ACRIN Protocol 6654

SUMMARY OF CHANGES

Cover Page
"Including Amendment #1-9" has been changed to "Including Amendments #1 - 10."

Index, Page 2
"Appendix VII Protocol Specific Application" and "Appendix XI NLST Regulatory Binder Contents" have been deleted from the table of content. The following items and page numbers have been renumbered accordingly.

8.1 Data Collection Form, Page 25
In item #13, the F1 form description, "F2" has been added and the now reads:

"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."

"MX: Medical Cost Form" has been deleted. The following items have been renumbered accordingly.

9.1.2, Page 27
The address for data submission has been updated. The change of address for ACRIN headquarters to "1818 Market Street, Suite 1600, Philadelphia, PA. 19103**".**

16.3, Page 38
The following paragraph has been added after the last bullet in this section and reads:
"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."

18.0 Adverse Event Reporting, Page 46
The adverse event reporting section has been extensively revised and now reads:

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						
0. Drinking sputum preservative	*Home sputum kit, inadvertent swallowing*	*1*	*2*	*3*	___	___
0. Syncope	*Phlebotomy, spirometry*	___	___	*Present*	*Life threatening consequences*	*Death*
0. 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*
0. Hyperventilation	*Phlebotomy, Spirometry*	*Not interfering with function*	*Interfering with function, but no interfering with ADL*	*Interfering with ADL*	___	___
0. Bruising from needles	*Phlebotomy*	*Localized or in a small, dependent area*	*Generalized*	___	___	___
0. Bronchospasm, Wheezing	*Spirometry*	*Asymptomatic*	*Symptomatic, not interfering with function*	*Symptomatic, interfering with function*	*Life-threatening*	*Death*
0. Vasovagal reaction	*Phlebotomy*	___	*Present without loss of consciousness*	*Present with loss of consciousness*	*Life-threatening consequences*	*Death*
0. Cardiopulmonary arrest (non-fatal)	*Spirometry*	___	___	___	*Life-threatening*	___
0. 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.*

17.5.0 *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:*

0. *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).*

0. *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.*

0. *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****.*

0. *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****.*

0. *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****	*0. Telephonic Report to NCI-CIP within 24 hours of first knowledge* *0. Expedited Report* *0. Routine Report*	*0. Telephonic Report to NCI-CIP within 24 hours of first knowledge* *0. Expedited Report* *0. 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.*

17.5.0 *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.*

17.5.0 *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.*

17.5.0 *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

17.7.0 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.

17.7.0 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.*

19.6 Source Documentation for Audit, Page 53

In the F1 form row, "F2" has been added and the row now reads:

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.

SUMMARY OF CHANGES

ACRIN 6654: *Contemporary Screening for the Detection of Lung Cancer*

March 14, 2003

Appendix XI: American Cancer Society Addendum

This appendix has been added. It is now also listed on the Index page.

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.

ACRIN 6654
CONTEMPORARY SCREENING FOR THE DETECTION OF LUNG CANCER

November 7, 2002

The changes for this protocol since 6-21-02 are written below in list and table form.

1. All specific forms were removed form the protocol, with the exception of the Eligibility checklist, which remains as Appendix VII.
2. Appendix IV, the Remnant Tissue Sample consent, previously included a statement that individuals must be able to withdraw their permission and have their samples destroyed. This has not been changed. It appears in the consent as follows:

    a. PARTICIPATION AND WITHDRAWAL:

    b. Your participation in this research is voluntary. If you choose not to participate, you may still participate in the screening portion of this study. In addition, if you choose not to participate, this will not affect your relationship with (*University or Institute*) or your right to health care or other services to which you are otherwise entitled. If you decide to participate, you are free to withdraw your consent and discontinue participation at any time without prejudice to your future care at (*University or Institute*).

    c. Your medical information and samples of your tissues and/or blood will be maintained in the computer database indefinitely. However, you can withdraw your consent and ask that all information and samples be destroyed at any time.

3. The exclusionary statement for other malignancies in the eligibility criteria has been standardized throughout the protocol and in the eligibility checklist. It is written as follows:

    a. 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.)

4. We have corrected our oversight in Table 5 of providing the numbers for a sample of 10,000 instead of 25,000. The numbers are now correct for 25,000 participants.

SECTION	PAGE	JUNE 21, 2002 PROTOCOL VERSION	PAGE	NOV. 7, 2002 PROTOCOL VERSION
	1	Version date was: June 21, 2002	1	Version date changed to: November 7, 2002
INDEX	2	**Page numbers changed as follows:** 7.0 Data Collection and Management 20 9.0 Image Submission 25 10.0 Experimental Procedures 26 11.0 Low dose Helical CT Techniques and Procedures 26 12.0 Categories of CT Screening Result and Recommended Diagnostic Pathways 28 13.0 Chest Radiographic Techniques and Procedures 30 14.0 Categories of Chest Radiographic Screening Result and Subsequent Diagnostic Pathways 31 15.0 Definitive Management of Participants with Suspected Lung Cancer 32 16.0 Screening Results Communication and Procedures for Participant Follow-up 33 17.0 Image Quality and Image Interpretation Quality Control Measures 37 18.0 Determination of Secondary Outcomes: Quality of Life 40 19.0 Determination of Secondary Outcomes: Health and Medical Resource Utilization 44 20.0 Cost-Effectiveness Assessment 45 21.0 Statistical Considerations 46 22.0 Sample Size Considerations 49 23.0 Correlative Study: Biomolecular Marker Bank and Discovery Network 51 References 53	2	**Page numbers changed as follows:** 7.0 Data Collection and Management 21 9.0 Image Submission 26 10.0 Experimental Procedures 27 11.0 Low dose Helical CT Techniques and Procedures 27 12.0 Categories of CT Screening Result and Recommended Diagnostic Pathways 29 13.0 Chest Radiographic Techniques and Procedures 31 14.0 Categories of Chest Radiographic Screening Result and Subsequent Diagnostic Pathways 32 15.0 Definitive Management of Participants with Suspected Lung Cancer 33 16.0 Screening Results Communication and Procedures for Participant Follow-up 34 17.0 Image Quality and Image Interpretation Quality Control Measures 39 18.0 Determination of Secondary Outcomes: Quality of Life 43 19.0 Determination of Secondary Outcomes: Health and Medical Resource Utilization 46 20.0 Cost-Effectiveness Assessment 47 21.0 Statistical Considerations 48 22.0 Sample Size Considerations 51 23.0 Correlative Study: Biomolecular Marker Specimen/ Tissue Bank and Discovery Network 54 References 56
INDEX	2	Appendix I Sample Consent Form 59	2	Appendix I Sample Consent Form/Biomarker
INDEX	2	**See Added Appendices**	2	**Added the following Appendices:** Appendix II Sample Consent Form/Non-Biomarker 68 Appendix III Sample Consent Form/Tissue, Blood, Urine 74 Appendix IV Sample Consent Form Remnant Tissue 78 Appendix V Information Guide: How is Tissue Used for Research? 80
INDEX	2	**Appendix numbering and page numbers change** Appendix II Sample Cover Letter 68 Appendix III Protocol Specific Application 69 Appendix IV Eligibility Checklist 70 Appendix V Biomarker Procedures 72	2	**Appendix numbering and page numbers change** Appendix VI Sample Cover Letter 84 Appendix VII Protocol Specific Application 85 Appendix VIII Eligibility Checklist 86 Appendix IX Biomarker Procedures 88
INDEX	2	**See Added Appendix**		**Added** Appendix X Remnant Tissue Banking 95

