given two (2) special containers for collecting sputum samples on six different days (a red-labeled cup and a blue-labeled cup). Upon arising in the morning, you should thoroughly rinse your mouth with water. You must cough deeply into the sputum cup. It is often easier to produce sputum after your morning shower. Cough on three successive mornings into the red-labeled cup, and then three more successive mornings into the blue-labeled cup. **Please indicate the last date of collection for each cup in the space provided on the enclosed Sputum Collection Form. This Sputum Collection Form (SP) should be enclosed with the specimens in the mail.**

   The samples do not need to be refrigerated prior to mailing, but they should be stored at room temperature in a safe place so that they are not inadvertently lost. Once you have provided the sputum, screw the caps tightly and mail the cups directly to the specimen bank using the postage-paid mailing container that has been provided to you.

WHAT ARE THE RISKS OF THE STUDY?

The following are known risks of your participation in this study. The treatments or procedures may involve risks that are currently unforeseen. If you have questions about these risks, the investigators or other designated research staff will answer these questions.

1. Blood Collection: When blood is drawn you may feel a little discomfort as the needle goes through the skin. There may be local bruising or bleeding at the puncture site. Pressing hard on the spot for 1 to 2 minutes after the needle is removed will help prevent a bruise. You may feel queasy around needles. Very rarely, the arm may become infected. The risk is the same as that of having blood drawn at your doctor's office or clinic.

2. Confidentiality: The greatest risk to you is the unintended release of information from your health records. The investigators will protect your records so that your name, address, phone number, and any other identifying information will be kept private. All information about you and your samples will be given a unique code, and your personal identifying information will be removed to protect your confidentiality. Information regarding your assigned identification number will be permanently kept in locked files with access limited to approved study investigators. The chance that this information will be given to someone else is very small. No individual identities will be used in any reports or publications resulting from this study.

ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?

Participation in this part of the study will not provide direct benefit to you. Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your health care. However, your participation in these additional studies, and the analysis of all of the specimens obtained in this study, may help physicians to establish a scientific understanding of what causes lung cancer and other diseases, how to prevent it, and how to treat it.

WHAT ARE THE ALTERNATIVES TO PARTICIPATION?

You may choose not to provide specimens of blood, urine and sputum for banking. You can still participate in the screening part of the trial and yet decline to provide these specimens.

IS THERE PAYMENT FOR PARTICIPATION?

Your samples will be stored and may later be used only for research. Your samples will not be sold. You will not be paid for the use of your samples or for any test or product that is discovered or developed through this research and that may be of commercial value. Neither you nor your insurance company will be billed for your participation in this research.

ARE THERE POTENTIAL COMMERCIAL PRODUCTS?

If a commercial product is developed based on the used of your samples from this study, the commercial product will be owned by the University/Institution or its designee. You will not profit financially from such a product.

WHAT ABOUT CONFIDENTIALITY?

In the future, people who do research may need to know more about your health. While the ACRIN-NLST investigators may given them information about your health, they will not give them your name, address, phone number, or any identifying information that would let other scientists know who you are. Even if your

specimens are used for genetic research (research about diseases that are passed on in families) the results will not be put in your health records or linked to your name.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

Your participation in the collection and storage of biological specimens (blood, urine, and sputum) is voluntary and you may refuse to participate and/or change your mind and withdraw your consent at any time without penalty. Furthermore, you may participate in the screening part of the trial and yet decline to have biologic samples stored for research purposes.

If you initially decide to provide samples of blood, urine, and sputum for future research and you do change your mind, just contact Dr. _____ in writing at (*institution*) and let him/her know that you do not want your samples to be used. We will destroy your samples and they will not be used for research. Otherwise, the samples may be kept until they are used up, or until the study investigators decide that they should be destroyed. No matter what you decide to do, it will not affect your care in this study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

(This section must be completed by institution)

For information about your screening or participation, and research-related injury, you may contact:

_____ _____
Name Telephone Number

For information about this study, you may contact:

_____ _____
Name Telephone Number

For information about your rights as a research participant, you may contact:
(OHRP suggests that this person not be the investigator or anyone else directly involved with the research)

_____ _____
Name Telephone Number

YOU CAN PARTICPATE IN THE SCREENING PORTION OF THE STUDY WITHOUT PROVIDING TISSUE, BLOOD AND URINE SPECIMENS.

