1/25/05  **FS Form – Multiple Visit Dates (first and last only):**
If, when completing the FS Form, the participant reports multiple visit dates only the first and last dates need to be documented. Report the reason for the visits and procedures, accumulatively within the first two rows. This decision was made to help make the FS easier to complete for both the participant and the study staff, yet still provide the information needed.

Example: Participant is having chemotherapy for renal cancer with 2-3 visits a month. Ask the participant for the dates (at least month/year) of the first and last visits for the given follow-up interval (7/2004, 1/2004) and record these visit dates in the first and second rows, respectively. None of these visits were lung or chest related so, ‘other’ reason should be selected in both rows. The participant had several CXRs and a Chest-Abdomen-Pelvis CT with the given follow-up interval. Record these procedures with in the first row – first visit date.

1/25/05  **Revised F1 and FC Instructions (dated 1/24/05):**
F1 Instructions were revised to describe process for unreturned F1 Forms and participant refusals. Both scenarios require follow-up data collection attempt(s), either a full or abbreviated version of the F1 Form, as described in revised instructions document.

FC Instructions were revised to further clarify form content and reflect previous discussions regarding FC completion.

9/14/04  **Images/exams performed outside the study center:**
Unable to use images performed at outside facilities as the study-screening exam (C2/DR). However, outside images can be used for historical image review/comparison (I8/I9).

**Radiology reports:**
Use of radiology reports without the actual images cannot be used for study purposes. The study forms (DR, C2, I8, I9) require review and comparison of the actual images.

8/31/04  **Out-of-Window Screening Exams:**
Guidelines were established to identify how to assign late/early screening exams. This was done as a point of harmonization with the LSS group, ensuring uniformity of assigning late/early screening exams across all sites (ACRIN and LSS). The OOWS document was distributed during the 9/14/04 Operational Call and has been posted to the ACRIN 6654 web site. These guidelines apply to all screening exams, past and future. Any case specific questions should be directed to data management.

6/17/04  **Form Revisions Notice effective 6-17-04** (Forms: C2, DR, I8, I9, IM)

**Operational implications due to form revisions:**
C2, DR, I8, I9: Included instruction for the radiologist to make a diagnostic follow-up recommendation for the result category "negative screen, significant abnormalities not suspicious for lung cancer." Previously, this was required only for positive screens.
I8, I9: Additional result category added “Positive screen, stable abnormality potentially related to lung cancer, no significant change since prior screening exam.” This was added in coordination with LSS. This response allows us to differentiate between new positive screens at T1 and T2 versus positive screens based on previous screen (T0 or T1).

4/01/04 MOP: Revision to Section 9.2 Scheduling the Annual Visit

Annual Screens – Lower Respiratory Infection

The presence of a lower respiratory infection can complicate the screening results/recommendations, possibly leading to false positives and unnecessary diagnostic follow-up. In an effort to avoid this problem, we ask that when scheduling the T1 and T2 screening visits all participants be asked whether they presently have a lower respiratory infection which is being treated with antibiotics; similar to the on-study process. Additionally, the participant should be informed to call and re-schedule the screening visit if this condition presents in the interim (between scheduling call and actual appointment). If a participant has a lower respiratory infection, severe enough to require antibiotic treatment, we ask that the screening visit be delayed 12 weeks from the date of the first dose of antibiotics. For participant safety and data quality issues, this process should be followed even if the delay means the screening visit will be performed outside the protocol-specified 4-month follow-up window.

To assist ACRIN in monitoring protocol compliance:

- If the screening exam is performed outside the 4-month follow-up window, submit a PR form documenting this and the reason.
- If the screening exam is performed while the participant has a lower respiratory infection (as described above), submit a PR form documenting this and the reason. Currently, this will need to be documented as “other” but the PR form will be revised to include this in the Q1 code table. It is important to remember that the reason for rescheduling the screening exam involves participant safety issues; presence of a lower respiratory infection increases the possibility of false positive findings and, therefore, otherwise unnecessary diagnostic follow-up. The exam should be rescheduled unless the participant refuses or is unable to do so; the exam should not be performed solely for the convenience to the study site.

2/17/04 Operational Change: Intent To Treat Analysis, document dated 2/25/04

ITT is a strategy for analyzing randomized controlled trials that compares participants in the groups to which they were originally randomized, regardless of whether they were actually eligible, received all trial interventions, received the wrong interventions, or subsequently withdrew from the protocol. Document circulated at ACRIN Spring Meeting on 2/27/04.

