LCCC 1822: Clinical Evaluation of Primary Sampling Scatter Correction for Chest Tomosynthesis

NCT#: NCT04076696

Document Version Date: December 12, 2021

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Sponsor: Lineberger Comprehensive Cancer Center

Funding Source: NCI Pending

Version Date: January 21, 2021

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: Ertan Pamuklar, MD

PI Signature: _____

Date:_____

Date of Protocol: January 21, 2021

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1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This is a study that will evaluate the utility of a scatter reduction technique in reducing dose and increasing the sensitivity of stationary digital chest tomosynthesis (s-DCT) in the detection of lung lesions. Digital tomosynthesis is an imaging modality that produces 3D sectional information using x-ray projections acquired over a limited scanning angle. Scatter is known to be the primary source of image degradation in x-ray based imaging.

We have developed an approach that measures scatter through a low dose (3% of the conventional scan) scatter measurement technique. Preliminary studies have shown that scatter reduction in DCT can significantly improve quality. We plan to characterize the reader confidence in lung nodule detection in our scatter corrected chest tomosynthesis imaging approach as compared to our conventional chest tomosynthesis.

Fifty (50) patients who have undergone a clinical non-contrast CT with lung nodules will be asked to have an s-DCT (scan) within 4 weeks (+/- 2 week) of their clinical CT with no intervening procedures or therapies (i.e. biopsy of lung nodules). We will then perform a reader study to evaluate the radiologist reader confidence in images generated from the scatter reduction technique versus more conventional chest tomosynthesis imaging.

1.2 Lung Cancer and Screening

Lung cancer continues to be the leading cause of cancer deaths in the world. Over 200,000 new cases of lung cancer were identified in 2010 in the US, and lung cancer death exceeds the total estimated deaths from breast, prostate and colon combined. Conventional chest radiographs are known to perform poorly in screening and identification of small stage I cancers due to the small lesion size and poor conspicuity. The low dose-CT based National Lung Screening Trial was published in 2011, and demonstrated that there was an overall 20% reduction in lung cancer mortality in the low dose CT screening group in patients at high risk of lung cancer as compared to conventional radiographs. Low dose CT was estimated to provide 1.5 mSv, at roughly 20 to 30 mAs for an average sized patient. Conventional chest CT is estimated to be approximately 8 mSv. This lower dose results in a lower radiation risk to patients.

1.3 Chest Tomosynthesis

Digital chest tomosynthesis (DCT) is a three-dimensional imaging technique that provides reconstruction planes from a limited-angle series of projection images. Clinical tomosynthesis applications include chest imaging [3-10], angiography [11], joints imaging [12], dental imaging [13], and breast imaging[3, 14, 15]. Compared to conventional chest radiography, DCT results in improved visibility of normal structures such as vessels, airway and spine. By reducing visual clutter from overlying normal anatomy, it also enhances detection of small lung nodules[2]. DCT has better resolution than CT in the plane of the image (but worse resolution in the depth direction) at a significantly lower radiation dose and cost [2]. In the current commercial systems, the projection images are collected by mechanically moving a single x-ray source to different

viewing angles, as illustrated in Figure 1. Two DCT systems are currently commercially available, the GE VolumeRAD and Shimadzu RADspeed. In the GE VolumeRAD [16, 17] system, the x-ray generator is mounted on a crane moving vertically with a variable source-to-detector distance of 180cm. A typical tomosynthesis scan includes 61 projections over 30° in 10 seconds

1.4 Chest Tomosynthesis for Lung Cancer Screening

A number of groups have explored the use of DCT for the screening and the identification of pulmonary nodules. The key attraction of DCT is that it exposes patients to lower doses of radiation than CT. As shown in Table 1, in terms of dose, DCT is typically 10 to 50 times lower than CT, and 3 to 5 times lower than 2D chest radiography (CR). In terms of diagnostic sensitivity and accuracy DCT is significantly better than CR, and is approaching that of CT. The reported effectiveness, as measured by sensitivity, of the GE system, as measured by the AUC (Area under Curve) using CT as the gold standard, varies from 0.73 to 0.96. [1] [18] [19]. The reported variation in AUC is partially attributed to patient motion during the scan. A recent study by Kim et al shows that when no respiratory motion artifacts are present, the detection performance of DCT for nodules (4–10 mm) is significantly better than that of CR; whereas there is not a significant difference in cases with motion artifacts. Using the Shimadzu RADspeed, which has a scanning time of 5s, Yamada et al reported AUC as high as 0.93 [20]. These results indicate that reducing image blurring due to respiratory motion is critical for improving the diagnostic accuracy of DCT. Patients with diseases of the lung, such as COPD or emphysema are severely compromised in their ability to hold their breaths for an extended period of time and consistently on command. *Because of the long travel distance (~1m), heavy weight of the x-ray generator, and the precision required, further reduction of the scanning time is difficult even if the x-ray source can produce sufficient flux.*