I have read (or someone has read to me) the information provided above. I have been given an opportunity to ask questions and all of my questions have been answered to my satisfaction. I have been given a copy of this form as well as a copy of the Subject's Bill of Rights. **By signing this form, I willingly agree to participate in the research it describes.**

_____ _____
Signature of Subject Date

_____
Name of Subject

INFORMATION ABOUT MY SPECIMENS

Below, you are asked to let us know if you would like to receive information about the results of this study. Please indicate by checking and initialing the category below what type of information you want to receive. It is your responsibility to let the investigator know if your address and/or telephone number changes. The contact information is in this informed consent form under "Identification of Investigators."

☐ I want to be given general information about what the study found.

☐ **I DO NOT WANT ANY INFORMATION ABOUT WHAT THE STUDY FOUND.**

OTHER RESEARCH QUESTIONS REGARDING MY SPECIMENS

1. My specimens may be kept for use in research to learn about, prevent or treat cancer.
   ☐ **YES** ☐ **NO**

2. My specimens may be kept for use in research to learn about, prevent or treat other health problems (for example: chronic lung disease, Alzheimer's disease or heart disease).
   ☐ **YES** ☐ **NO**

3. Someone from ACRIN or this institution may contact me in the future to ask me to take part in more research.
   ☐ **YES** ☐ **NO**

_____ _____

Signature of Participant **Date**

SIGNATURE OF INVESTIGATOR or RESEARCH ASSOCIATE

I have explained the research to the subject or his/her legal representative and answered all of his/her questions. I believe that he/she understands the information described in this document and freely consents to participate.

_____ _____

Signature of Investigator/ Research Associate Date

_____

Name of Investigator/ Research Associate

Appendix IV

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

ACRIN 6654

National Lung Screening Trial

(Remnant Tissue Collection)

Lay Title: Contemporary Screening for the Detection of Lung Cancer:
A Study to Collect and Store Leftover Tissue Specimens to Help Establish New Methods for Detecting Lung Cancer Early

Title of Study: Contemporary Screening for the Detection of Lung Cancer
(Remnant Tissue Collection)

WHY IS THIS STUDY BEING DONE?

You are going to have a biopsy (or surgery) to see if you have cancer. Your doctor will remove some body tissue to do tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the tissue that is left over for future research. If you agree, this tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How is Tissue Used for Research" to learn more about tissue research. The samples will be given only to researchers approved by the American College or Radiology (ACRIN) and the National Cancer Institute (NCI). Any research using these samples must also be approved by a research or interval review board (IRB).

Your tissue may be helpful for research whether you do or do not have cancer. The research that may be done with your tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Participants in clinical trials include only those who choose to take part. Please take you time making your decisions. We encourage you to discuss your decision with your doctor, family, and friends.

WHAT ARE THE RISKS OF THE STUDY?

The greatest risk to you is the unintended release of information from your health records. The NLST investigators will protect your records so that your name, address, phone number, and any other identifying information will be kept private. The chance that this information will be given to someone else is very small.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

Participation in this part of the study will not provide direct benefit to you. Reports about research done with your tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your health care. However, the benefits of research using your tissue and that of others in this trial include learning more about what causes lung cancer and other diseases, how to prevent them, and how to treat them.

WHAT ARE THE ALTERNATIVES TO PARTICIPATION?

You may decide not to have your tissue kept for future research. You can still participate in the screening part of the trial and yet decline to have left over tissue stored.

WHAT ARE MY RIGHTS AS A PARTICIPANT?

The choice to let us keep the left over tissue for future research is up to you. **No matter what you decide to do, it will not affect your care.**

If you decide now that your tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any tissue that remains will no longer be used for research.

WHAT ABOUT CONFIDENTIALITY?

In the future, people who do research may need to know more about your health. While the NLST investigators may give them reports about your health, they will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue is used for genetic research (research about diseases that are passed on in families). Even if your tissue is used for this kind of research, the results will not be put in your health records.

