Title: Comparison of a Novel Weight Bearing Cone Beam Computed Tomography (CT) Scan to Gravity Stress X-ray for Determining Instability of Supination-External Rotation Type Ankle Fractures

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PROTOCOL TITLE: Comparison of a novel weight bearing cone beam computed tomography (CT) scan to gravity stress X-ray for determining instability of supination-external rotation type ankle fractures

INSTRUCTIONS: Complete Research Protocol (HRP-503)

- *Depending on the nature of what you are doing, some sections may not be applicable to your research. If so, you must provide the reason why the section is not applicable for the response. For example, most behavioral studies would answer all questions in section 30 with words to the effect of "drugs and medical devices are not used in this study."*
- *When you write a protocol, keep an electronic copy. You will need to modify this copy when making changes.*
- *Do not remove the italics instructions or headings.*
- *If you are pasting information from other documents be sure to use the "Merge Formatting" paste option so that the formatting of the response boxes is not lost. If information is presented outside of the response boxes, it will not be accepted.*
- *If this study involves multiple participant groups who participate in different research procedures, consent processes, etc., be certain to provide information in each applicable section for each participant group and clearly label each participant group within a section or subsection.*

PROTOCOL TITLE:

Include the full protocol title.

Response: Comparison of a novel weight bearing cone beam computed tomography (CT) scan to gravity stress X-ray for determining instability of supination-external rotation type ankle fractures

PRINCIPAL INVESTIGATOR:

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Response:
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PROTOCOL TITLE: Comparison of a novel weight bearing cone beam computed tomography (CT) scan to gravity stress X-ray for determining instability of supination-external rotation type ankle fractures

VERSION NUMBER:

Include the version number of this protocol.

Response: 1

DATE:

Include the date of submission or revision.

Response:

Grant Applicability:

Describe whether or not this protocol is funded by a grant or contract and if so, what portions of the grant this study covers.

Response: Carestream Health is providing funding for the research procedures involved in the study. In addition, Carestream is supplying the 3D CT scanner for this study to be housed in the Department of Radiology at the Erie County Medical Center.

PROTOCOL TITLE: Comparison of a novel weight bearing cone beam computed tomography (CT) scan to gravity stress X-ray for determining instability of supination-external rotation type ankle fractures

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1.0 Objectives

1.1 Describe the purpose, specific aims, or objectives.

Response: The primary objective of this study is to compare measures of ankle stability from an investigational weight bearing cone beam computed tomography (CT) scanner to the same measures on gravity stress X-ray in patients who have supination-external rotation ankle fractures.

The secondary objective is to assess inter-rater reliability of ankle stability measures from the investigational cone beam CT scanner and gravity stress X-ray between 2 independent radiologists.

An exploratory objective of this study is to determine if sensitivity of the investigational cone beam CT scan can be verified using the gravity stress X-ray as the gold standard.

1.2 State the hypotheses to be tested.

Response: The primary hypothesis is that the mean medial clear space will be different for the investigational weight bearing cone beam CT scan versus the gravity stress X-ray.

2.0 Background

2.1 Describe the relevant prior experience and gaps in current knowledge.

Response: Supination-external rotation (SER) or Weber B type ankle fractures are considered the most common type of ankle fracture[1-4]. An SER fracture is considered unstable when it is associated with deltoid ligament rupture. Clinical findings of medial tenderness, swelling, and ecchymosis were once thought to be reliable for correctly determining the stability of SER ankle fractures, but have since proven to be poor predictors of deltoid ligament disruption[3, 5]. Rupture of the deltoid ligament allows lateral talar shift, and can be identified by widening of the medial clear space on standard radiographs as well as stress radiographs[6, 7].

2.2 Describe any relevant preliminary data.

Response: Many studies have shown that gravity stress radiographs are necessary and are currently considered to be the gold standard for diagnosis of SER fractures[5]. Of all the methods that have been used to diagnose instability and investigate deltoid ligament integrity (clinical examination, weight bearing radiographs, stress radiography, magnetic resonance imaging (MRI), arthroscopy, ultrasound), none have been shown to be cost-effective, rapid, reliable, and easy to use[4]. Gravity stress

radiographs are performed without a uniform method, are known to lack sensitivity, and are very user dependent. Therefore, more research is needed to determine which method is most accurate and efficient for SER fracture diagnosis.