Table 1: Comparison of dose, scan time, diagnostic accuracy between CT, CR, DCT, and the UNC stationary DCT systems.

	CT	CR	GE DCT	Shimadzu DCT	UNC s-DCT
Dose (mSv)	3~10	0.02~0.06	0.06~0.2	0.2	~0.2
Dose (mAs)	130-300	~1	3-15	3	3
Scan time (s)	~2s	< 1s	10s	5s	2s
Coverage (deg)	360	0	30	40	20 ~ 40
# of views	~1000	1	60	74	60
AUC	1.0	0.7~0.77	0.73~0.96[1]	0.93[20]	TBD
AUC with motion without motion			0.73[19] 0.85 [19]		

1.5 Rationale

The proposed research, if successfully implemented, will result in a low-dose, low-cost, and highly effective method for screening of lung nodules, which may result in earlier treatment of patients with early stage lung cancer. Using the scatter corrected s-DCT system the imaging dose for a full tomosynthesis scan is expected to be only 10% of that from a low-dose CT, and half of a conventional tomosynthesis scan. Beyond lung cancer screening, the low-dose and sensitive 3D lung imaging modality will likely to find applications in areas such as monitoring of pediatric cystic fibrosis patients where reduction of imaging dose is critical.

The proposed study is a close collaboration between 2 clinical researchers (Lee, MD/PhD, Ertan Pamkular, MD) utilizing the technology invented by two basic scientists (Otto Zhou, PhD, and Jianping Lu, PhD) at UNC. It leverages the resources from several ongoing R&D programs in our lab on new imaging and radiotherapy devices based on the CNT x-ray source array technology, including the stationary digital breast tomosynthesis[25, 26] and microbeam radiation therapy systems[27] that are also invented by our team. We believe the success of this pilot project will lead to a larger scale multidisciplinary project to translate the low-dose stationary digital chest tomosynthesis technology to a clinically viable modality for lung cancer screening.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

Evaluate the reader confidence in the evaluation of s-DCT image with and without PSSC scatter correction.

2.2 Secondary Objectives

The sensitivity of the scatter corrected s-DCT system to conventional s-DCT in the detection of lung nodules.

2.3 Primary Endpoint

The reader confidence in the interpretation of scatter corrected s-DCT images to conventional s-DCT images

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

3.1.1 Patients with a known lung lesion(s)

3.1.2 Patients having undergone a chest CT

3.1.3 Patients 18 years of age and older

3.1.4 Patients able to provide informed consent

3.2 Exclusion Criteria

3.2.1 Patients unable to provide consent

3.2.2 Patients who may not fit on a 35 x 35 detector (BMI > 35).

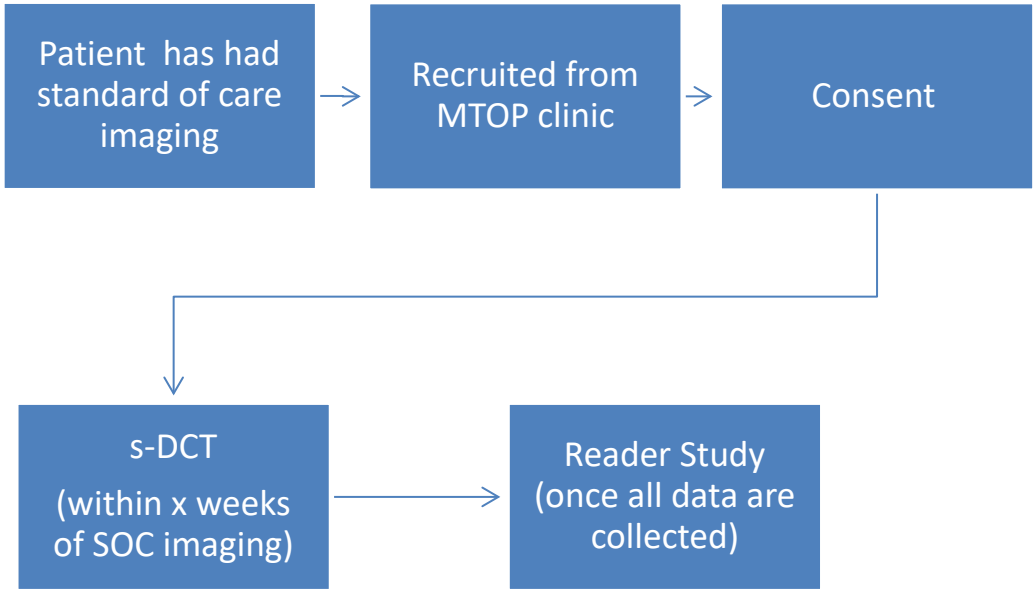
3.2.3 Planned procedures or therapies during study (in between SOC scans and study scan on s-DCT) (biopsy or excision of lung lesion)