SECTION	PAGE	JUNE 21, 2002 PROTOCOL VERSION	PAGE	NOV. 7, 2002 PROTOCOL VERSION
Sites	3	**Active Sites Group 1** UCLA School of Medicine Dartmouth-Hitchcock Medical Center Beth Israel Deaconness Medical Center Brigham & Women's Hospital Harvard Medical School Mayo Clinic Brown University MD Anderson Cancer Center Wake Forest University Moffitt Cancer Center; University of South Florida University of Michigan	3	**Active Sites Group 1: Numbers have been added** 1. UCLA School of Medicine 2. Dartmouth-Hitchcock Medical Center 3. Beth Israel Deaconness Medical Center 4. Brigham & Women's Hospital Harvard Medical School 5. Mayo Clinic 6. Brown University 7. MD Anderson Cancer Center 8. Wake Forest University 9. Moffitt Cancer Center; University of South Florida 10. University of Michigan
Sites	3	**Added Sites Group 2 have been added**	3	**Added Sites Group 2 have been added as shown below in the table:**

ADDED SITES GROUP 2		
11. Johns Hopkins University School of Medicine	Elliot Fishman, MD	efishman@jhmi.edu
12. Jewish Hospital Heart and Lung Institute	Robert Falk, MD	robert.faulk@jhhs.org
13. Emory University	Kay Vydareny, MD	kvdare@emory.edu
14. University of Pennsylvania	Warren Gefter, MD	gefter@oasis.rad.upenn.edu
15. Ochsner Clinic Foundation	Michael Sullivan, MD	msullivan@oschner.org
16. University of Iowa	Geoffrey McLennan, MD	geoffery_mcLennan@uiowa.edu
17. Medical University of South Carolina	James Ravenel, MD	ravenjg@musc.edu
18. Vanderbilt University	John Worrell, MD	john.worrell@vanderbilt.edu
19. University of California, San Francisco		
ALTERNATE SITES		
Northwestern University	Eric Hart, MD	ehart@radiology.northwestern.edu
Duke University	Edward N. Patz, MD Phillip Goodman, MD	patz0002@mc.duke.edu goodm008@mc.duke.edu

SECTION	PAGE	JUNE 21, 2002 PROTOCOL VERSION	PAGE	NOV. 7, 2002 PROTOCOL VERSION
Schema	4	**Schema has been modified to reflect the designation of sites as:** ▪ **Group 1 = sites that will collect biomarker specimens and perform quality of life (QoL) studies** ▪ **Group 2 = sites that will not collect biomarker specimens or perform QOL studies** **Changes include:** **Box 1** High Risk Individuals **Box 2** Health Status/Health Habit, QOL Instruments, etc. Experimental Arm Control Arm	4	**Box 1** ALL Sites: High Risk Individuals **Box 2** Health Status/Health Habits Quality of Life Questionnaires [Group I Sites only] EXPERIMENTAL Arm I CONTROL Arm 2
		Spirometry Baseline Samples of Blood, Sputum, Urine Baseline Low-Dose Helical CT	→	Spirometry Baseline Low-Dose Helical CT **(Added separately as sub-boxes to both Experimental and Control Arms)** [Group 1 Sites Only] Baseline Samples of Blood, Sputum, Urine
		ANNUAL incidence screens x 2 Low dose helical CT (or PA chest radiograph) Samples of blood, sputum, urine (Baseline, Yrs, 1,2) Questionnaires: Interval Health, QOL, etc.	→	ANNUAL incidence screens x 2 Low dose helical CT (or PA chest radiograph) Questionnaires: Interval Health Group 1 Sites only] Samples blood, urine, sputum (Yrs 1,2) QOL Questionnaires
		q6 months: Interval health status QOL instruments	→	q6 months: Interval health status x 6-8 Yrs
Schema	4	*QOL instruments will be complete by subsets of participants in both Arms (See Section 18.)	4	Deleted
Eligibility	4	- No treatment for cancer and having been told by a doctor that there is evidence of cancer within the preceding five years, (excluding non-melanoma skin cancers)	4	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.)

Eligibility	4	No prior removal or any portion of the lung, excluding lung biopsy	4	……excluding percutaneous lung biopsy
Eligibility	4	No present symptoms suggestive of current lung cancer, including: unexplained weight loss of over 15 pounds within the past 12 months or hemoptysis	4	No present symptoms suggestive of current lung cancer, including: unexplained weight loss of over 15 pounds within the past 12 months or unexplained hemoptysis
Eligibility	4	**The order of the following criteria has been changed to parallel those in Section 4.0. In addition, typographical errors have been corrected.** - No chest CT scan within the preceding 18 months *(These individuals would be eligible 18 months after chest CT).* - 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).*	4	- 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.)*
Sample Size	4	10,000	4	25,000
Abstract	5	The abstract was modified to reflect differences in experimental methods occasioned by the addition of new sites, some of which will not be collecting specimens for biomarkers, completing quality of life instruments, or assessing the impact of screening on smoking behaviors. The following text was deleted:	5	The following revisions were made to the abstract:

June 21, 2002		Previous large screening trials using combinations of chest radiographs and sputum cytology showed no significant improvement in lung cancer-specific or all-cause mortality among screened high-risk cohorts. However, contemporary computed tomography *(CT)* offers the potential to detect lung cancers at early stages amenable to surgical cure. This project involves using a multicenter, randomized controlled trial of 10,000 individuals at high risk of developing lung cancer to see whether screening with low-dose helical CT can reduce lung cancer-specific mortality relative to chest radiographs. A secondary objective is to create a bank of specimens from well-characterized high-risk cohorts that can be used to test future potential biomolecular markers of lung cancer…… Prior to randomization, standardized eligibility, health, sociodemographic, and quality of life questionnaires as well as spirometry will be performed. Both Experimental and Control participants will provide blood, sputum and urine samples for archive at study entry and at the time of the second incidence screen. The Experimental group will undergo screening with low dose helical CT. The Control group will undergo screening with chest radiographs. Both groups will be screened annually for at least two incidence screens. Both groups will be contacted at six-month intervals to document interval health status and annually to complete quality of life questionnaires. Subgroups of both cohorts will complete questionnaires to determine the differential psychological impact of screening for lung cancer. Similarly, subgroups of Experimental and Control participants who have positive screening results will complete questionnaires to determine the psychological impact of positive screening tests, using as case-matched controls subgroups of Control and Experimental participants with negative screening results. The primary end-point of the trial is lung cancer-specific mortality. Intermediate end-points will include all-cause mortality; surgical stage at diagnosis; medical resource utilization; the impact of screening on quality of life and psychological effects; and the economic consequences of helical CT screening.		
August 8, 2002		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 approximately 20 sites across the nation and will enroll 25, 000 individuals at high risk of developing lung cancer…….. 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.		
Backgro und	14	**Paragraph 3:** ▪ The cohorts in this study….. ▪ All participants.. **Paragraph 4: (words deleted)** ….evaluated at the same time.	15	**Paragraph 3:** ▪ The cohorts in this study participating in biomarker collection ▪ Participants **Paragraph 4:** evaluated.
Specific Aims	16	**Added an additional Secondary Aim**	17	3.2.7 To assess the impact of screening on smoking behaviors
2.3		**Changed a reference number from 30b**		28, 29, 29b
2.3		**Change a reference number from 30b**		29b
4.1.1	16	**1st paragraph, second to last sentence:** ….with the principal investigators of the NLST.	17	….with the principal investigators of the NLST or other representatives.
4.1.1	16	**Word deleted:** **2nd paragraph, 1st sentence**: ….protocol specific for the NLST trial.	17	….protocol specific for the NLST.
4.1.1	16	**2nd paragraphs: Revisions and additions to eligibility criteria as follows:**	17	**Revisions and additions as follows** ▪ No treatment for, or advisement by a

		▪ Not currently in treatment for any cancer (except basal cell carcinoma of skin)		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 chest CT within the prior 18 months
4.1.1	16	**Deleted word: 4th paragraph**: Printed material, including a brochure describing the NLST trial	17	Printed material, including a brochure describing the NLST
4.1.5.4	17	**The entire paragraph is rewritten completely, since the E1 Form in its entirety is not made available in web version. Only certain questions from the E1 form are allowed to be made available in web-based version for self-administration.**	18	Some sites may elect to allow potential participants to complete portions of the E1 Form by mail or from a web site. 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 all remaining eligibility questions, and advise individuals of their eligibility status.
4.3.4	18	Treatment for cancer or having been told by a doctor that there is evidence for cancer within the past five years (excluding non melanoma skin cancers).	19	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.)
4.4	18	**Correction of various punctuation errors**	**19**	**Corrected punctuation errors**
5.1.2	18	**Added reference to chest radiographic equipment:** ….including specification of CT scanners to be used…… (*See Appendix III*).	19	….including specification of CT scanners and chest radiographic machines to be used …(*see Appendix VI*).
6.1.1.1	18	**Typo:** Explanation of the study intention and design	20	Explanation of the study intention and design.
6.1.1.2	18	**Typo:** (See Medical Record Release Authorization)	20	(see Medical Record Release Authorization)
6.1.1.2	18	**A clause has been deleted and replaced by a new sentence as follows:** … to determine medical outcomes, as well as consent to collect and bank specimens of blood, sputum, and urine (*specimen consent is not mandatory for participation in the ACRIN-NLST trial*) will be reviewed.	20	…to determine medical outcomes. In addition, consent to collect and bank blood, sputum, and urine specimens (amongst biomarker specimen participants) 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 NLST*).
6.1.1.2		**A description of revised consents is added**	**20**	**Added are the various consents and the participants to whom they will be administered as follows below:**

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]

SECTION	PAGE	JUNE 21, 2002 PROTOCOL VERSION	PAGE	NOV. 7, 2002 PROTOCOL VERSION
6.1.1.4	19	Quality of Life Instruments:	20	**Addition:** Quality of Life Instruments [Group I Participants only]:
6.1.1.6	19	Collection of Specimens for Banking:	21	**Addition:** Collection of Specimens for Banking [Group I Participants only]:
6.1.1.6	19	**The Colorado SPORE name has been revised through-out the protocol** Colorado SPORE ; the Colorado Biorepository	21	Colorado Lung SPORE Tissue Bank ; the Colorado Lung SPORE Tissue Bank
8.1	22	**1st paragraph, a sentence has been added.**	23	**The last sentence of 1st paragraph has been added:** All forms are completed at all sites unless otherwise specified
8.1	22	**As regards the data collection forms section: Punctuation has been standardized, typographical errors have been corrected, and descriptions have been revised as follows:** 1) E1 Pre-Registration Eligibility Form: The form is complete prior to informed consent and enrollment and determine eligibility for the ACRIN-NLST trial. 2) A0 Eligibility/Registration Form **Deleted**: This form is the online registration form. 4) DP: Demographic/Health Status/Health Habit/Symptom/Alcohol Assessment Form: 5) SS: Smoking Status/Assessment Form 6) MRRA: Medical Records Release/ Authorization Form 7) CS Cover Sheet Form 8) QP (Baseline SF-36v2™ and EQ Euroquol (EQ-5D) Form	24	**Corrections are as follows:** 1) E1: Pre-Registration Eligibility Form: The form is complete prior to informed consent and enrollment and determine eligibility for the ACRIN-NLST. 2) A0: Eligibility/Registration Form 4) DP: Demographic/Health Status/Health Habit/Symptom Form 5) SS: Smoking Status Form 6) MRRA: Medical Records Release Authorization 7) CS: Quality of Life Cover Sheet Form [Participants of Group 1 sites only] 8) QP: (Baseline SF-36v2™ and EQ Euroquol (EQ-5D) Form [Participants of Group 1 sites