2.3 Provide the scientific or scholarly background for, rationale for, and significance of the research based on the existing literature and how will it add to existing knowledge.

Response: Weight bearing on the extremity is thought to be more representative of the normal use of the ankle joint, and CT scan is known to deliver excellent bone detail for interpretation of images. The ability of weight bearing cone beam CT scanning to measure medial clear space may present a new opportunity to evaluate instability of SER ankle fractures.

2.4 Include complete specific citations/references.

Response:

1. Gill JB, Risko T, Raducan V, Grimes JS, Schutt RC, Jr. Comparison of manual and gravity stress radiographs for the evaluation of supination-external rotation fibular fractures. The Journal of bone and joint surgery American volume. 2007 May;89(5):994-9. Epub 2007/05/03.

2. Egol KA, Amirtharajah M, Tejwani NC, Capla EL, Koval KJ. Ankle stress test for predicting the need for surgical fixation of isolated fibular fractures. The Journal of bone and joint surgery American volume. 2004 Nov;86-a(11):2393-8. Epub 2004/11/04.

3. Stufkens SA, van den Bekerom MP, Knupp M, Hintermann B, van Dijk CN. The diagnosis and treatment of deltoid ligament lesions in supination–external rotation ankle fractures: a review. Strategies in Trauma and Limb Reconstruction. 2012;7(2):73-85.

4. Croft S, Furey A, Stone C, Moores C, Wilson R. Radiographic evaluation of the ankle syndesmosis. Canadian journal of surgery Journal canadien de chirurgie. 2015 Feb;58(1):58-62. Epub 2015/01/27.

5. van den Bekerom MP. Diagnosing syndesmotic instability in ankle fractures. World journal of orthopedics. 2011 Jul 18;2(7):51-6. Epub 2012/04/05.

6. Nielson JH, Gardner MJ, Peterson MG, Sallis JG, Potter HG, Helfet DL, et al. Radiographic measurements do not predict syndesmotic injury in ankle fractures: an MRI study. Clinical orthopaedics and related research. 2005 Jul(436):216-21. Epub 2005/07/05.

7. Beumer A, van Hemert WL, Niesing R, Entius CA, Ginai AZ, Mulder PG, et al. Radiographic measurement of the distal tibiofibular syndesmosis

has limited use. Clinical orthopaedics and related research. 2004 Jun (423):227-34. Epub 2004/07/03.

3.0 Inclusion and Exclusion Criteria

3.1 Describe the criteria that define who will be included or excluded in your final study sample.

I**nclusion**: Subjects will be recruited from the clinical practices of the study investigators and will:

- have an isolated fibula fracture
- have medial clear space measuring less than 5 mm with clinical suspicion of instability and would normally require a gravity stress x-ray
- be willing and able to provide written informed consent
- be 18 or more years of age

Exclusion: Subjects will be excluded from study participation if they:

- are pregnant at the time of screening
- are prisoners
- have an open fracture
- have clinical signs of ankle deformity
- have had any type of previous ankle trauma or surgery on the affected foot
- have significant osteoarthritis or pre-existing ligamentous instability or pain in the affected ankle
- have an inability to stand in the weight bearing position during the CT scan

3.2 Describe how individuals will be screened for eligibility.

Response: Patients will be screened (see **Eligibility Form Attachment A** that will be used for screening purposes) and recruited by the research team in the Emergency Department or clinical offices of the investigators. Patient history will be obtained and physical examination will be performed, and standard X-rays will be obtained. When the medial clear space is less than 5 mm with clinical suspicion of ankle instability, patients are referred for a routine gravity stress X-ray.

3.3 Indicate specifically whether you will include or exclude each of the following special populations: (You may not include members of these populations as subjects in your research unless you indicate this in your inclusion criteria.)

