Evaluation of a Carbon Nanotube Enabled Solid-State Head CT

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PROTOCOL TITLE
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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:_____

PI Signature: _____

Date:_____

Date of Protocol: June 08, 2023

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ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ACR	American College of Radiology
ART	Algebraic Reconstruction Technique
CDE	Common Data Elements
CNT	Carbon nanotube
CT	Computed Tomography
FOB	Forward Operating Base
GPU	Graphics Processing Unit
MRI	Magnetic Resonance Imaging
MTF	Modulation Transfer Function
NPS	Noise Power Spectrum
PACS	Picture Archiving and Communication System
ROC	Receiver Operator Curve
s-HCT	Stationary Head Computed Tomography
TBI	Traumatic Brain Injury
TV-ART	Total Variation minimization method with Algebraic Reconstruction Technique
UQI	Universal Quality Index
XCAT	Extended Cardiac-Torso

1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This investigation will be a single arm, prospective clinical trial evaluating stationary head CT (s-HCT) as a diagnostic tool in patients with known head trauma. We hypothesize that a stationary head CT (s-HCT) system based on the carbon nanotube linear array x-ray source can provide diagnostic quality head CT images. Patients included in the study will be 50 people who have had either a head trauma or a brain bleed and have undergone a head CT in the past 5 days or who will undergo a CT scan of the head.

1.2 Disease Background

The diagnosis of traumatic brain injury (TBI) has become of paramount importance in combat casualty care. In a resource poor environment, the lack of advanced cross-sectional imaging modalities such as computed tomography (CT) limits the ability of forward surgical teams to diagnose life threatening head injuries. As a result, the vast majority of patients with head trauma must be transported to facilities with CT or MRI capabilities to better assess the extent of head trauma. This approach leads to medically unnecessary transport of soldiers and potentially delays in appropriate care. Unfortunately, conventional imaging modalities such as ultrasound and conventional radiographs are essentially useless in diagnosing life-threatening conditions in the brain, including intraparenchymal hemorrhage, subdural or epidural hematomas. To achieve the appropriate level of care, advanced imaging modalities are necessary. Current computed tomography systems, unfortunately, are highly complex instruments requiring the rapid rotation of an x-ray tube and detector system. This approach does not lend itself to use except for in well controlled environments, such as within a hospital.

1.3 Investigational Imaging Modality

Recently, we have developed the carbon nanotube (CNT) linear x-ray source array. This x-ray generation approach utilizes field emission which allows two primary advantages: precise x-ray pulse control and close physical placement of multiple x-ray sources. A solid state x-ray source array can provide the necessary x-ray projections to generate CT images without any mechanical motion of components. The goal of this study is to evaluate a solid-state no-rotation x-ray CT system for applications in head trauma imaging in the field.

We have designed a solid-state head CT system to enable head CT scanning at Forward Operating Bases (FOBs) and potentially in patient transport vehicles (ambulance or helicopter). A number of mobile dedicated head CT scanners are commercially available.[1] These devices, for the most part, have been used in intensive care unit or otolaryngology clinical applications. Some have been utilized in ambulance settings, requiring significant maintenance and ambulance modification to provide a stable imaging platform.[2] The slip-ring technology that enables these and other modern CT systems allows the transmission of data and power to the rotating source and detector. The slip-ring interface, however, also