3.2.4 Institutionalized patient (prisoner or nursing home patient)

4.0 STUDY PLAN

4.1 STUDY SCHEMA

This is a one arm study of 50 patients with one or more lung nodules who have had standard imaging (chest CT) who consent to undergo an experimental scatter correction s-DCT to characterize the number and extent of lung nodules. This experimental scan will be compared with CT to define the sensitivity of lung nodule detection among this group. The CT scan is used as the gold standard to assess for the presence of a nodule and will be interpreted by consensus to identify the target nodule for each case.



4.2 Duration of the Study

It is anticipated that the total study duration encompassing recruitment, enrollment, and data analysis will take approximately 1 year. Patient participation will last approximately 1 to 3 weeks.

4.3 Study Procedures

4.3.1 Enrollment/Recruitment

We will review upcoming clinical chest CT studies for lung nodule follow-up. We will ask patients to participate in this study to evaluate the utility of the scatter reduction approach for stationary digital chest tomosynthesis (s-DCT) machine, using the standard of care chest CT for comparison.

Once a patient has been identified, or we have collaborated with the treating clinic regarding the eligibility of a subject, the patient will be approached by a coordinator from Radiology to assess interest in participation. The coordinator will either go to the treating clinic, or will call the patient at home.

If the patient is interested in participation, he/she will be consented either then (in their treatment clinic) or when he/she arrives to have his/her s-DCT, but prior to any study procedures. Review of the consent will take place in the privacy of an exam room, or when possible, a sample consent will be sent to the patient via email prior to arriving for the scan to allow for ample review.

4.3.2 Research Imaging

4.3.2.1 Imaging Procedures

The study scan, s-DCT and correction scan, will be performed within two weeks of his/her clinical evaluations by chest CT and x-ray. The study scan may be done within 2 weeks prior or two weeks following standard of care imaging. There cannot be any intervening therapies or procedures (i.e. biopsy or excision of lesions) done in between the SOC imaging and the s-DCT.

All patients will have a breath held s-DCT scan in an anterior-posterior direction. Images will be reconstructed off-line and transferred for review on conventional PACS workstations. Images will be reviewed by radiologists.

4.3.3 Reader Study

Three thoracic imaging specialty radiologists will be asked to separately evaluate the two sets of s-DCT images in a paired reader study. The radiologists will be presented with deidentified images from one modality (either with or without PSSC correction), then asked to identify the lesion and then determine a likelihood of malignancy based on the overall image set. A likelihood of malignancy score (1 to 10) will be initially assigned by the reader. The reader will then be given the deidentified images from the second modality, and their relative confidence in interpretation of the first modality as compared to the second will be evaluated on a 7 point scale. A washout period of four weeks will be provided and the images reviewed in reverse. Confidence scores in the evaluation of lung lesions, locations and involved structures will also be assessed. The CT scan is used as the gold standard to assess for the presence of a nodule and will be interpreted by consensus to identify the target nodule for each case.

