Wrist Fracture Evaluation with a Desktop Orthopedic Tomosynthesis System

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Wrist Fracture Evaluation with a Desktop Orthopedic Tomosynthesis System

Short Title: Wrist Fracture Evaluation with Tomo-E

Drug or Device Name(s): Tomo-E

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Amendment 2 Date:

Amendment 3 Date:

Amendment 4 Date:

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PROTOCOL TITLE: Wrist Fracture Evaluation with a Desktop Orthopedic Tomosynthesis System

Short Title: Wrist Fracture Evaluation with Tomo-E

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Protocol Version: 1.0

Version Date: January 1, 2019

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 Name: _____

Principal Investigator Signature: _____

Date: _____

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ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
CNT	Carbon Nanotube
Tomo-E	Extremity Tomosynthesis System
MSK	Musculoskeletal
PACS	Picture Archiving and Communication System

PROTOCOL SYNOPSIS

Study Title	Wrist Fracture Evaluation with a Desktop Orthopedic Tomosynthesis System
Funder	The University of North Carolina (NC TraCS Institute)
Clinical Phase	Pilot Study
Study Rationale	Tomosynthesis is a quasi-3D imaging modality that uses a series of limited-angle projection images to produce a 3D representation of the object. It provides depth information and removes structural overlaps at significantly reduced radiation dose and cost compared to CT. It is now widely used clinically for breast cancer detection with significantly higher sensitivity and accuracy compared to digital mammography. The value of tomosynthesis for orthopedic imaging has also been demonstrated.
Study Objective(s)	**Primary Objective** The primary objective is to compare (using a reader study) the sensitivity of Tomo-E compared to radiography of the wrist in detecting wrist fractures. **Secondary Objectives** *Specificity* The secondary aim is to determine the specificity of Tomo-E compared to radiography of the wrist in detecting wrist fractures. *Reader Confidence* To compare radiologist confidence of Tomo-E compared to wrist radiography for the evaluation of: • Articular surfaces • Cortical surface of the bones • Joint spaces • Soft tissue structures • Subarticular structures *Area Under the Curve (AUC) Comparison* To compare the area under the curve (AUC) for Tomo-E compared to wrist radiography for fracture detection.

Investigational Device	This study will be an evaluation of a compact extremity tomosynthesis ("Tomo-E") device to provide 3D imaging at the price and radiation dose of 2D radiography at the point-of-care in orthopedic and radiology clinics. Compared to the current standard practice, 2D radiography, Tomo-E offers increased sensitivity and specificity resulting in better diagnostic accuracy without increasing the radiation dose to the patient or cost to the healthcare system. Successful implementation of the technology will reduce misdiagnosis and overtreatment, and reduce the use of CT scans.
Study Design	This is a prospective, one arm, single center study of 50 that have undergone radiographic imaging of wrist for presumed or known scaphoid, wrist or distal radius fractures to demonstrate Tomo-E's clinical utility for diagnosis of wrist injury.
Subject Population key criteria for Inclusion and Exclusion:	**Inclusion Criteria** • Age 18 or older • Undergone radiographic imaging of wrist for presumed or known scaphoid, wrist or distal radius fractures within 2 weeks or are scheduled to undergo such imaging. • Able to provide informed consent **Exclusion Criteria** • Patients with an intervening surgical procedure performed prior to study imaging. • Institutionalized subject (prisoner or nursing home patient)
Number Of Subjects	A total of 50 participants will be consecutively recruited from individuals that have recently undergone radiographic imaging of wrist for presumed or known scaphoid, wrist or distal radius fractures.
Study Duration	Subjects will be followed for 2 months after initial imaging with the Tomo-E device.
Statistical And Analytic Plan	We will perform sensitivity, specificity and area under the curve (AUC) analysis of the imaging modalities based on radiologist reader studies. We will also perform reader confidence studies in evaluation of imaging characteristics relevant to wrist pain imaging. The primary outcome of interest is the sensitivity of Tomo-E is defined as the ability of readers (radiologists) to detect wrist