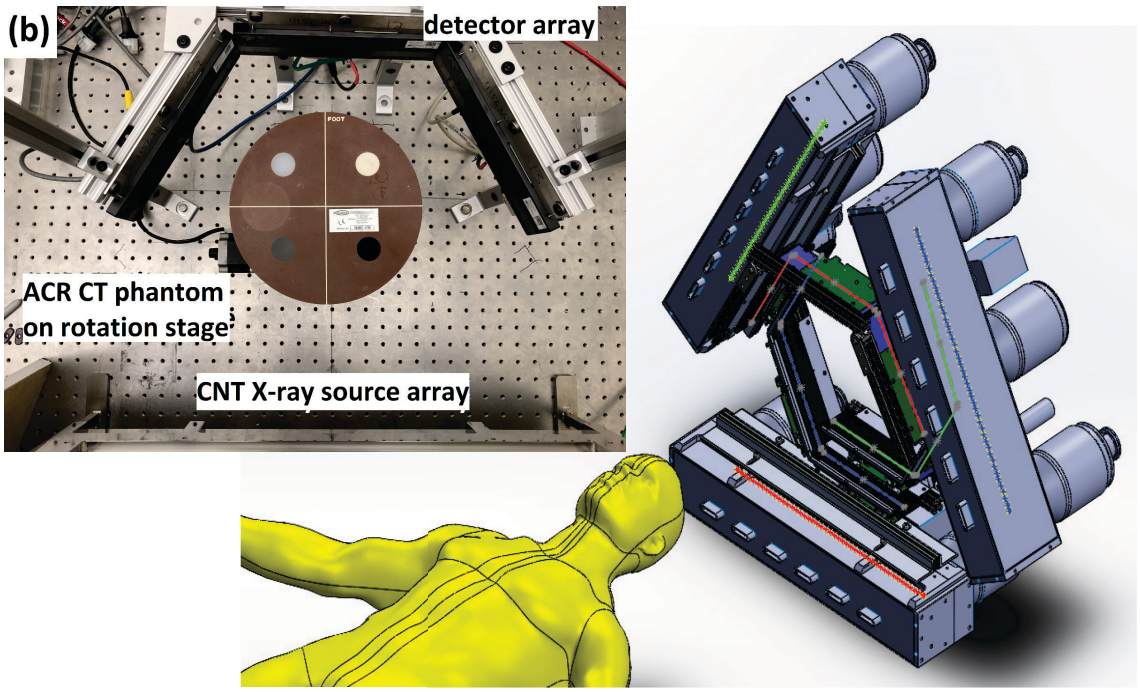
requires high precision and regular maintenance to preserve transmission, making them unsuitable for FOBs.[3]

A solid-state system could eliminate the mechanical limitations of placing a scanner at an FOB or within a vehicle, and bring the diagnostic device closer to the patient.

The figures below represent the current prototype of the proposed Head CT system. Three, 45 (forty-five) beam x-ray sources individually are positioned opposite a set of three detectors that are positioned similar to Figure 1(b), with the position of the head represented by the ACR phantom (brown cylinder with small inserts). The x-ray tubes, Model IND1645, are manufactured by NuRay (http://www.nuraytech.com/en/) and were custom developed for this purpose.

The detectors that will be used are the Xineos 2301 (Teledyne DALSA) (https://www.teledynedalsa.com/en/products/imaging/medical-x-ray-detectors/xineos-scanning/, a 7 x 23 cm detector with high sensitivity in the relevant diagnostic x-ray energies. So, the system will consist of a total of three x-ray sources and nine x-ray detectors. The subjects will be positioned on a medical procedure table that will move the subject through the scanning system at the rate of roughly 1 cm per second, during which the necessary x-ray projections will be acquired. The head will be positioned in a carbon fiber head holder from a clinical CT scanner that is secured to the table.

We are estimating approximately 150 projection angles per slice, with less than a minute per slice reconstruction. Radiation dose will be configured as to not exceed that of a conventional head CT, or 2 mSv. The workflow for the system will be similar to that of a conventional CT, such that the patient is positioned within the head holder on the scanner. Then, once scanning begins, the patient will be automatically advanced into the system across the scan range of the head, during which the necessary x-ray projections will be acquired.



1.4 Rationale

The current Neurosurgery and Severe Head Injury guidelines in the Joint Trauma System (JTS) Clinical Practice Guide (CPG) dictate that all moderate to severe head injuries received a head CT. However, though neurosurgical support is available at Role 3 facilities, CT scanner capability is only available at Role 4. Thus, there is a significant discrepancy need for improved neuroimaging at Role 3 facilities to prevent unnecessary transport to Role 4 facilities at high, unnecessary cost. Imaging TBI patients earlier could also offer more timely transport to the higher level of care necessary to prevent delay of care which may contribute to the patient condition deterioration.

Per the JTS CPG guidelines, subjects with Glasgow Coma Scores from 9 to 12 are considered a moderate level of injury, with severe injury between 3 and 8. Unfortunately, it is also well known that the GCS does not fully capture the extent of TBI, especially in closed head injury. Recently, studies have also shown that identifying intracranial hemorrhage, is an essential component in providing the appropriate level of care and predicting patient outcomes.