		9) QL: Annual Screen SF-36v2™ and EQ-5D Form 10) QF (Screening SF-36v2™, EQ-5D, and STAI Y-1) Form ….. correct typo: --corrected typo: (Arm 1 and 2) 11) PQ Patient Questionnaire Form 12) PA Pulmonary Function Test Form 13) C2 CT Imaging Form 14) DR Chest Radiographic Screening Form 15) I8 Form: This form is completed by the radiologist if historical images become available for review within three weeks of obtaining a trial screening exam (CT or CXR) in which potential abnormalities are detected 16) C3 Follow-up Form 17) BL Blood/Urine Collection Form 18) PC Specimen Packing Form: This form is used to document shipping and receipt of processed blood and urine specimens to the Colorado Specimen Bank (CSB) for those participants who consent to biomarker collection. The form is completed by the RA and the CSB and submitted via mail/fax to ACRIN headquarters by the RA at the time of mailing samples and be the CSB at the time of receipt of samples. 19) ST Sputum Transmittal Form. ….Colorado Specimen Bank is renamed. ….envelope to the Colorado Specimen Bank. Upon arrival at the Colorado Specimen Bank 20) F1 Follow-up ….both Arms I and II 21) DE Form …in both Arms I and II 22) TF Treatment Form This form is completed by as part of the …. 23) MX Medical Costs Form 24) EX Economic Costs Form 25) QC Form 26) LX Summary Recruitment Form This form is completed by the site and faxed twice monthly to ACRIN headquarters (215-		(EQ-5D) Form [Participants of Group 1 sites only]: The following sentence is deleted from the description: A subset of participants will complete this at each annual and follow-up visit, according to the methods for the sub-studies for quality of life (See Section X). 9) QL: Annual Health Status Questionnaire (SF-36v2™ and EQ-5D) [Participants of Group 1 sites only]: …..(see Section X). 10) QF: Health Status/Anxiety Questionnaire (Screening SF-36v2™, EQ-5D, and STAI Y-1) [Participants of Group 1 sites only] corrected typo: (Arms 1 and 2) 11) PQ: Participant Impact Questionnaire [Participants of Group 1 sites only] 12) PA: Pulmonary Function Test Form 13) C2: Screening CT Form 14) DR: Screening Chest Radiograph Form 15) I8: Historical Images –CXR Arm Form: This form is completed by the radiologist at Baseline, Year 2 and Year 3 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. 17) C3: Follow-up Diagnostic CT Form 18) BL: Blood/Urine Collection Form [Participants of Group 1 sites only]: 19) 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. 20) ST: Sputum Transmittal Form [Participants of Group 1 sites only]: …Colorado Lung SPORE Tissue Bank (CTB). ….envelope to the CTB. Upon arrival at the CTB….. 21) F1: Interval Follow-up …both Arms 1 and 2 22) DE: Diagnostic Evaluation and Staging Form …in both Arms 1 and 2 23) TF: Treatment Form This form is completed as part of the …. 24) MX: Medical Costs Form 25) EX: Economic Costs Form 26) QC: Image Quality Form 27) LX: Summary Recruitment Form: This form is completed by the site and records recruitment procedures, outcomes, and the

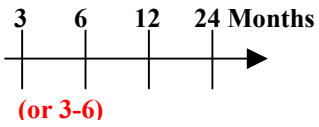
		717-0936, Attn: Irene Mahon). The form records recruitment strategies, including numbers of eligible, ineligible, and randomized individuals. The form is submitted via fax.		demographics of participants for purposes of tracking effective recruitment strategies, including numbers of eligible, ineligible, and randomized individuals. The form is submitted twice per month. Alternatively, an Enrollment Log database has been developed on a central server that enables sites to log each caller (recorded by site-specific code) in real-time. Queries to this log can generate summary recruitment data for each site without the need to submit the LX Form.
8.1	23	**I9 Form added**	25	**I9: Historical Images-CT Arm Form:** This form is completed by the radiologist at Baseline, Year 2 and Year 3 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.
8.1	24	**IM Form added**	26	**28 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.
10.0	26	**Table of Experimental Procedures is revised to reflect that only Group 1 participants will complete collection of specimens and QOL instruments:** ▪ Collect blood, sputum, and urine samples ▪ QOL Instruments: SF-36v2, EuroQoL-5D	28	**See Revisions** ▪ Participants in Group 1 only Collect blood, sputum, and urine samples ▪ Participants in Group 1 only QOL Instruments: SF-36v2, EuroQoL-5D
10.0	26	**Legend of table corrected:** …from the Experimental and Control arms of Group 1 sites	28	…from the Experimental and Control Arms of Group 1 sites
11.0	26	▪ **Revise sentences:** **Line 1:** …baseline and annually thereafter ▪ **Line 5**: ….. nodule size at the level	28	▪ ..baseline and annually in Years 2 and 3… ▪ .. nodule size and nodule attenuation
11.1	26	**Revised CT Acquisition Parameters** ▪ Because there is moderate variation in image quality across scanner platforms, the following ranges in technical parameters will be followed. Radiation exposures will be as low as possible in keeping with good image quality. The following technical parameters will be followed: ▪ mAs = 40-80	28	▪ 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: ▪ mAs = 40-100
11.2	27	▪ **Revised Line 1**: All CT studies will be evaluated by a study radiologist.	29	▪ All CT studies will be interpreted by a study radiologist according to the standards of practice at their institution

		▪ **Revised Line 2**: (width 1500 HU Level –650 HU) ▪ **Deleted line 2 sentence**: The review of soft tissue window (width 400 HU, level 40 HU) is not required). ▪ **Added a new line** ▪ **Added the requirement and basis for fixed sequential review of current then historical images** ▪ **Paragraph 2, line 3:** I8 Form changes		▪ (width 1500-1700 HU, level –500 to –700 HU) ▪ New Line: Measurements will be obtained at full view or with magnification. ▪ Added the following: 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 and study in context will be recorded. Although the isolated report is not truly representative of screening test performance, both of these data points will be important for modeling the benefit of screening under different conditions of time interval, etc. ▪ I9 Form
11.3	27	▪ **Abnormal nodule margin descriptions revised,** (spiculated, non-spiculated)	29	▪ (spiculated, smooth, poorly defined, other)
21.1	28	▪ **Line 3, added the word,** "recommendations"	30	▪ Management recommendations of the…
21.1	28	**Table of Screening Results corrected to better conform to the types of screening results reportable on the data forms and the types of letters sent to participants and their health care providers as follows:**	30	Negative screen now includes: ▪ Minor abnormalities, not suspicious for lung cancer Positive screen has been divided into two types of positive screening results, having different implications for diagnostic follow-up as follows:

From Revised Protocol 9/30/02:

Sept 30, 2002	Positive	▪ Nodule*(s)* 4 -10 mm diameter ▪ Enlarging nodules < 7 mm diameter ▪ Other suspicious change in nodule	▪ TSCT at intervals of 3, 6, (or 3-6), 12, 24 months from the date of the [+] screening CT
	Positive	▪ Nodule*(s)* >10 mm diameter ▪ Enlarging nodules > 7 mm diameter ▪ Etc…..	Additional diagnostic tests, which may include: ▪ Limited thin-section CT of nodule*(s)* at intervals of Baseline, 3, 6, (or 3-6), 12, 24 months ▪ Etc…..