	fractures in patients. This will be determined by performing a reader study with radiologists. Using these results, we can determine the mean confidence score of radiologist readers using the new device as compared to the competing modality. We will also test the primary null hypothesis that the difference between the two mean confidence scores is zero in the target population. For the confidence study, 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-effects model 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 Tomo-E modality compared to the other modality. The estimated mean confidence score is given by the grand mean parameter and its 95% confidence interval will be reported. We anticipate that it would be meaningful to detect a mean confidence score of greater than 1 between the modalities.
DATA AND SAFETY MONITORING PLAN	The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to an independent Medical Monitor. The medical monitor will review any reported Unanticipated Adverse Device Effects after patients 5, 25, and 50.

1. BACKGROUND AND RATIONALE

Trauma to the extremities such wrist, ankle, limb is very common and affects all population groups. It constitutes a significant public health issue. Standard radiography remains the basic imaging tool. However, as a 2-dimensional (2D) imaging modality it lacks sensitivity and specificity. Misdiagnosis rates are known to be high, especially for non-displaced fractures of the scaphoid and talus as well as erosions due to rheumatoid arthritis [1-3]. Misdiagnosis leads to over treatment and unnecessary loss of productivity and quality of life including 6-12 weeks in a cast. Missed fractures can result in a chronic, non-healing fracture that may require surgical fixation and early arthritis of the joint. From a physician perspective, a missed diagnosis can result in a lawsuit and an expensive settlement/penalty.

Computed tomography (CT) offers high resolution and excellent visualization of bone and joint morphology, and Magnetic Resonance Imaging (MRI) delivers soft tissue and cartilage visibility. However, cost, space and workflow related issues make them prohibitive for small orthopedic clinics. Although the radiation dose of a CT scan has been reduced considerably in recent years, it is still significantly higher than a regular radiograph. The whole-body scanners also have difficulties in imaging patients in portable and weight-bearing conditions. Dedicated extremity CT scanners (Figure 1) have been commercialized recently in an attempt to address the current deficiency. They still suffer from higher cost and at such have a limited installation base.

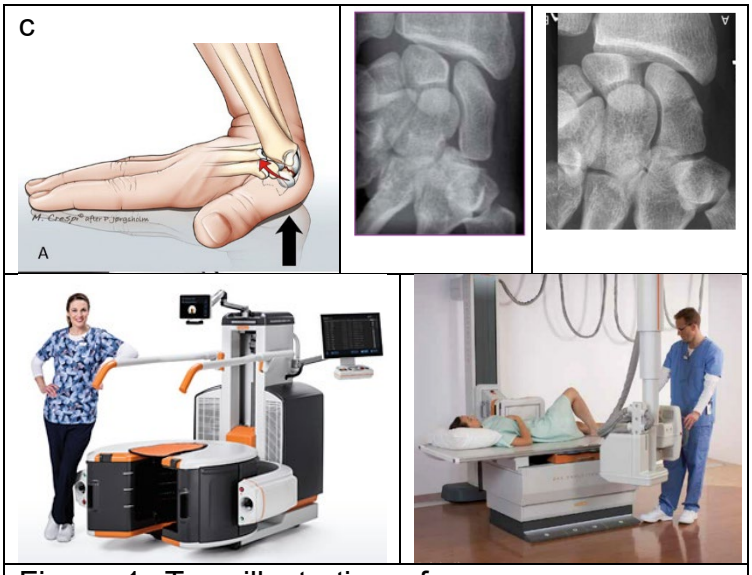

Figure 1: Top: illustration of common a common cause of scaphoid fracture (left), which was not revealed by 2D x-rau (middle), but clearly resolved by tomosynthesis (right). Bottom: A commercial extremity CT (left) and a tomosynthesis scanner (right)

1.1 Introduction

Tomosynthesis is a quasi-3D imaging modality that uses a series of limited-angle projection images to produce a 3D representation of the object [4]. It provides depth information and removes structural overlaps at significantly reduced radiation dose and cost compared to CT. It is now widely used clinically for breast cancer detection with significantly higher sensitivity and accuracy compared to digital mammography. The value of tomosynthesis for orthopedic imaging has also been demonstrated [1, 2, 5].