Computed tomography (CT) has become one of the most commonly used imaging modalities. The popularity of CT as a diagnostic imaging tool is understandable – no other modality offers 3-D imaging with the same rapidity and soft tissue discrimination as CT. An estimated 62 million CT scans were performed in 2010 in the US. However, these devices remain complex and difficult to deploy in Forward Operating Bases where they are most needed as a diagnostic tool.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

To estimate sensitivity of stationary head CT for the detection of a hemorrhage using a reader study.

2.2 Secondary Objectives

- To estimate specificity of stationary head CT for the detection of a hemorrhage using a reader study.
- To estimate sensitivity of stationary head CT for the detection of a fracture using a reader study.
- To estimate specificity of stationary head CT for the detection of a fracture using a reader study.
- To evaluate the reader confidence for the stationary head CT in detecting hemorrhage or fracture as compared to a conventional CT.

2.3 Outcome Variables

Sensitivity of stationary head CT for the detection of a hemorrhage using a reader study is defined as the ability of readers (radiologists) to use the stationary head CT to predict hemorrhage using the clinical assessment at 3 months as the gold standard. The interpretation of the clinical data will be made by the study PI (Brian D. Sindelar). A neuroradiologist (J. Keith Smith) may re-interpret images as necessary at the request of the PI.

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

3.1.1 18 years of age or older

3.1.2 Medically stable ambulatory patient (outpatient) with head trauma or known intracranial hemorrhage (subdural or intraparenchymal) or skull fractures

3.1.3 Patient has undergone conventional head CT imaging at UNC hospitals within the past 5 days or will undergo a CT scan of the head

3.1.4 Willing and able to provide written informed consent

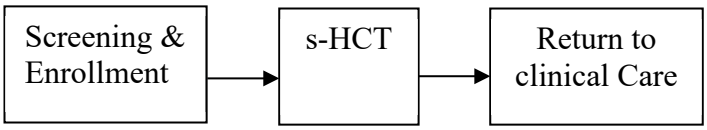
3.2 Exclusion Criteria

3.2.1 Unable to provide consent

3.2.2 Severe claustrophobia

4.0 STUDY PLAN

4.1 STUDY SCHEMA



4.2 Study Procedures

4.2.1 Enrollment/Recruitment

We will recruit 50 medically stable patients who have undergone conventional head CT imaging for imaging within 5 days with the s-HCT system. We will recruit medically stable patients with head trauma or known intracranial hemorrhage (subdural or intraparenchymal) or skull fractures with recent CT imaging. Subjects will be serially recruited with the assistance of the neurosurgery department at our institution. If the attending physician deems a patient stable, a clinical coordinator will obtain informed consent from the subject. If the coordinator has questions about patient competency to provide informed consent, a qualified healthcare provider will make the appropriate determination. In some cases, patients may have recently suffered from a trauma and may be seen for a follow up appointment. In these cases, the s-HCT scan may be obtained prior to the follow up head CT as long as it meets the 5 day window.

Given our high institutional volume of ruptured brain aneurysms and our Level I trauma status, we do not anticipate difficulty with patient volume.

Participants' involvement is limited to one single visit, which will include the s-HCT scan. No follow-up is necessary.

4.2.2 Research Imaging Procedures

Once the study participant has signed the consent forms, either the research coordinator or the radiology technologist will escort them to the study room for the imaging exam.

The participant will not wear any head jewelry during the scan. The participant will have the s-HCT scan performed in a similar manner as the clinical head CT. They will lie on the patient table, and the technologist will position their head in the s-HCT system. Once positioned, the total scan time is a few minutes. The length of time for the positioning and examination may vary, but it is expected that the entire imaging procedure will take about 5-10 minutes, including the positioning time.

4.2.3 Medical Record Abstraction

Data will be collected from participants and their medical records, as applicable. We will follow participants' medical records for 3 months following imaging to

assess for treatment decisions and clinical gold standard as to the presence of a hemorrhage or fracture.