- *Adults unable to consent*
- *Individuals who are not yet adults (infants, children, teenagers)*
- *Pregnant women*
- *Prisoners*

Response: Adults unable to consent, individuals who are not yet adults, pregnant women, and prisoners will be excluded from this study.

3.4 Indicate whether you will include non-English speaking individuals. Provide justification if you will exclude non-English speaking individuals.
(In order to meet one of the primary ethical principles of equitable selection of subjects, non-English speaking individuals may not be routinely excluded from research. In cases where the research is of therapeutic intent or is designed to investigate areas that would necessarily require certain populations who may not speak English, the researcher is required to make efforts to recruit and include non-English speaking individuals. However, there are studies in which it would be reasonable to limit subjects to those who speak English: e.g., pilot studies, small unfunded studies with validated instruments not available in other languages, numerous questionnaires, and some non-therapeutic studies which offer no direct benefit.)

Response: Non-English speaking subjects will be included in this study. Based on previous experience, we expect that most if not all of our potential study subjects will be English-speaking. However, if we encounter a non-English speaking subject we will find someone who can orally translate (i.e., fluently speaks the same language as the subject, such as a family member) the study description and consent form to the subject.

4.0 Study-Wide Number of Subjects (Multisite/Multicenter Only)

4.1 If this is a multicenter study, indicate the total number of subjects to be accrued across all sites.

Response: This is not a multisite/multicenter trial.

5.0 Study-Wide Recruitment Methods (Multisite/Multicenter Only)

If this is a multicenter study and subjects will be recruited by methods not under the control of the local site (e.g., call centers, national advertisements) describe those methods. Local recruitment methods are described later in the protocol.

5.1 Describe when, where, and how potential subjects will be recruited.

Response: Not applicable, this is not a multi-site study.

5.2 Describe the methods that will be used to identify potential subjects.

Response: Not applicable, this is not a multi-site study.

5.3 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

Response: Not applicable, this is not a multi-site study.

6.0 Multi-Site Research (Multisite/Multicenter Only)

6.1 If this is a multi-site study where you are the lead investigator, describe the processes to ensure communication among sites, such as:

- *All sites have the most current version of the protocol, consent document, and HIPAA authorization.*
- *All required approvals have been obtained at each site (including approval by the site's IRB of record).*
- *All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.*
- *All engaged participating sites will safeguard data as required by local information security policies.*
- *All local site investigators conduct the study appropriately.*
- *All non-compliance with the study protocol or applicable requirements will reported in accordance with local policy.*

Response: Not applicable, this is not a multi-site study.

6.2 Describe the method for communicating to engaged participating sites:

- *Problems.*
- *Interim results.*
- *The closure of a study*

Response: Not applicable, this is not a multi-site study.

7.0 Study Timelines

7.1 Describe the duration of an individual subject's participation in the study.

Response: The subject will be enrolled in the study once informed consent is obtained. The study will conclude once they have had a gravity stress X-ray as standard of care, and a CBCT scan with the investigational weight bearing cone beam scanner.

7.2 Describe the duration anticipated to enroll all study subjects.

Response: It is anticipated that it will take 8 months to 1 year (based on analysis of the past frequency of patients with the diagnosis of an unstable SER fracture and the difficult nature of enrolling study patients) to enroll all study subjects.

7.3 Describe the estimated date for the investigators to complete this study (complete primary analyses)

Response: The estimated date for the investigators to complete the primary analysis is the first quarter of 2017.

8.0 Study Endpoints

8.1 Describe the primary and secondary study endpoints.

Response: The primary endpoint is after enrollment of 20 subjects estimated to provide significance by power analysis.

8.2 Describe any primary or secondary safety endpoints.

Response: The primary safety endpoint is the presence of any adverse event.

9.0 Procedures Involved

9.1 Describe and explain the study design.

Response: This study is a cross-sectional study designed to compare measures of stability from a gravity stress X-ray to the same measures on an investigational cone beam CT scanner.

9.2 Provide a description of all research procedures being performed and when they are performed, including procedures being performed to monitor subjects for safety or minimize risks.

Response: **Screening/Enrollment Visit**: If a patient presents with a potentially unstable SER type ankle fracture the subject's physician will screen them, in the emergency room or physician's office, to determine if they are eligible for the study (see attached **Eligibility Form, Attachment A**).