SECTION	PAGE	JUNE 21, 2002 PROTOCOL VERSION	PAGE	NOV. 7, 2002 PROTOCOL VERSION
12.1.1	28	**Original version:** *Negative Screen, no significant abnormalities, benign nodules, or non-calcified micronodules < 4 mm:* Participants with no significant abnormalities, benign nodules, or non-calcified micronodules < 4	30	**Added** ..or minor abnormalities…. **and changed wording as follows:** *Negative Screen, no significant abnormalities, benign nodules, non-calcified micronodules < 4 mm, or minor abnormalities not suggestive of lung*

		mm on screening CT will continue with annual screening.		*cancer:* Participants with these screening results will continue with annual screening.
12.1.2	28	**Line 3**...physician according to standard practices.	30	…physician for follow-up according to standard..
12.1.3	28	▪ **Paragraph 1, Line 1**…Indeterminate Nodules: ▪ **Paragraph 2, Line 1**: For nodules classified as "indeterminate" by the above definitions, standard practice….. ▪ **Paragraph 2, Line 4**: 3, 6, 12, and 24 months ▪ **Paragraph 2, Line 6**: (…and without IV contrast,) ▪ **Paragraph 3, Line3**: growth to satisfy definitions of "abnormal" will be **….**	30	▪ **Line 1**: Indeterminate Nodules 4-10 mm diameter: ▪ **Line 1**: For nodules of 4-10 mm diameter, standard practice…. ▪ **Line 4**: 3, 6, (or 3-6), 12, and 24 months ▪ **Line 6**: (…and without IV contrast) ▪ **Paragraph 3, Line 3:** ..growth of > 7 mm
12.1.3	28	**Paragraph 3, Line 4:** Indeterminate Nodule Pathway	31	**Paragraph 1, Line 1**: Limited Thin-Section CT Pathway
Figure 3	29	▪ **Title revised**: Recommended Pathway for Indeterminate Nodule Seen on Screening CT ▪ **Annotation added to Repeat Limited Thin Section Nodule CT Graphing**…	31	▪ Recommended Pathway for Nodules of 4-10 mm Diameter on Screening CT ▪ 
12.1.4	29	▪ **Line 1:** Positive Screen: Abnormal Nodules(s) or Lung Mass ▪ **Line 1-2:** "abnormal" lung nodules or lung masses are detected ▪ **Revised schema as shown** **ABNORMAL NODULE** **Diagnostic CT for staging (with nodule contrast densitometry)**	31	▪ Positive Screen: Nodules(s) > 10 mm Diameter or Lung Mass ▪ Lung nodules > 10 mm diameter or masses are detected ▪ **Schema changes as shown:** **ABNORMAL NODULE > 10 mm** **Diagnostic CT for staging (± nodule contrast densitometry) and/or FDG-PET**
13.1	30	**Table of CXR parameters has been revised to reflect current imaging practice across the country as follows**: Screen:Film / CR / DR kV 120-140 / 110-120 / 110-140 SID 72 inches / 72 inches / 72 inches	32	**Revised table:** Screen:Film / CR / DR kV 120-150 / 110-140 / 110-150 SID ≥ 72 inches / ≥ 72 inches / ≥ 72 inches
13.1	30	**Table of CXR parameters:** **Line added regarding skin entrance exposures**	32	**Line added:** * Skin entrance exposure may exceed these guidelines in large individuals
13.2	31	**New paragraph added**	33	**Paragraph added to reflect the structured sequential reading format as follows:** 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 and study in context will be recorded. Although the isolated report is not truly representative of screening test performance, both of these data points will be important for modeling the benefit of screening under different conditions of time interval, etc.
14.0	31	**Table of recommended pathways for positive CXR screen has been expanded from:** Additional diagnostic tests, which may include: ▪ Immediate follow-up CXR with or without additional views ▪ Follow-up CXR with /without additional views in 3 months ▪ Other additional evaluation for findings possibly related to lung cancer	34	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-* ▪ 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
15.1	32	**Added a second paragraph**	35	**Added this paragraph:** 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	32	**Deleted underlined text and added text as follows:** Cytologic or histologic tissue samples obtained from participants in the course of these procedures may be banked…. in this study.		Cytologic or histologic tissue samples obtained from participants may be banked …in this study (see Section below).
16.1	33	**Modifications as follows:** ▪ **Line 5: …**will be offered ▪ **Line 6**: …of the participant ▪ **Line 9**: …by telephone or fax.	36	▪ **Line 3:** will have been offered ▪ **Line 4:** of the participant at the time of enrollment. ▪ **New sentence:** Under- or uninsured participants will be offered information on potential sources of financial assistance and access to health care services ▪ **Line 8:** by mail or fax, and telephone where appropriate.

16.2	33	**Contents of Participant Letters have been revised to include one new bullet and one revision:** ▪ A statement that the screening test result has been sent to his/her physician of choice;	36	▪ **Revised letter contents for participants:** ▪ 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.
16.3	33	**Contents of Physician Letters have been revised. The following bullet has been deleted and replaced.** ▪ A description of the diagnostic pathways recommended for the abnormal screening result of the participant, including the rationale for the diagnostic pathway, the tests to be performed, and the frequency of any recommended tests;	36	▪ 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*]."
16.3	33	**The following Bullet has been added to the physician letters**	36	▪ 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;
16.4	34	**A 6th bullet point has been added**	37	**Added to the bullets is:** ▪ Determine that under- or uninsured participants with positive screens receive referrals to facilitate access to health care services and financial assistance mechanisms.
Figure 5	36	**Figure 5: Probabilities for Chart Abstraction** **Participant numbers have been revised to reflect accrual numbers of 25,000 by ACRIN-NLST.**	38	**See Revised Figure 5: Probabilities for Chart Abstraction**
17.1.1	37	**Radiologists qualifications have been revised to include:**	40	**Bullet 1 addition** ▪ 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.
17.1.1	37	**Bullet 5 revision** Participation in continuing medical education …which requires 150 hours	40	**Bullet 5** ▪ Participation in continuing medical education …which recommends 150 hours
17.1.1	37	**Paragraph 2 wording revised** In addition to the above, all physicians serving as readers for the screening tests will undergo an initial training session … This training session will consist of screening data sets that demonstrate:		**Revision:** In addition to the above, all physicians serving as readers for the screening tests will review training set of images … This training set (available on CD) will consist of screening exams that demonstrate:
17.1.1	37	**Paragraph 3 minor word changes** **Line 1:** …training set will have been… **Line 2:** The image data will be reviewed…. **Line 3**: Added text **Line 3**: and (will) be available **Line 4:** Readers will interpret the images…		**Changes:** **Line 1:** ….training set was determined **Line 2:** the image data was reviewed **Line 3, added:** …training sessions including both ACRIN and LSS physicians **Line 3:** …and is available **Line 4:** Readers will review the…
17.1.2	37	**Paragraph 1bullet 1, line added**	41	**Added:** ▪ This requirement is waived in those states in which state licensure is not required.
17.1.2	37	**Qualifications of Radiologic Technologists have been modified:** ▪ Possess an unrestricted license in the appropriate state of practice. ▪ Be certified by the American Registry of Radiological Technologists *(ARRT)*		**Revisions:** ▪ 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).
17.1.2	37	**Qualifications of Radiologic Technologists: Punctuation and formatting corrected** • CT technologists must have documented.. • CT technologists must maintain compliance with ARRT requirement for CME of 24 credits per two (*2*) year period • Each technologist will have completed a training program and signed a written …	41	**Revisions:** • (CT technologists) Have documented training…. • Maintain compliance with ARRT requirement for CME of 24 credits per two (*2*) year period • Complete a training program and sign a written attestation….
17.1.2	37	**Deleted one bullet and merged with another:** • General technologists performing chest radiographs must maintain compliance with ARRT requirements for CME of 24 credits per two (*2*) year period		• Maintain compliance with ARRT requirement for CME of 24 credits per two (*2*) year period
17.1.3	38	**Revised CME statement** Participation in CME in accordance with the ACR		Participation in CME in accordance with the