We will document clinical information using the TBI common data elements[29] (CDE) and a local data research electronic data capture system (REDCap). However, as these patients and their imaging data are obtained in a sub-acute setting and from a variety of pathologies, we will not utilize the full TBI CDE data documentation. Specifically, we will utilize the General Core, Demographics, and Injury Presentation. Our clinical scans adhere to the Imaging Diagnostic Imaging Parameters for MRI and Protocols for MRI and CT Guidelines.

4.2.4 Reader Study

All images will be de-identified before inclusion within a reader study. We will perform a reader study with physician readers comparing the acquired imaging s-HCT images and conventional head CT. We hypothesize that the sensitivity of reader's in the interpretation of images from the s-HCT system will be similar to that of the conventional CT imaging. The paired images will be presented to five readers. Readers will be blinded to which imaging modality is being presented. There is, however, readers may be able to distinguish the imaging modality based on the images. Our readers will consist of a trauma surgeon, neurosurgeon or neuro radiologist and non-study radiologists to better reflect the different clinical backgrounds that may be available in a Role 3 environment.

Reconstructed images will be presented in a clinical PACS environment. The readers will be presented images for interpretation in a two-phase study with an interim washout period. First, for each patient, either the s-HCT or conventional head CT images will be presented in random order, and the readers will be asked to identify the presence of hemorrhage (yes/no), the location of the pathology if present and confidence level (0 through 100% in 10% increments). Readers will also be asked to perform interpretations with the appropriate Imaging CT CDE, including the Marshall CT TBI classification code 30, hemorrhage and fracture elements. Four weeks later, the other modality for each patient will be presented in a random order and the same scoring obtained.

The scoring scheme used by readers will include 1) hemorrhage (yes/no) with confidence 0-100% in 10% increments, 2) fracture (yes/no) with confidence 0-100% in 10% increments, 3) streak artifacts (yes/no), and) other artifacts (yes/no).

4.3 Time and Events Table

	Pre-study	Imaging Visit	Conclusion of all data collection
Informed Consent		X	

SOC Imaging	X		
Research Imaging		X	
Medical Record Abstraction/ Questionnaires		X	
Reader Study			X

5.0 INVESTIGATIONAL DEVICE

5.1 Investigational Device Description

The basic system geometry requirements includes a 25 cm field-of-view and the capability of scanning a 30 cm axial field of view. The approximate power is 1.2 kW. Reconstruction time is estimated to be significantly less than one minute for 40 slices.

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

Radiation dose will be no more than a conventional head CT (2 mSv), which is considered negligible risk by the Radiation Safety Committee and Institutional Review Board at our institution. All appropriate Institutional Review Board, Electrical and Radiation safety approvals will be obtained prior to the commencement of imaging.

Practically, we anticipate that many of the scans will be obtained in a subacute post-trauma / event time frame, to insure there is no additional risk to the subjects due to subject transport.

Claustrophobia (fear of being enclosed in tight spaces) may occur during the procedure and the noise of the x-ray machine could be uncomfortable. Some people may feel discomfort lying on the CT table or may experience anxiety while the table slides in and out of the CTscanner.

6.0 UNANTICIPATED CONCERNS (DEVICES)

6.1 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)).

6.2 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.

6.3 Reporting

6.3.1 UADEs

UADEs must be reported by the clinical investigator to 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. The sponsor-investigator 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-investigator 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.

6.3.2 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 6.2 must be reported to the UNC IRB using the IRB's web-based reporting system.

7.0 STATISTICAL CONSIDERATIONS

7.1 Study Design

This is a single arm, non-randomized study to calculate sensitivity and specificity for stationary head CT for the detection of a hemorrhage and fracture using a reader study.