4.4 Time and Events Table

	Baseline	**Within 2 weeks of baseline SOC imaging**
Screening	X	
Informed Consent	X	
SOC imaging	X	
Research Scan		X

5.0 INVESTIGATIONAL DEVICE

5.1 Investigational Device Description

We recently demonstrated a high-speed, and low-dose *stationary* digital tomosynthesis system (s-DCT) for 3D lung imaging[21]. The system is based on the carbon nanotube (CNT) x-ray source array technology invented by our team at UNC[22-24]. Instead of mechanically moving a large x-generator to different viewing angles for the projection images, s-DCT generates the images by electronically and sequentially activating the individual x-ray sources inside spatially distributed CNT x-ray source array without moving the source, detector or the patient. Our initial trial of lung nodule detection resulted in mixed results, with reasonable, but not sufficiently accurate identification of smaller lung nodules. One of the critical limitations is the reduction in image quality due to x-ray scatter, inherent in all x-ray based imaging systems.

As shown in Figure 1, the clinical test ready prototype device has already been constructed by retrofitting a commercial mobile digital radiography system with a dedicated CNT x-ray source array (XinRay Systems Inc., NC). A flat panel detector (Varian Inc., CA) is placed underneath the patient. An external collimator is connected to the source array to confine the x-ray radiation only to the region of interests to minimize the radiation to the patient and the staff.

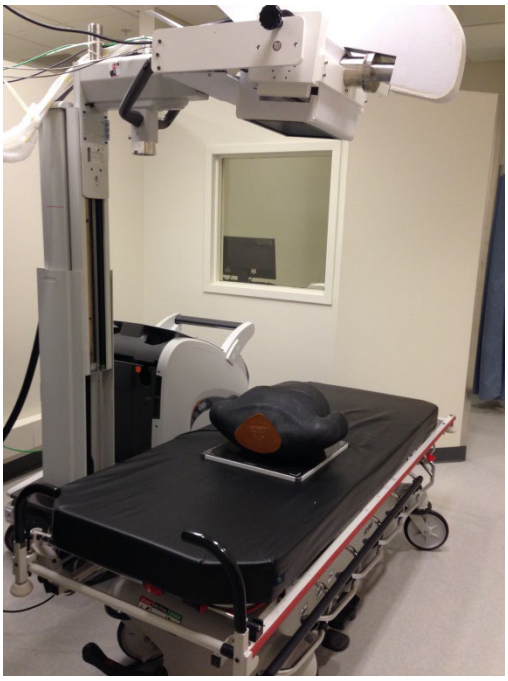


Figure 1: A photograph of the stationary digital chest tomosynthesis imaging system with a CNT x-ray source array.

In all x-ray imaging approaches, the detector measures both the photons that have passed directly through an object (primary photons) and those that are scattered by the object (scattered photons). Unfortunately, only the primary photons are useful for imaging in conventional diagnostic imaging. The presence of scattered photons is a major source of image degradation and extra dose to the patient. Scatter also increases as the imaging subject thickness increases. The scatter-to-primary ratio (SPR) in mammography can vary from 30% to 150%. In chest radiography the SPR can vary from 100% to 500%. Conventional radiography systems use anti-scatter grids placed in front of the detector to block some of the scattered photons from reaching the detector. Unfortunately, the grids also block significant portion of primary beam, and thus a large increase in dose (up to 500%) is required to obtain the same exposure to the detector. Analytical approaches to reduce scatter, such as Monte Carlo simulations and using peripheral field for modeling are generally time consuming and inaccurate. The slot-scan method, though effective, is very slow and impractical for clinical applications.

We have extended our system by developing a scatter correction technique that can be applied to all of x-ray imaging, but is particularly useful in tomosynthesis scanning. Our approach is to estimate scatter by placing a large plate with holes that allow a small fraction (3%) of the primary beam to pass, which generates a patient specific scatter map. This scatter map can then be subtracted from the diagnostic scan.

Preliminary thoracic phantom and large animal imaging results have demonstrated the feasibility of our approach (Figure 2). Furthermore, by accurately estimating scatter, we

can also potentially reduce the dose of primary diagnostic scan. Our proposed implementation of the scatter reduction plate is in Figure 3.