		Standard, which requires 150 hours		ACR Standard, which recommends 150 hours
17.2.1	38	**Bullet #3: Added explanatory text:** ▪ Water phantom tests	41	▪ Water phantom tests for purposes of water calibration and field uniformity
17.2.1	38	**Revised Bullet #4** ▪ Subject dose as measured by a thermolucent dosimetry *(TLD)* strip placed on the mid-anterior chest on three clinical screening CT studies using the technical parameters defined in the NLST protocol. These will be read by a commercial vender to ensure that subject exposure conforms to that defined by the protocol.	41	**Revision:** ▪ Participant dose as measured by an appropriate dosimetry method, such as optical stimulated luminescence *(OSL)* dosimetry or thermolucent dosimetry (*TLD*). Dosimetry will be measured on three participants on each CT scanner used to acquire images in the NLST, using the technical parameters defined in the NLST protocol. The dosimeters will be read by a commercial vender to ensure that participant exposure conforms to that defined by the protocol.
17.2.1	38	**Added a new paragraph**	41	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.
17.2.1	38	**Paragraph 2:** **Reference to ACR phantom has been deleted**	42	The ACR has recently launched a voluntary CT accreditation program.
17.2.2	39	**Bullet #3:** Delete "." at end of phrase (i) display devices.	42	**Corrected:** (i) display devices
17.3	39	**Bullet #7: add phrase**	42	▪ …. System performance assessment (if applicable)
17.3	39	**Delete Bullet #8:** ▪ Entrance skin kerma (exposure for chest phantom	42	**Deleted bullet**
17.3	39	**Paragraph 3: Deleted:** (c) quarterly phantom images	42	**Lettering for the quality control tests changes:** (c) monthly visual checklist, (d) quarterly review of repeat analysis, (e) annual screen cleanliness and screen-film contact, and (f) semi-annual analysis
17.3	39	**Last sentence revised from:** The documentation of these or other site quality control tests will be submitted…		**Revised to:** An attestation that these or other site quality control tests are performed will be submitted…
17.4	40	**2nd paragraph, first bullet removed:** ▪ kV and mA (or mAs) **3rd paragraph includes an additional bullet**	43	**New bullet added under DICOM fields to be monitored:** ▪ Participant NLST ID
17/5	40	**Bullet 1 removed:** Appropriate kV and mA (*mAs*) ranges		
18.0	40	**Paragraph 1: Typographical error** (Figure 6.:	43	(Figure 6).
18.1	42	**Title of Figure 6 has been revised:** ACRIN NLST Schema for Administration of the Quality of Life and Anxiety Instruments	45	ACRIN NLST Schema for Administration of the Quality of Life and Anxiety Instruments To be Performed Only at Group 1 ACRIN Sites
18.3	43	**Line 2:** patients, changed to	46	**Line 2**: participants
21.1	46	**A sentence has been added to the paragraph**	49	**Sentence added:** It should be noted that the trial, as designed with 50,000 individuals (combined with the Lung

				Screening Study of the NLST) is not adequately powered to detect a meaningful difference in all cause mortality.
21.4	47	**Added last sentence**	50	***[Participants at Group 1 sites only].***
21.6	48	**Added last sentence**	52	***[To be collected from participants at Group 1 sites only].***
22.2	50	**Added brackets to title**	53	***[Group 1 sites only]***
22.3	51	**Paragraph 1, last sentence:** We assume that our 20,000 recruited patients will…	53	**Sentence corrected:** We assume that our 25,000 recruited participants will…
22.3	51	**Table of Planned Minority Inclusion** **Figures have been revised proportionately from accrual of 10,000 to 25,000**	53	**See Table below**

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	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Total
Males	46	145	742	636	3,445	5,014
Female	54	57	625	629	3,621	4,986
Total	100	202	1,367	1,265	7,066	10,000

Version September 30,2002

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Total
Male	114	363	1,854	1,590	8,613	12,534
Female	136	143	1,561	1,573	9,053	12,466
Total	250	506	3,415	3,163	17,666	25,000

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23.2	51	**Paragraph 1, line 3:** With input from the…….current lung cancer SPORES		**Added:** With input from the NCI and appropriate internal review boards of the current lung cancer SPORES….
23.3	52	**Specimen Collection and Banking Section has been completely rewritten as separate sections to describe:** ▪ **Blood, urine, and sputum collection from participants in CT and CXR screening arms at Group I sites only** ▪ **Remnant tissue specimen collection from participants at all sites in whom biopsy or resection is performed** ▪ **Storage of all specimens**	54 55	▪ **See Sections 23.3** ▪ **See Sections 23.4** ▪ **See Sections 23.5**

23.3 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. *(Please see Appendices VI: Figure VII: Biomarker Collection and Processing for collection and processing procedures*).

23.4 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.

23. 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.

CHANGES TO THE ACRIN-NLST CONSENT FORMS:

The number of ACRIN sites participating in the NLST has increased from 10 to 19 sites. All sites will collect data for the primary mortality endpoint; however, only half of the sites are collecting biological specimens or collecting data on screening-related quality of life. The consent forms have been modified to facilitate their use by sites, depending upon which of the trial sub-studies will be addressed at the respective institution. The following table broadly outlines the content of the consent forms that have now been developed:

CONSENT FORM	COMPONENTS OF STUDY DESCRIBED	SITES INVOLVED
Appendix I **General Consent I**	General Consent for participation in trial ▪ Randomization to screening CT or Chest x-ray ▪ Breathing test at start-up ▪ Completion of questionnaires on demographics, general health, smoking habits, work history, and contact information ▪ **Quality of Life (QOL) questionnaires** ▪ **References collection of specimens of blood, urine and sputum**	▪ Sites performing QOL study (~ 10 sites) ▪ Sites collecting biomarkers
Appendix II General Consent 2	General Consent for participation in trial (same as above) ▪ **No QOL Questionnaires** ▪ **No specimen collection**	▪ Sites not performing QOL ▪ Sites not collecting biomarkers
Medical Records Research Authorization	Medical Record release authorization	▪ **ALL** sites
Appendix III Consent for Collection of Blood, Urine and Sputum for Banking	Collection of blood, urine, and sputum specimens for banking	▪ Sites involved in specimen collection (~ 10 sites)
Appendix IV and V Consent for Banking of Remnant Tissues	**IV** Permission for use of Remnant Tissues for banking **V** Information Guide: How is Tissue Used for Research?	▪ **ALL** Sites

The following is an itemized listing of all changes to the consent forms.