7.2 Sample Size Rationale

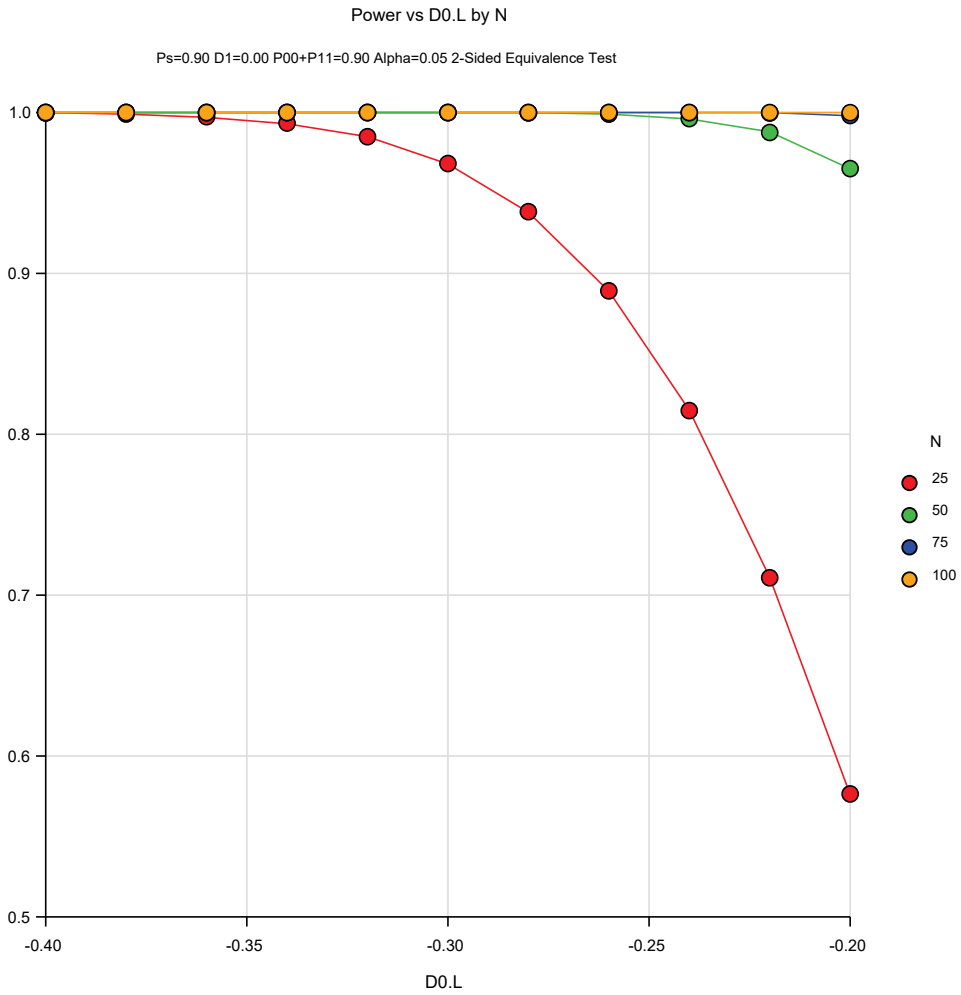
For an equivalence test of the difference between conventional HCT and s-HCT, a sample size of 25 subjects achieves at least 80.0% power at a significance level of 0.050 when the lower equivalence difference is -0.237, the upper equivalence difference is 0.237, sensitivity of conventional HCT and s-HCT is assumed to be 90.0%, and the proportion of concordant pairs is assumed to be 0.900.[34-37]

A table of power calculations for various values of N and various equivalence differences is shown below. For reference, a recent review of the sensitivity of skull radiographs to intracerebral hemorrhage gives a sensitivity range of 3 to 75%. [38]

Power	N	Lower Equivalence	Upper Equivalence	CHCT Sensitivity	s-HCT Sensitivity	Concordance	Alpha
0.99969	25	-0.4	0.4	0.9	0.9	0.9	0.05
1	50	-0.4	0.4	0.9	0.9	0.9	0.05
1	75	-0.4	0.4	0.9	0.9	0.9	0.05
1	100	-0.4	0.4	0.9	0.9	0.9	0.05
0.99906	25	-0.38	0.38	0.9	0.9	0.9	0.05
1	50	-0.38	0.38	0.9	0.9	0.9	0.05
1	75	-0.38	0.38	0.9	0.9	0.9	0.05
1	100	-0.38	0.38	0.9	0.9	0.9	0.05
0.9974	25	-0.36	0.36	0.9	0.9	0.9	0.05
1	50	-0.36	0.36	0.9	0.9	0.9	0.05
1	75	-0.36	0.36	0.9	0.9	0.9	0.05
1	100	-0.36	0.36	0.9	0.9	0.9	0.05
0.99346	25	-0.34	0.34	0.9	0.9	0.9	0.05
1	50	-0.34	0.34	0.9	0.9	0.9	0.05
1	75	-0.34	0.34	0.9	0.9	0.9	0.05