1.2 Extremity Tomosynthesis

This study will be an evaluation of a compact extremity tomosynthesis ("Tomo-E") device to provide 3D imaging at the price and radiation dose of 2D radiography at the point-of-care in orthopedic and radiology clinics. Compared to the current standard practice, 2D radiography, Tomo-E offers increased sensitivity and specificity resulting in better diagnostic accuracy without increasing the radiation dose to the patient or cost to the healthcare system. Successful implementation of the technology will reduce misdiagnosis and overtreatment, and reduce the use of CT scans. The device is enabled by the unique UNC-invented carbon nanotube (CNT) x-ray source array [6] and stationary tomosynthesis technologies [7].

This will be carried out using an existing and re-configurable imaging set-up (Figure 4), and an iterative image reconstruction algorithm developed in-house, which has been utilized in our preliminary studies using cadaveric hands. The device will be modified to meet the safety standards for patient imaging and will be characterized and tested.

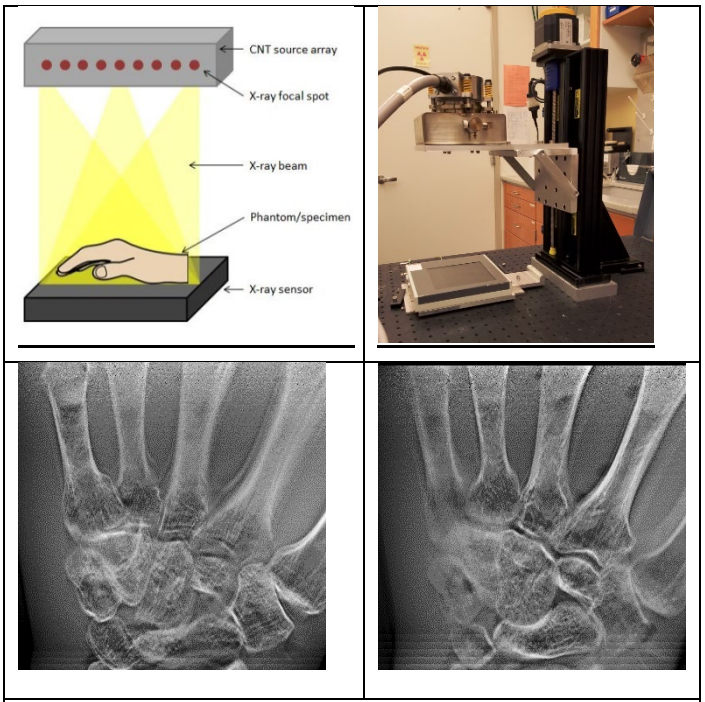

Figure 2: Top: An illustration of the Tomo-E device with a CNT x-ray source array (left). A photo of the experimental set-up to be used in

this study (right). Bottom: Reconstructed tomosynthesis images of a hand phantom at different depth. The images were collected using the experimental set-up shown above

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.

1.3 Non-Clinical and Clinical Study Findings

Two dimensional radiography is the most commonly used diagnostic tool for orthopedic examinations. Although its low accuracy is well known, it remains the most cost effective screening tool. Tomosynthesis is gaining clinical acceptance as a low-dose modality that increases diagnostic sensitivity compared to 2D radiography while using significantly lower radiation dose compared to 3D.

Current commercial approaches: Commercial tomosynthesis scanners collect the projection images needed for reconstruction by mechanically moving a large single-beam x-ray tube mounted on a motorized arm across a long distance while taking the x-ray exposures (Figure **1**). Because of the tube motion blurring its spatial sensitivity and consequently the detection sensitivity are lower than what the modality can intrinsically provide (Figure **1**). Furthermore, the device is expensive (~$150K), and requires a dedicated imaging room. The technology has not made a significant inroad to orthopedic clinics.