Refer to ITT document for detailed description

The following rules should be followed in order to preserve the integrity of the ITT analysis in NLST:

- Do NOT randomize participants who do not meet the eligibility criteria at the time of randomization.
ONCE RANDOMIZED, perform all study activities on participants, regardless of whether they were later shown not to satisfy some eligibility criteria.

If a randomized participant did not receive their screening intervention at T0 as a result of earlier trial instructions, the participant WILL receive the screening interventions at T1 and T2 and will participate in all other study activities.

If a randomized participant did not receive their screening intervention at T0 AND T1 as a result of earlier trial instructions, the participant WILL receive the screening intervention at T2 and participate in all other study activities.

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Below are process changes related to the protocol amendments. Refer to protocol and summary of changes for complete, detailed list of amendments.

- 10.0-Removed requirement to re-administer E1 for participant’s who did not receive their baseline screening exam within 4 weeks of randomization. Eligibility is determined at randomization and is not affected by subsequent events. However, site RA should inquire about respiratory infections/antibiotics when scheduling the screening exam (T0, T1, T2). Screening exams should be delayed 12 weeks from the date of the first dose of antibiotics.
- 16.1-Screening Results Withheld: Optional source document provided for use when participants decline to have screening results sent to their provider. Alternatively, can continue to document within study chart. Document previously distributed and is included in protocol as Appendix IX.
- 16.1-Window for screening results letters extended to 4 weeks (previously a 3 week window).
- 16.2/16.3-Removed requirement for 2-month follow-up call.
- 20.0-Confidentiality section of the consent form was revised; participants should be re-consented. Questions regarding consents should be directed to ACRIN Regulatory and Protocol Development.

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2/05/04 Protocol: Amended NLST Protocol sent to CTEP for review and approval. Version date: 2/5/04, Amendments #1-9.

2/05/04 Lateral CXR: Per protocol, only a PA projection radiograph should be performed on participants randomized to CXR. There are two separate protocol variations related to this: (1) lateral projection was performed and (2) lateral projection was used for study screening interpretation.

If a lateral projection is obtained:
- Document on PR.
- Send the image to ACRIN as part of the exam.
- Include the lateral projection when recording DR 4a and 4b.
- Since a lateral projection results in a higher exposure than a PA projection, DR q6-10 should report the exposure factors for the lateral projection.
- To avoid bias, the radiologist should not review the lateral projection prior to completing the DR; screening exam findings and results should be reported independent of the lateral projection. The lateral projection can be reviewed as part of the I8 interpretation (historical-interval images).
If a lateral projection is used for the DR screening interpretation:
- Document on PR.

1/22/04 DECISION REVISED ON 2/27/04

Ineligible participants: As of 1/8/04, going forward all randomized participants that are later determined ineligible will continue with the screening exams and all other protocol interventions. Participants already randomized and determined ineligible will continue with annual screening exams and all other protocol interventions ONLY if the baseline screen was performed. If the baseline screen was not performed, do not screen now.

1/22/04 Follow-Up and Annual Screens: Four-month window for T1/T2 visit; from one month prior to three months after the randomization anniversary date. Annual screens are expected to be performed on all participants unless:
- Participant dies
- Participant is diagnosed with lung cancer
- Participant refuses

Follow-up for participants diagnosed with lung cancer:
- No annual screening exam
- Continue biomarker collection at T1 and T2 if participant is able/willing (group 1 only)
- Collect QF/QL (if participant selected, group 1 sites only)
- Collect F1 every 6 months per routine protocol requirement

Follow-up for participants diagnosed with ANY other cancer:
- Continue annual screening exam if participant is able/willing
- Continue biomarker collection at T1 and T2 if participant is able/willing (group 1 only)
- Collect QF/QL (if participant selected, group 1 sites only)
- Collect F1 every 6 months per routine protocol requirement

1/22/04 BL and ST forms: In lieu of faxing, please batch-mail all biomarker forms to the DMC once or twice a month and include a cover sheet listing which forms are included in packet.
- Mail a copy to ACRIN DM
- Retain a copy in the study file
- Include original form with the specimen/sputum kit

1/08/04 DECISION REVISED ON 1/22/04

Ineligible participants: Going forward, all randomized participants that are later determined ineligible will continue with the screening exams and all other protocol interventions. This is a process change.

No final decision has been made on procedures for participants that were previously registered and deemed ineligible. DM will notify all sites once procedures have been confirmed with the Stat Center and Study Team.