Your tissue will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.

MAKING YOUR CHOICE

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No." **No matter what you decide to do, it will not affect your care.** If you have any questions, please talk to your doctor or nurse, or call our research review board at (*IRB's phone number*).

1. My specimens may be kept for use in future research to learn about, prevent or treat cancer.
   ☐ **YES** ☐ **NO**

2. My specimens may be kept for use in research to learn about other health problems (for example: chronic lung disease or heart disease).
   ☐ **YES** ☐ **NO**

3. Someone from ACRIN or this institution may contact me in the future to ask me to take part in more research.
   ☐ **YES** ☐ **NO**

_____ _____

Signature of Participant Date

_____ _____

Signature of Investigator/ Research Associate Date

_____

Name of Investigator/ Research Associate

APPENDIX V

AMERICAN COLLEGE OF RADIOLOGY IMAGING NETWORK

NATIONAL LUNG SCREENING TRIAL

HOW IS TISSUE USED FOR RESEARCH?

Where does the tissue come from?

Whenever a biopsy (or surgery) is performed, the tissue that is removed is examined under the microscope by a trained doctor to determine the nature of the disease and assist with the diagnosis. Your tissue will always be used first to help make decisions about your care. After all tests have been done, there is usually some left-over tissue. Sometimes, this tissue is not kept because it is not needed for the patient's care. Instead, a patient can choose to have the tissue kept for future research. People who are trained to handle tissue and protect the donor's rights make sure that the highest standards are followed by the institution responsible for storing the tissue (Colorado Lung SPORE Tissue Bank). Your doctor usually does not work for the Colorado Lung SPORE Tissue Bank, but has agreed to help collect tissue from many patients. Many doctors across the country are helping in the same way. If you agree, only left-over tissue will be saved for research. Furthermore, at the time of your surgery or biopsy, your doctor will only remove the tissue needed for your care.

The Colorado Lung SPORE Tissue Bank stores your tissue with a special identification number, but the Tissue Bank does not know your name or have access to any information about you. All of your personal information is kept confidentially by the ACRIN investigators.

Why do people do research with tissue?

Research with tissue can help to find out more about what causes cancer, how to prevent it, and how to treat it. Research using tissue can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's disease.

What type of research will be done with my tissue?

Many different kinds of studies use tissue. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs.

Some research looks at diseases that are passed on in families (called genetic research). Research done with your tissue may look for genetic causes and signs of disease.

How do researchers get the tissue?

Researchers from universities, hospitals, and other health organizations conduct research using tissue. They contact the ACRIN-NLST researchers and the NCI and request samples for their studies. ACRIN and the NLST review the way that these studies will be done, and decide if any of the samples can be used. If the request for tissue is approved, ACRIN will have the Colorado Lung SPORE Tissue Bank send the tissue samples and will also provide some information about you to the researcher. The ACRIN investigators and the Colorado Lung SPORE Tissue Bank will not send your name, address, phone number, social security number, or any other identifying information to the researcher.

Will I find out the results of the research using my tissue?

No, you will not receive the results of research done with your tissue. This is because research can take a long time and must use tissue samples from many people before results are known. Results from research using your tissue may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Though research involves the test results of many different people, your biopsy result involves only you. Your doctor will give you the results of your biopsy when results are known. These test results are ready in a short time and will be used to make decisions about your care.

Will I benefit from the research using my tissue?

There will be no direct benefit to you because your tissue may not be used for some time after you donate it and because research can take a long time. However, it is hoped that the results of research on your tissue and tissues from other patients will provide information that will help other patients in the future. Your tissue will be helpful whether you have cancer or not.

Why do you need information from my health records?

In order to do research with your tissue, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher includes your age, sex, race, diagnosis, treatments, and possibly some family history. This information is collected by your hospital from your health record and sent to the Colorado Lung SPORE Tissue Bank but without your name or other identifying information. If more information is needed, the Colorado Lung SPORE Tissue Bank may send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number, and anything else that could identify you will be removed before they go to the researcher.