Our innovation: Tomo-E is a compact and stationary device that utilizes a distributed CNT x-ray source array that will be specially designed for extremity imaging to collect all the projection views without any mechanical motion, as illustrated in **Figure 2.** X-ray exposure is synchronized with a high frame-rate x-ray detector, which is controlled via dedicated control electronics. The entire device is packaged in radiation shielding and will be operated at the point-of-care (Figure 3). The projection images are processed by a fast iterative tomosynthesis reconstruction algorithm developed at UNC. The reconstructed images are generated in the DICOM format and can be viewed in standard clinical PACS systems. Imaging can be performed with the patient either

sitting in the examination chair or with the patient standing in the load-bearing situation (Figure 3).

Figure 3**:** Photos illustrating the proposed compact Tomo-E device for quasi-3D extremity imaging (The photo on the right is a commercial 2D radiography machine. Tomo-E is expected to have a similar dimension)

Compared to 2D radiography this quasi-3D method offers higher diagnostic accuracy to allow physicians to make better treatment decisions, prevent unnecessary patient casting, and reduces the use high-dose/cost MRI or CT imaging. Compared to commercial tomosynthesis systems, Tomo-E will be the world's first compact 3D orthopedic imaging system that can be used as point-of-care, is low cost, and offers higher spatial resolution.

Figure 4: Left: a FDA approved CNT x-ray based digital mobile x-ray radiography system on display at RSAN 2017. Right: a schematic showing a CNT x-ray source array

Preliminary studies using phantoms and cadaveric tissue have been performed to optimize the system configuration for orthopedic imaging. **Figure 2** shows an example of the reconstructed tomosynthesis images of a cadaveric hand obtained from this

device. Utilizing a set of 25 cadaveric hands (Draeger, MD), we have established the geometry, dose parameters and image resolution necessary to provide diagnostic quality wrist radiographs through a reader study with musculoskeletal radiologists.

2. STUDY OBJECTIVES

The aim of this one-year study is to demonstrate Tomo-E's clinical utility for diagnosis of wrist fractures.

2.1 Primary Objective

The primary objective is to compare (using a reader study) the sensitivity of Tomo-E compared to radiography of the wrist in detecting wrist fractures.

2.2 Secondary Objectives

2.2.1 Specificity

The secondary aim is to determine the specificity of Tomo-E compared to radiography of the wrist in detecting wrist fractures.

2.2.2 Reader Confidence

To compare radiologist confidence of Tomo-E compared to wrist radiography for the evaluation of:

- Articular surfaces
- Cortical surface of the bones
- Joint spaces
- Soft tissue structures
- Subarticular structures

2.2.3 Area Under the Curve (AUC) Comparison

To compare the area under the curve (AUC) for Tomo-E compared to wrist radiography for fracture detection.

3. INVESTIGATIONAL PLAN

3.1 Study Design

This is a prospective, one arm, single center study of 50 that have undergone radiographic imaging of wrist for presumed or known scaphoid, wrist or distal radius fractures to demonstrate Tomo-E's clinical utility for diagnosis of wrist injury.

3.2 Study Duration, Enrollment and Number of Subjects

We will include a total of 50 participants in this trial. These subjects will be followed for 2 months after initial imaging with the Tomo-E device.

3.3 Study Population

3.3.1 Inclusion Criteria

3.3.1.1 Age 18 or older

3.3.1.2 Undergone radiographic imaging of wrist for presumed or known scaphoid, wrist or distal radius fractures within 2 weeks or are scheduled to undergo such imaging.

3.3.1.3 Able to provide informed consent

3.3.2 Exclusion Criteria

3.3.2.1 Patients with an intervening surgical procedure performed prior to study imaging.

3.3.2.2 Institutionalized subject (prisoner or nursing home patient)

4. STUDY PROCEDURES

A patient study focusing on wrist injury will be carried out by comparing Tomo-E with conventional 2D radiographs obtained from a clinical device at UNC Radiology or Orthopedic clinics. Fifty patients who have wrist injuries and have been imaged by conventional 2D radiography at UNC orthopedic clinic (at the Ambulatory Care Center) or Urgent Care will be recruited and be imaged using the Tomo-E device which will be installed in our clinical imaging space in the Marsico Hall, located approximately 200 yards away. We will recruit subjects ages 18 and above to evaluate the device in the adult population. The images will be compared and evaluated by 3 experienced musculoskeletal radiologists from UNC. Clinical outcome reviewed up to 2 months after initial imaging will serve as the clinical standard for the presence of fracture.