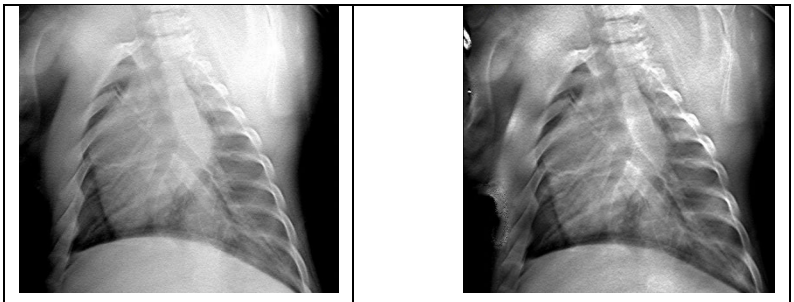


Figure 2: Chest tomosynthesis image slice from a respiratory gated acquisition of a 30 kg normal pig model without (left) and with (right) scatter correction performed with the PSSC approach.

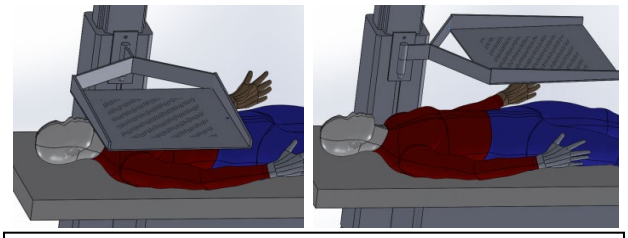


Figure 1: CAD drawing of the PSSC device designed to be implanted with s-DCT system which swings in front and away from the patient during the study. The PSSC can be rapidly moved in and out of the field to minimize the breath hold and patient imaging time.

The research images will not be interpreted or analyzed for clinical decisions related to the patient. As such, this study will request that the IRB make a determination that this study is no greater than minimal risk. This study meets all the requirements for an NSR determination including:

- The device will not be implanted.
- The device is not intended to support or sustain human life.
- The device is not being used of substantial importance in diagnosing, curing, mitigating, or treating disease.
- The device does not present a potential for serious risk to health, safety, or welfare of a subject.

5.2 Expected Risks

This research protocol presents minimal risk to participants, investigators and study personnel. The radiation dose from the device about 10% of the dose comparing to a low-dose CT. Hardware, though experimental, is built on an FDA approved system. The components that will physically have contact with the patient will be a part of the original

FDA approved device. Only the x-ray source has been modified. All x-ray and electrical interlocks will be maintained. Prior to implementation, this study will be reviewed by the Radiation Safety Committee.

6.0 UNANTICIPATED CONCERNS (DEVICES)

6.1.1 Unanticipated Adverse Device Effect (UADE)

The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s)).

6.1.2 Unanticipated Problems (UP)

As defined by UNC's IRB, unanticipated problems involving risks to study subjects refers to any incident, experience, or outcome that:

- Is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- Is related or possibly related to a subject's participation in the research; and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

6.1.3 Reporting

6.1.4 UADEs

UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

For this device study, investigators are required to submit a report of a UADE to the FDA, the manufacturer of the device and the UNC IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)), using the MedWatch Form 3500A. Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, the UNC IRB, and participating investigators within 10 working days after the sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)).

For this device study, we will submit a report of a UADE to the manufacturer and the IRB as soon as possible, but no later than 10 working days after the investigators first learn of the event.

6.1.5 UP

Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the Study Coordinator using the IRB's web-based reporting system.

Any unanticipated problem that occurs during the conduct of this study and that meets **at least** the first two criteria listed in section 8.2 must be reported to the UNC IRB using the IRB's web-based reporting system.

6.2 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight (Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of study participants treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

7.0 STATISTICAL CONSIDERATIONS

7.1 Study Design/Study Endpoints

This is a nonrandomized, single-center, observational study. The purpose and endpoint of this study is to compare, in a radiologist reader study, the reader preference of the s-DCT scatter corrected images as compared to uncorrected s-DCT images.

Fifty (50) patients undergoing a clinical non-contrast CT for their lung nodules will be asked to have this procedure (scan) within 4 weeks of their clinical CT, with no intervening procedures or therapies involving the lung lesion (ie, excision or biopsy).

7.2 Sample Size and Accrual

Assuming 50 cases are available for the comparison, and the standard deviation of the average reader score to be 2 (the range of the score is from +3 to -3), we will have at least 80% power to detect 0.7 confidence score of using scatter correction over without correction. In the data analysis, we will fit a linear mixed effect model with the confidence score as the outcome and a constant intercept. The working correlation matrix among readers is assumed to be compound symmetry. We will estimate grand mean from this model and test whether the mean confidence score is different from zero.