How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members. For diseases caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

The Colorado Lung SPORE Tissue Bank is in charge of making sure that information about you is kept private. The Colorado Lung SPORE Tissue Bank will take careful steps to prevent misuse of records. Your name, address, phone number and other identifying information will be taken off anything associated with your tissue before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person, which will help to protect your privacy.

Appendix VI

Sample Cover Letter

Dear _____,

Thank you for your continued participation in the ACRIN-NLST trial on lung cancer screening. This trial and the information that you provide us as a participant will be very important in determining future health care policy on lung cancer.

When you were first enrolled in the study, we indicated that we would periodically send you brief questionnaires about your overall health and feelings. Two questionnaires are enclosed for you to complete. In addition, we have enclosed a stamped, self-addressed envelope for you to mail back the questionnaires.

It is very important that you complete all of the questions on these questionnaires. We estimate that it may take 10-20 minutes of your time to complete these questions. Please return these forms as soon as possible in the envelope provided.

Please feel free to contact me if you have any questions or if you need help answering the questions. I can be reached at the following telephone number:

_____.

Again, thank you for your time. Your participation in this trial is very important to us, and we appreciate your efforts in answering these important questions.

Sincerely,

_____
RA by name

Institution # _____ **APPENDIX VII**

ACRIN 6654 **ELIGIBILITY CHECK**

Case # _____ ***(page 1 of 2)***

_____(Y) 1. Individual is between the ages of 55-74 years and 364 days.

_____(Y) 2. Individual has a current or previous cumulative cigarette smoking history of ≥ 30 pack years.

_____(NA or Y) 3. If a former smoker, individual has ceased smoking within the previous 15 years.

_____(Y) 4. Individual has no medical or psychiatric condition precluding informed consent.

_____(Y) 5. Individual is able to lie on his/her back with arms raised above his/her head.

_____(Y) 6. Individual has no metallic implants or devices in the chest or back (*pacemakers or Harrington fixation rods, etc.).*

_____(Y) 7. Individual has no prior diagnosis of lung cancer.

_____(Y) 8. Individual has had no treatment for, or advisement by a physician of evidence of *any* cancer within the past five years, with the exceptions of non-melanoma skin cancer and most in-situ carcinomas. (Treatment for, or evidence of, melanoma or in-situ bladder/transition cell carcinomas within the preceding five years renders the potential participant ineligible.)

_____(Y) 9. Individual has no prior removal of any portion of the lung, excluding percutaneous lung biopsy.

_____(Y) 10. Individual does not require home oxygen supplementation.

_____(Y) 11. Individual is not currently enrolled in another cancer screening trial *(PLCO, ELCAP)*.

_____(Y) 12. Individual is not currently enrolled in another cancer prevention trial other than smoking cessation programs.

_____(Y) 13. Individual does not have present symptoms suggestive of lung cancer, including unexplained weight loss of over 15 lbs within the past 12 months, or unexplained hemoptysis.

_____(Y) 14. Individual has no medical conditions that pose a significant risk of mortality during the trial period.

_____(Y) 15. Individual has *not* had a chest CT within the preceding 18 months of study enrollment. *(Individual will be eligible 18 months from the time of the CT)*.

_____(Y) 16. Individual is *not* within 12 weeks of a pneumonia or acute respiratory infection treated with antibiotics by a physician.

_____(Y) 17. Individual is *not* within 6 months of receipt of cytotoxic agents for any condition.

_____(Y) 18. A study-specific informed consent has been signed prior to registration.

The following questions will be asked at Study Registration:

_____ 1. Name of institutional person registering this case?

_____(Y) 2. Has the Eligibility Checklist been completed?

_____(Y) 3. Is the participant eligible for this study?

_____ 4. Date the study-specific Consent Form was signed? *(must be prior to study entry)*

Institution # _____ **APPENDIX VII**

ACRIN 6654 **ELIGIBILITY CHECK**

Case # _____ ***(page 2 of 2)***

_____	5.	Participant's Initials
_____	6.	Verifying Physician (*Site PI*)
_____	7.	Participant's ID Number
_____	8.	Date of Birth (*mm-dd-yyyy*)
_____	9.	Ethnic Category
_____	10.	Race
_____ (M/F)	11.	Gender
_____	12.	Participant's Country of Residence
_____	13.	Zip Code
_____	14.	Participant's Insurance Status
_____ (N/Y)	15.	Will any component of the participant's care be given at a military or VA facility?
_____	16.	Calendar case date (dd-mm-yyyy)
_____	17.	Randomization date (dd-mm-yyyy)
_____	18.	Other Country of Residence
_____	19.	Participant's Age Group (55-59) (60-64) (65-69) (70-74)
_____ (N/Y)	20.	Has the participant signed consent to have his/her tissue kept for use to learn about, prevent or treat cancer?
_____ (N/Y)	21.	Has the participant signed consent to have his/her tissue kept for use to learn about, prevent or treat other health problems?
_____ (N/Y)	22.	Did participant come to the study from the 1-800-4-CANCER hotline?
_____	23.	What recruitment methods prompted the participant to contact the study site?
_____ (Y)	24.	The participant has signed an annual Medical Record Release Authorization?
_____ (N/Y)	25.	Has the participant signed consent to have his/her blood, urine, sputum specimens kept for use to learn about/prevent/treat cancer?
_____ (N/Y)	26.	Has the participant signed consent to have his/her blood, urine, sputum specimens kept for use to learn about/prevent/treat other health problems?
_____ (N/Y)	27.	Has the participant signed consent to allow someone from NLST to contact him/her in the future to ask them to take part in more research?

Appendix VIII: Screening Results Withheld Statement
ACRIN NLST 6654

As a participant in the National Lung Screening Trial (NLST), I am writing to request that my health care provider not be notified of the results of any screening examinations I receive while participating in this study. I realize that I am responsible for contacting my health care provider in the event that I receive an abnormal screening examination and that the [*Insert Site Name*] will not notify my health care provider of such a result. I also realize that the [Insert Site Name] will not function as a primary healthcare provider on my behalf and does not have any responsibility regarding my care beyond providing me with the results of my screening examinations.

If, at any time during the study, I decide that I would like for my health care provider to begin receiving the results of my NLST screening examinations, I realize that I must contact the [*Insert Site Name*] *in writing* to request this change. The contact information for the NLST site is:

Site Name
Site Address
City, State, Zip

If I have any questions regarding my screening examination results or any other aspect of the NLST, I can contact [*Insert Study Coordinator Name*] at [*Insert Site Telephone Number*].

_____

Signature of Participant

_____

Printed Name of Participant

_____

Date

APPENDIX IX

Addendum to the National Lung Screening Trial sponsored by the NCI in cooperation with the PLCO and ACRIN

In an effort to maximize early and sustained accrual to the National Cooperative Trials assessing the early detection of lung cancer, the American Cancer Society (ACS) will initiate a major educational campaign designed to increase study awareness and increase participation. Multimedia informational advertising will be supplemented through telephone contact with health educators delivering eligibility information and offering information regarding local tobacco cessation programs for which the callers might be eligible.

General educational media announcements will address the reason for the study, eligibility requirements, and contact information for those interested in pursuing participation in the study. Individuals calling the National Cancer Information Center (NCIC) of the ACS will be asked to voluntarily supply a minimal amount of information which will be kept confidential and only used for these study purposes as part of the effort to evaluate the impact of various methods of advertising as part of the quality improvement process. The information solicited will include the following:

Name
Current Address
Age
Smoking History
History of previous cancer (non-melanoma skin cancer excluded) within 5 years
Ethnicity
Highest Level of Education Attained
Source of Information Leading to this Phone Inquiry

The callers will be provided with information about the study, their potential eligibility, and contact phone numbers providing access to investigators proximate to the caller. The actual determination of eligibility and the consummation of the consent process will be conducted by the investigators conducting the study.

The primary purpose of this multimedia educational effort will be to accelerate and sustain study accrual in an effort to complete the study in a timely fashion. Data related to demographic information, potential study eligibility and the source of the information leading to the initial call, would be descriptively analyzed using standard techniques. This information will be used to informal subsequent educational advertising efforts.