4.1 Screening/Baseline Visit procedures

A total of 50 participants will be enrolled to this study. The 50 study subjects will be consecutively recruited from individuals that have recently undergone radiographic imaging of wrist for presumed or known scaphoid, wrist or distal radius fractures. Eligible patients will be identified by research staff review in coordination with the UNC Radiology Clinic.

Once a patient has been referred, the patient will be approached by a coordinator from Radiology to assess interest in participation.

All eligible participants who agree to participate in the study will be asked to come to their scheduled appointment thirty minutes early to complete the informed consent process. For patients who have already undergone their clinical imaging, they will be scheduled to return to UNC for the study visit.

Review of the consent will take place in the privacy of an exam room, or when possible, a sample consent form will be sent to the patient via email prior to the patient's visit to allow for ample review.

4.2 Research Imaging Procedure

Participants who consent for the study will be escorted by the research coordinator to the dedicated study room for the imaging exam.

The patient will have the Tomo-E scan performed in a similar manner as conventional wrist radiography. The research technologist will assist in positioning the wrist in the tomosynthesis unit. Once positioned, the total scan time is approximately 15 seconds. The length of time for the positioning and examination of a subject's wrist may vary but it is expected that the entire imaging procedure will take about 5-10 min, including positioning time.

4.3 Medical Record Abstraction

Participants' medical record will be reviewed for 2 months following their initial research imaging to meet the primary and secondary aims.

4.4 Reader Study

Upon completion of all study image data collection, a reader study will be performed with three MSK fellowship trained radiologists. All images will be reconstructed with our fast-reconstruction algorithm and presented on 3MP viewing monitors with PACS viewing software with conventional zoom/pan/window and level tools. The readers will not be blinded whether the images are from Tomo-E.

Each radiologist will be randomly presented with either the patient's diagnostic radiographs or tomosynthesis study in a random order. They will be asked to review the scan for the presence of a fracture, and comment on location (specific bone) and fracture type. They will be asked their confidence rating on a scale of 0 to 100%.

A washout period of four weeks will be utilized so that the radiologists will have "forgotten" their initial interpretations. At this timepoint, the other modality for each patient will be randomly presented. Diagnostic accuracy will be defined by the presence of a fracture as defined by the clinical diagnosis by the attending orthopedic surgeon at 2 months post imaging during the patients' routine clinical care, such as cast placement, surgery, or follow-up imaging. Sensitivity and specificity to the presence of fractures will be estimated and evaluated between the modalities.

The order that imaging modalities will be presented will be randomly assigned using a computational software in collaboration with the study biostatistician. This randomization schedule will be created prior to the beginning of the reader study and will not be shared with any of the readers.

4.5 Variables of Interest

Primary Variables of Interest:

- Presence of fracture based on imaging (T/F)
- Confidence in interpretation of image set (0 to 100%)

Secondary Variables of Interest

- Reader confidence in articular surface evaluation (1-5)
- Reader confidence in Cortical surface evaluation (1-5)
- Reader confidence in Joint Space evaluation (1-5)

- Reader confidence in Soft tissue Structures evaluation (1-5)
- Reader confidence in Subarticular structure evaluation (1-5)

5. STATISTICAL CONSIDERATION

5.1 Primary Endpoint

The sensitivity of Tomo-E is defined as the ability of readers (radiologists) to detect wrist fractures in patients. Diagnostic accuracy will be defined by the presence of a fracture as defined clinically by the attending orthopedic surgeon at 2 months post imaging.

5.2 Secondary Endpoint

The specificity of Tomo-E is defined as the ability to distinguish between individuals that do not have a wrist fracture. Diagnostic accuracy will be defined by the presence of a fracture as defined clinically by the attending orthopedic surgeon at 2 months post imaging.

5.3 Statistical Methods

A total of 50 participants will be recruited for this study. Three radiologists will be recruited to conduct the reader study.