1	100	-0.34	0.34	0.9	0.9	0.9	0.05
0.98497	25	-0.32	0.32	0.9	0.9	0.9	0.05
0.99999	50	-0.32	0.32	0.9	0.9	0.9	0.05
1	75	-0.32	0.32	0.9	0.9	0.9	0.05
1	100	-0.32	0.32	0.9	0.9	0.9	0.05
0.96829	25	-0.3	0.3	0.9	0.9	0.9	0.05
0.99996	50	-0.3	0.3	0.9	0.9	0.9	0.05
1	75	-0.3	0.3	0.9	0.9	0.9	0.05
1	100	-0.3	0.3	0.9	0.9	0.9	0.05
0.93837	25	-0.28	0.28	0.9	0.9	0.9	0.05
0.99979	50	-0.28	0.28	0.9	0.9	0.9	0.05
1	75	-0.28	0.28	0.9	0.9	0.9	0.05
1	100	-0.28	0.28	0.9	0.9	0.9	0.05
0.88916	25	-0.26	0.26	0.9	0.9	0.9	0.05
0.99902	50	-0.26	0.26	0.9	0.9	0.9	0.05
1	75	-0.26	0.26	0.9	0.9	0.9	0.05
1	100	-0.26	0.26	0.9	0.9	0.9	0.05
0.81472	25	-0.24	0.24	0.9	0.9	0.9	0.05
0.99623	50	-0.24	0.24	0.9	0.9	0.9	0.05
0.99996	75	-0.24	0.24	0.9	0.9	0.9	0.05
1	100	-0.24	0.24	0.9	0.9	0.9	0.05
0.71079	25	-0.22	0.22	0.9	0.9	0.9	0.05
0.98761	50	-0.22	0.22	0.9	0.9	0.9	0.05
0.99969	75	-0.22	0.22	0.9	0.9	0.9	0.05
0.99999	100	-0.22	0.22	0.9	0.9	0.9	0.05
0.57643	25	-0.2	0.2	0.9	0.9	0.9	0.05
0.96515	50	-0.2	0.2	0.9	0.9	0.9	0.05
0.99816	75	-0.2	0.2	0.9	0.9	0.9	0.05
0.99993	100	-0.2	0.2	0.9	0.9	0.9	0.05

Here is a plot as a function of N and the equivalence difference.



All power calculations were conducted using PASS 2020 software.

7.3 Data Analysis Plans

We will estimate the sensitivity and specificity from the two modalities
To compare the results from the two imaging modalities, we will adopt the mixed effect ANOVA based on the Dorfman-Berbaum-Metz method. To test the main hypothesis, the F-test statistic from the model parameter estimates will be used to compare the mean sensitivity / specificity metrics between the conventional head CT and the simulated solid-state head CT. Possible interactions between the modalities and the readers and the hemorrhage type/locations will also be included and tested for statistical significance. Sensitivity and specificity on the presence of clinically actionable pathology will also be assessed, based on consensus read of the conventional imaging.

For each confidence comparison, the average confidence scores and the corresponding standard deviations will be reported. 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 than 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-HCT modality compared to the other modality. ROC curves will be evaluated.

We will also descriptively compare inter-reader agreement by modality for image quality, confidence in image interpretation, presence and location of hemorrhage, and presence and location of fractures by computing and reporting Fleiss' kappa.

All statistical estimates of population parameters will be tabulated along with corresponding confidence intervals (CIs) and/or standard errors (SEs) to convey levels of precision / imprecision. Hypothesis tests that are deemed to be not statistically significant will be indicated as inconclusive.

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 REDCap®, a web based clinical research platform by one of the Study Coordinators.