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I	59	**General Consent Group I Sites** **Addition to title** SAMPLE CONSENT FOR RESEARCH STUDY	62	SAMPLE CONSENT FOR RESEARCH STUDY (Include Biomarker Specimens and QOL)
	59	**Paragraph 3 sentence modified,** "… risk of lung cancer because of your age…"	62	"increased risk of lung cancer due to your age.."
	59	**Paragraph 5, line 2:** "About 10,000 people will participate…"	62	: "About 25,000 people will participate…"
	60	**First paragraph deleted,** "… As a participant in this trial, you may be asked to give specimens of..	62	
	60	**Paragraph 2, line 1: word deleted:** "…require that you will lie still…	63	"…require that you lie still….
	60	**A new paragraph has been added**	63	As a participant in this study, you will also be

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				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 will 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.
	60	**Word deleted:** **Paragraph 4, bullet 4**: (beginning of the study), and at year one (1), and year 2…	63	(beginning of the study), at year one (1), and year 2…
	60	**Grammar corrected:** **Paragraph 8, line 4**: Your address and phone number and contact information….	64	Your address, phone number and contact information….
	61	WHAT ARE THE RISKS OF THE STUDY? **First sentence revised from:** While on the study, you are at risk for these side effects.	64	**Revision:** While on the study, you are at risk of the following side effects.
	61	**Under Very Likely Risks, bullet 2:** …,which is much less than of the average annual…	64	…,which is much less than the average annual…
	61	WHAT ARE THE RISKS OF THE STUDY **Paragraph 4, lines 2-5 have been moved to the very end of the section**	65	**Lines remain the same, but have been moved to the bottom of the section.** "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

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				your doctor."
	63	WHERE CAN I GET MORE INFORMATION? **Corrected the words:** Web sites and Web site	67	Websites Website
II (New)	59	**Paragraph 5** **Line 2:** "About 10,000 people will participate…" **Line 3:** "Approximately 1,000 participants…"	68	**Line 2:** "About 25,000 people will participate…" **Line 3:** "Approximately 1,500 participants…"
	60	**Paragraph 2, line 1: word deleted:** "…require that you will lie still…	69	"…require that you lie still….
	60	**Paragraph added regarding the collection of remnant tissue**	69	**Paragraph added regarding the collection of remnant tissue:** 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.
	60	**These references to completion of quality of life (QOL) forms have been deleted in the description of what participants will undergo:** ▪ Questionnaires about your quality of life (QOL) at baseline (beginning of the study), and at year one(1) and year two (2) follow-up. ▪ 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. (removed from both Experimental and Control Arm bullet descriptions)	69	**All references to QOL forms have been deleted because this consent applies to the Group 2 sites in which QOL studies will not be performed.**
	60	**Last paragraph deleted:** If you are asked to complete the QOL and anxiety questionnaires, sometimes you will complete them	70	**Paragraph deleted**

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		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 and phone number and contact information for a close friend or family member will be provided to ACRIN for this purpose.		
	61	**Paragraph 1, line 2: deleted** The QOL questionnaires will take approximately 20-30 minutes to complete.	69	**Sentence deleted**
	61	WHAT ARE THE RISKS OF THE STUDY? **First sentence revised from:** While on the study, you are at risk for these side effects.	70	**Revision:** While on the study, you are at risk of the following side effects.
	61	WHAT ARE THE RISKS OF THE STUDY **Paragraph 4, lines 2-5 have been moved to the very end of the section**	70	**Lines remain the same, but have been moved to the bottom of the section.** "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."
	61	**Under Very Likely Risks, bullet 2:** …,which is much less than of the average annual…	62	…,which is much less than the average annual…
	64`	WHERE CAN I GET MORE INFORMATION? **Corrected the words:** Web sites and Web site	73	Websites Website
III	65	**Biomarker Specimen Consent Form** **Title changed from:** **Biomolecular Markers (Tissue, Blood and Urine Samples):**	74	**Blood, Urine and Sputum Specimens for Banking**
	65	**WHY IS THIS STUDY BEING DONE has been largely replaced from the original:** This biomolecular study seeks to develop new biologic markers of early forms of lung cancer. 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 may influence whether people develop lung cancer and other conditions that affect your age group.	74	**Revised text:** 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

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				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
	65	**WHAT IS INVOLVED IN THE STUDY has been entirely replaced from the original:** If you would like to participate in this part of the study, about one tablespoon (30cc) of blood, small samples of sputum, and a urine sample will be collected at your initial visit. You will also be asked to provide samples when you return for your next (2) two annual screening visits. You will also take home containers for collecting your sputum samples, with a pre-paid envelope addressed to the research storage facility. Also, if you later have surgery for diagnosis or treatment of lung cancer or a related condition, some of your tissue will be removed. As is usually done, this tissue will go to the hospital's pathology department for routine testing and diagnosis. After that process is complete, a small portion of the tissue may be prepared for storage at a centralized ACRIN research storage facility. The remaining tissue sample is stored in the pathology department. Since this tissue was removed at the time of surgery or biopsy, your permission to use this tissue will not lead to any additional procedures or expense. You are being asked for permission to use the remainder of the tissue samples specimens for additional tests. This tissue sample, and the blood, sputum, and urine specimens will be stored at the centralized ACRIN research storage facility for review and research into the factors that cause cancer and influence its progression. It is believed that lung cancer is caused by both environmental and genetic factors. Therefore, the samples that you contribute may be used in biochemical and genetic studies to identify these causes.		**Revised Text:** 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 (spit) Collection:** You will be given two (2) special containers for collecting sputum samples on two different days. Directions for obtaining sputum in the morning, ideally after a warm shower, and throughout the day in a single cup will be provided. You will also be given a pre-paid envelope addressed to the centralized ACRIN research storage facility located at the University of Colorado Lung SPORE Tissue Bank. 4. **Medical records analysis.** You will be asked to allow investigators to review your medical records to gather information about your health. Your medical information will be coded with an identification number and all personal identifying information removed in order to maintain confidentiality. The information will then be placed into a computer database developed and maintained at the American College of Radiology Imaging Network (ACRIN) Data Management Center. The information and samples in this database may be analyzed by investigators in attempts to understand 1) who develops lung

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				cancer, 2) how to detect or prevent early lung cancer, and 3) how to treat lung cancers.
	65	**WHAT ARE THE RISKS OF THE STUDY?** **This section has also been revised as follows:** ▪ **Paragraph 1, line 1 has been replaced from: "**There are certain risks and discomforts that might be associated with the additional procedures." ▪ **Paragraph 1, line 4 has been rewritten from:** There may also be uneasiness associated with needles. ▪ **Added a paragraph on confidentiality under risks.**	74-75	**Revisions or additions:** ▪ **Paragraph 1, line 1:** 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. ▪ **Paragraph 2: Blood statement revised to:** You may feel queasy around needles. ▪ **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.
	66	**ARE THERE BENEFITS TO TAKING PART IN THIS STUDY?** **Words or phrases have been added to the following:** Participation in this part of the study will not provide direct benefit to you. However, your participation in these additional studies may help answer questions related to the health and life span of persons in your age group and may help establish a scientific understanding of the factors that influence the development and progression of lung cancer.	75	**Revision:** 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 or other diseases, how to prevent it, and how to treat it.
		The following section has been shortened and simplified to reflect that this consent is for banking of specimens and not genetic testing: **WHAT ABOUT CONFIDENTIALITY:** Results of these additional studies will be reported in the scientific literature. This notification will be		**Revision:** **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