We will perform sensitivity, specificity and area under the curve (AUC) analysis of the imaging modalities based on radiologist reader studies. We will also perform reader confidence studies in evaluation of imaging characteristics relevant to wrist pain imaging.

The primary outcome of interest is the sensitivity of Tomo-E is defined as the ability of readers (radiologists) to detect wrist fractures in patients. This will be determined by performing a reader study with radiologists. Using these results, we can determine the mean confidence score of radiologist readers using the new device as compared to the competing modality. We will also test the primary null hypothesis that the difference between the two mean confidence scores is zero in the target population.

For the confidence study, 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-effects model 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 Tomo-E modality compared to the other modality. The estimated mean confidence score is given by the grand mean parameter and its 95% confidence interval will be reported. We anticipate that it would be meaningful to detect a mean confidence score of greater than 1 between the modalities.

For the primary and secondary objective, we will estimate the sensitivity and specificity for a pre-specified cutoff of review scores to detect wrist fracture. Generalized estimating equation will be used to produce such estimates, where diagnosis outcomes from readers are treated as clustered data and a compound symmetry working covariance matrix is used. Normal distributions will be used to construct 95% confidence intervals. Bootstrap method may be used when the normality assumption is of concern. For the AUC analysis, the same estimating procedures will be used to obtain the sensitivity and specificity when varying cutoff scores then the AUC will be calculated using the trapezoidal rule. The confidence of the AUC will be obtained from bootstrap method.

For the confidence study, we expect no missing data or drop out. For any missed data during the reader study, we will question the reader to collect the data. The only primary hypothesis test is whether the mean confidence score is zero with a significance level of 0.05. There is no need to adjust multiple tests. All hypothesis tests that are observed to be not statistically significant will be reported as being inconclusive.

5.4 Sample Size and Power

A typical sensitivity of radiographs for wrist fractures is approximately 65%[5] We estimate that our sensitivity using the Tomo-E system will be approximately 80%. Thus we will need 50 patients to detect this difference, assuming a prevalence of approximately 33% in our test population and with 3 readers, that we will have 70% power to detect differences between the two modalities.

5.5 Interim Analysis

Interim analyses will not be conducted.

6. SAFETY MANAGEMENT

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

6.3.3 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to an independent Medical Monitor. The medical monitor will review any reported Unanticipated Adverse Device Effects after patients 5, 25, and 50.

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 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 Scientific Review Committee (SRC), the Office of Clinical Trials (OCT), or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The PI will be responsible for submitting the following information for review by the independent medical monitor: 1) safety and accrual data including the number of study participants imaged; 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 medical monitor review will be disseminated by memo.

7. STUDY MANAGEMENT

7.1 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.

7.2 Registration Procedures

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

7.3 Data Management and Monitoring/Auditing

The wrist radiograph and Tomo-E scan that are obtained of all eligible enrolled subjects will be de-identified for inclusion in the appropriate 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 REDCap in preparation for the reader study.

Information regarding why a data value is missing will be documented in the study database in REDCap.

7.4 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.

7.5 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.

7.6 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 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 according to the UNC IRB reporting requirements.

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.

7.7 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.

7.8 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.

7.9 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.

7.10 Conflict of Interest

Any investigator who has a conflict of interest (COI) with this study as defined by the policies of the University of North Carolina will have the conflict reviewed by a properly constituted Conflict of Interest Review Committee with a committee-sanctioned conflict management plan that has been reviewed and approved by the IRB prior to participation in this study. All University of North Carolina investigators will follow the University conflict of interest policy.

8. PLANS FOR PUBLICATION

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

9. REFERENCES

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10. APPENDIX

10.1 Appendix A: Reader Study Data Collection Form

Subject ID: _____ **Reader:_____**

Date:_____

Overall Assessment:

Is there a fracture?

If yes, which bone?

Overall confidence in presence of a fracture (0-100) _____%

Please indicate your overall confidence for each of the items below.

	Very Poor	Poor	Fair	Good	Excellent
Articular Surfaces					
Cortical Surfaces of Bones					
Joint Spaces					
Soft Tissue Structures					
Subarticular Structures					