8.3 Data Management

8.3.1 Data Collection and Documentation

We will utilize TBI CDE to document the imaging data of patients for data analysis purposes. The online REDCap software system provided by UNC's TraCS Institute will be used for data collection and management, which will ensure that data collected are consistent and follow standardized coding. Data will be entered into REDCap by the study coordinator within 5 business days.

All data requested on the case report forms (CRFs) will be recorded by the study coordinator. All missing data will be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, the study team will write "N/D". If the item is not applicable to the individual case, the study team will write "N/A". Every attempt will be made to ensure that there is as little missing data as possible including reminder phone calls and follow-up phone calls, if a subject misses a visit. However, this study is limited to a single subject visit so missing values will be minimal. If subjects withdraw, the reason for subject withdrawal will be documented in the study database.

8.3.2 Data Quality

The study team will adhere to the Department of Radiology Internal Monitoring and Quality Assurance Standard Operating Procedures to ensure data quality, completeness, and accuracy are maintained for this study. The Department of Radiology's Internal Quality Assurance program will verify a random selection of at least 25% of all source documents for accuracy and completeness.

8.3.3 Data and Safety Monitoring

This study will not have a data and safety monitoring board. The principal investigator will maintain overall responsibility for data and safety monitoring.

Safety Monitoring will be performed by a licensed physician who is not a study investigator. Medical monitoring will occur at least annually for the duration of this study.
The research coordinator will monitor the study files on a monthly basis to ensure the appropriate regulatory and IRB documentations are on file and up to date. The research coordinator will also be responsible for ensuring proper study documentation in order to verify compliance with Institutional policy, IRB, FDA and GCP guidelines in the following areas: Informed consent, Protocol, Source Documents and Electronic Case Report Forms.

The principal investigator and research coordinator will be responsible for maintaining IRB correspondence. IRB approved forms maintained, as part of the study will include the subject consent form and the HIPAA authorization form.

The investigator will permit study-related monitoring, audits, and inspections by the Research Quality Assurance Office, IRB, and government regulatory bodies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.)

8.3.4 Data archival and data sharing

Data from this study may be submitted to the Federal Interagency Traumatic Brain Injury (FITBIR) informatics system. FITBIR is a computer system run by the National Institutes of Health that allows researchers studying traumatic brain injury to collect and share information with each other.

8.4 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.

8.4.1 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.

8.4.2 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: 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.

8.5 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.

8.6 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, essential 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.

8.7 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.

9.0 PLANS FOR PUBLICATION

Study results will be submitted to a peer-reviewed journal for publication. This study will also be listed on Clinicaltrials.gov and study results will be posted in accordance with appropriate regulations and ICJME requirements.

Neither the complete nor any part of the results of the study carried out under this protocol will be published or passed on to any third party without the consent of the study sponsor-investigator. Any investigator involved with this study will be obligated to provide the sponsor-investigator with complete results and all data derived from the study.

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11.0 APPENDICES

READER STUDY: Evaluation of a Carbon Nanotube Enabled Solid-State Head CT

Subject ID:_____
Reader:_____
Date:_____

1) Hemorrhage: _____ Yes _____ No
   Hemorrhage confidence 0-100% in 10% increments: _____%
   Location (lobe):_____

2) Fracture: _____ Yes _____ No
   Fracture confidence 0-100% in 10% increments: _____%
   Location (bone):_____

Rotterdam CT Scale using sHCT

1. Basal cisterns

0	1	2
Normal	Compressed	Absent

2. Midline Shift

0	1
No Shift or Shift ≤ 5 mm	Shift > 5mm

3. Epidural Mass Lesion

0	1
Present	Absent

4. Intraventricular blood or traumatic Subarachnoid hemorrhage (tSAH)

0	1
Absent	Present

5. Sum score (+1): _____

6. Image Quality

1	2	3	4	5
Non-interpretable; Artifact present;	Artifact present; moderately interferes with	Artifact present; mildly interferes with interpretability	Artifact present; does not interfere with	High quality, no artifacts

severely interferes with interpretability	interpretability		interpretability	

7. Streak Artifacts: _____ Yes _____ No

   Location (lobe):_____

8. Other artifacts: _____ Yes _____ No

   Location (lobe or bone):_____

Reader comments regarding the images:

_____

Reader comments regarding artifacts:

_____

_____
_____