7.3 Data Analysis Plans

The study will be performed as a reader confidence study. For each comparison, the average confidence scores and the corresponding standard deviations will be reported. Furthermore, to test whether the mean confidence score is larger than zero, a linear mixed effect will be used to analyze data, where the outcome variable is the confidence scores collected in this study and only a grand mean parameter is in the independent list. Additionally, a random intercept is used in the model to account for the correlation among readers when reading the images from the same patient. The Wald's test based on model fit will be used to test whether the grand mean parameter is larger zero. When the p-value from this test is less than 0.05, it will be concluded that there exists significant evidence that readers have more confidence with the s-DCT scatter corrected modality compared to the conventional s-DCT.

The reader preference study form (including both primary and secondary evaluations) is located in the Appendix.

7.4 Data Management

The non-contrast chest CT, s-DCT, and SC s-DCT, if available, that are obtained of all eligible enrolled subjects will be de-identified for inclusion in the readers study. Copies of the clinical report forms as well as the de-identified images described in the preceding will be submitted for each case to the Study Coordinators for maintaining the study record and entering the data into a spreadsheet in preparation

for the reader study.

As an investigator initiated study, this trial will also be audited by the Lineberger Cancer Center audit committee every six or twelve months, depending on the participation of affiliate sites.

7.5 Teaching File

After completion of the study, the de-identified study images will be developed into a teaching file by the PI. It will be used by the PI to educate radiologists in evaluating and interpreting s-DCT imaging.

8.0 STUDY MANAGEMENT

8.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

8.2 Registration Procedures

Study participants will be registered into OnCore®, a web based clinical research platform by one of the Study Coordinators.

8.3 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

8.3.1 Emergency Modifications

UNC investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC's IRB/IEC approval/favorable opinion.

For any such emergency modification implemented, an IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

8.3.2 Single Subject Exceptions

Eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials under any circumstances. Other types of single subject exceptions may be allowed if proper regulatory review has been completed in accordance with Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy. Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

Protocol Deviations: UNC personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

Unanticipated Problems:
Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the study team using the IRB's web-based reporting system.

8.4 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

8.5 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

8.6 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study participants. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

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10.0 APPENDICES

Scatter Corrected versus Uncorrected s-DCT
Reader Study

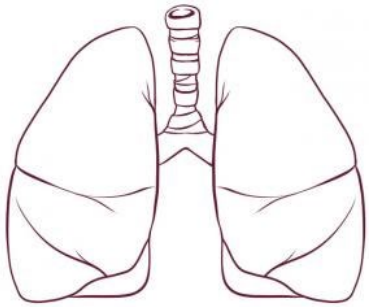
Study #_____ **Reader # _____**
Date _____

1. **Confidence in the presence of a lesion:**

1	2	3	4	5
Definitely no lesion	Probably no lesion	unequivocal	Probably pulmonary lesion	Definitely pulmonary lesion

If the confidence rating is 3 or greater (3, 4 or 5)

Lesion location (mark on figure):



Lesion size (measured in the coronal plane):

Presence of calcifications: Y / N

Comparing both modalities:

2. Scatter Corrected s-DCT versus Uncorrected: Shape/Morphology

-3	-2	-1	0	+1	+2	+3
significantly less confident in the Chest Tomo representation	less confident in the CHEST TOMO representation	slightly less confident in the CHEST TOMO representation	have the same confidence in the CHEST TOMO	slightly more confident in the CHEST TOMO representation	more confident in the CHEST TOMO representation	significantly more confident in the CHEST TOMO representation

2. Scatter Corrected s-DCT versus Uncorrected: Calcifications

-3	-2	-1	0	+1	+2	+3
significantly less confident in the CHEST TOMO representation	less confident in the CHEST TOMO representation	slightly less confident in the CHEST TOMO representation	have the same confidence in the CHEST TOMO	slightly more confident in the CHEST TOMO representation	more confident in the CHEST TOMO representation	significantly more confident in the CHEST TOMO representation

3. Scatter Corrected s-DCT versus Uncorrected: architectural distortion

-3	-2	-1	0	+1	+2	+3
significantly less confident in the CHEST TOMO representation	less confident in the CHEST TOMO representation	slightly less confident in the CHEST TOMO representation	have the same confidence in the CHEST TOMO	slightly more confident in the CHEST TOMO representation	more confident in the CHEST TOMO representation	significantly more confident in the CHEST TOMO representation