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		in the scientific literature. This notification will be of results for all participants together. No individual results will be provided from these additional studies. Information concerning your participation in the tissue and specimen study will be kept confidential and used only for scientific purposes, in accordance with applicable state and federal laws. Because the tests to be carried out are for research purposes only, no results from these tests will be placed in your medical records or linked to your name. In order to protect the confidentiality of your samples, they will be stored and used for medical research by code number only. No one who has access to your name will have access to the coded test results identifying you. No individual will be identified in any report. To help us protect your privacy, we have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below. The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA). You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.		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.
		The following section has been revised for better lay translation: **WHAT ARE MY RIGHTS AS A PARTICIPANT?** Your participation in the biological samples (tissue,		**Revision**: Your participation in the collection and storage of biological specimens (blood, urine, and sputum) is voluntary and you may refuse to participate or change your mind and withdraw consent at any time without penalty. Furthermore, you may

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		blood, sputum and urine testing) is voluntary and you may refuse to participate and/or withdraw your consent and discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled. You may participate in the screening part of the trial and yet decline to have biologic samples stored for research purposes. Further, if you initially decide to have your biologic samples stored for research purposes, but later change your mind by written notification to Dr. _____ at *(institution)*, whatever remains of your biologic samples will then be destroyed. Your decision will not affect your care.		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.
	66	**Several new sections of the consent have been added as shown below.** **Note: The section "OTHER RESEARCH QUESTIONS REGARDING MY SPECIMENS" has been slightly revised and reformatted.**	75	See below

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.

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 MY SAMPLE.**

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

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App IV		**Consent Form for Remnant Tissue Collection (Leftover Tissue) is NEW**		**Consent Added**
App V		**Added the Following:** **Information Sheet: How is Tissue Used for Research?**		**Information Sheet Added to accompany the Remnant Tissue Consent**
App VII		**Person to send the PSA to has changed**		ACRIN Administrator/American College of Radiology
Appen VIII	70	**ELIGIBILITY CHECK has corrections as follows:** 4. No medical or psychiatric condition precluding informed consent. 8. Individual has not been treated for cancer or been told by a doctor that they have evidence of cancer within the preceding (5) five years *(excluding non-melanoma skin cancer)*. 14. No medical conditions that pose a significant risk of mortality during the trial period.		**Corrections as follows:** 4. Individual has no medical or psychiatric condition precluding informed consent. 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.) 14. Individual has no medical conditions that pose a significant risk of mortality during the trial period.
App VIII	71	**CONTINUING THE ELIGIBILITY CHECK**: 8. Date of Birth (*mm- yyyy*) 11. Social Security Number (deleted) 20. Age 21. Verification of completion of the E1 Form (deleted) 22. Has the participant signed consent to have his/her tissues kept for use to learn about, prevent or treat cancer? 23. Has the participant signed consent to have his/her tissues kept for use to learn about, prevent or treat other health problems?		8. Date of Birth (*mm-dd-yyyy*) 19. Participant's Age Group (55-59) (60-64) (65-69) (70-74) 20. Has the participant signed consent to have his/her tissue kept for use to learn about, prevent or treat cancer? 21. Has the participant signed consent to have his/her tissue kept for use to learn about, prevent or treat other health problems? **The following have been added:** 25. Has the participant signed consent to have his/her blood, urine, sputum specimens kept for use to learn about/prevent/treat cancer? 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?

App IX	72	**PROTOCOL FOR BIOMARKER COLLECTION AND PROCESSING** **Figure 7: Has been revised to show that the peripheral blood samples undergo a second centrifugation prior to harvesting the plasma.**	86	**Figure 7 Revised**
X.3	73	**Eligibility Criteria Paragraph 2, Bullet 2 revised from:** Signed consent form for the collection of the biomolecular markers and permission to use them in future biomarker analyses.	87	**Revision** Signed consent form for the collection of the various specimens and permission to store them for future biomarker analyses.
X.4	73	**Reference to** Colorado Specimen Bank **has been revised**	90	Colorado Lung SPORE Tissue Bank
X.4.1	73	**Revisions (Numbers correspond to numbered paragraphs)** **2.** ….four 10 ml Citrate (yellow top) tubes…. **3.** Bullet 1: 4-5ml cryovials Bullet 2: 4-2ml cryovial (pink top) **4. Paragraph 1, Line 4**: The Colorado SPORE biorepository.. **4. Paragraph 2, bullet 1**: …use four 10 ml…. **4. Paragraph 2, bullet 5**: Aliquot …into the four 5-ml cryovials with orange caps **4. Paragraph 2, bullet 6**: and plasma, approx. 1 ml) and place into each of the four 2-ml cryovials with the pink cap	90	**Revisions:** **2 .** … four 8 ml Citrate (yellow top) tubes. **3.** Bullet 1: 4 5-ml cryovials Bullet 2: 4 2-ml cryovials (pink top) **4. Paragraph 1, Line 4**: Colorado Lung SPORE Tissue Bank **4. Paragraph 2, bullet 1**: ..use four 8 ml…. **4. Paragraph 2, bullet 5**: Aliquot ..into the two 15 ml centifuge tubes provided **4. Paragraph 2, bullet 6**: …and plasma, approximately 1 ml) and place into each of the bar-coded four 2-ml cryovials **4. Paragraph 2, bullet 7 has been added:** Centrifuge the plasma at 1500 X G for 10 minutes and aliquot the spun plasma into the four 5 ml bar-coded cryovials with orange caps. Plasma must be clear before freezing; no cells or debris should be present
X.4.2	74	**Revised:** The Colorado SPORE biorepository	91	Colorado Lung SPORE Tissue Bank
X.4.3	75	**Revised name of Colorado SPORE Biorepository in paragraphs 2 and 3**	92	**Revisions in Paragraphs 2 and 3:** Colorado Lung SPORE Tissue Bank
X.4.4	75	**Revised name** **Number 1, bullet 3:** University of Colorado specimen bank **Number 3, paragraph 1:** ..the Colorado SPORE.. **Number 3, paragraph 2:** ..the Colorado SPORE biorepository)	92	**Revisions at all locations is:** Colorado Lung SPORE Tissue Bank
X.5	76	**Revised name:** University of Colorado specimen bank	93	**Revision:** Colorado Lung SPORE Tissue Bank
X.5.2	77	**Revised name:** The Colorado bank	94	Colorado Lung SPORE Tissue Bank
Appen X		**Appendix X: Remnant Tissue Specimen Banking Procedures for the ACRIN-NLST has been added to the protocol appendices**	97-	**See NEW Appendix X**