The determination of a potentially unstable SER type ankle fracture is made via a standard X-ray showing medial clear space less than 5 mm with clinical suspicion of instability. This criteria substantiates the potential diagnosis of an unstable SER ankle fracture with need for

radiographic evaluation by a gravity stress X-ray. To confirm their diagnosis and for surgical treatment planning, patients are sent for a gravity stress X-ray as part of their standard of care.

The study will be explained to eligible subjects, and informed consent to participate in the study will be obtained at the time the subject is thought to have an unstable SER type ankle fracture (in the emergency room or physician's office). For females of childbearing age who consent to be in the study, a urine pregnancy test will be done in the emergency department or physician's office to confirm that the patient is not pregnant. Pregnant females will be excluded from the study (see attached **Eligibility Form, Attachment A**).

Study Visit: The subject will undergo a weight bearing CBCT scan of their affected ankle with the investigational portable cone beam CT scanner. This will be done at the same time or within 7 days as the gravity stress X-ray that is part of the routine clinical work-up for this injury. The scan with the investigational CBCT scanner is estimated to last approximately 25 seconds. The patient will be weight-bearing during the scan and can hold on to the built-in handles of the scanner for stability during the scan. The subject will be shielded from radiation to the thyroid and genitals with commercially available shields. The risks involved with this study include the risk of additional exposure to radiation delivered by the investigational CT scan. The investigational CBCT scanner exposes the patient to approximately 50% less radiation per scan than a conventional CT scanner. (Carrino et al 2014) With the investigational CBCT scan, there is the risk of pain caused by the need for weight bearing and/or flexion of an injured ankle. If for any reason the subject experiences undue discomfort the study will be stopped and the patient will be excluded from the study if the scan cannot be performed.

The patient will also fill out a visual analogue pain scale after both the investigational CT scan and gravity stress X-ray (**Attachment D**).

Reference: Carrino, J.A., et al., Dedicated cone-beam CT system for extremity imaging. Radiology, 2014. 270(3): p. 816-824.

9.3 Describe procedures performed to lessen the probability or magnitude of risks.

Response: The risks involved in inclusion in the study include the risk of additional exposure to radiation from the investigational CT scan. The investigational cone beam CT scanner exposes the patient to approximately 50% less radiation per scan than a conventional CT scanner. (Carrino et al 2014) The investigational scanner will be shielded per manufacturer specifications (see attachment B). The subject will be

shielded from radiation to the thyroid and genitals with commercially available shields. To address the risk of pain caused by the need for weight bearing on the injured ankle, the scans will only last about 25 seconds. The subject will be provided with assistance entering and exiting the scanner, and the handles attached to the housing of the scanner can be held by the subject for balance (but not for substantial unloading of weight bearing) on the extremity to prevent falling.

Reference: Carrino, J.A., et al., Dedicated cone-beam CT system for extremity imaging. Radiology, 2014. 270(3): p. 816-824.

9.4 Describe all drugs and devices used in the research and the purpose of their use, and their regulatory approval status.

Response: This study involves the use of an investigational portable weight bearing 3D cone beam CT scanner produced by Carestream Health, Inc. Supporting evidence contends that the prototype is a non-significant risk device (see **Attachment C**).

9.5 Describe the source records that will be used to collect data about subjects. (Attach all surveys, scripts, and data collection forms.)

Response: Data will be collected from the patient's medical records for screening potential research subjects (see attached **Eligibility Form, Attachment A**). Demographic, X-ray and CT data, and a visual analogue pain scale score will be documented by the research coordinator, surgeon and radiologist (see attached **Data Collection Forms, Attachment D**).

9.6 What data will be collected including long-term follow-up.

Response: Demographic data (age, gender, race, height, weight), data from the gravity stress X-rays and CT scans (medial clear space distance, superior clear space distance, lateral overlap distance, lateral clear space distance, and lateral talar shift) and pain VAS data will be collected (**Attachment D**). The measures will be obtained by two independent radiologists. Additionally, a visual analogue pain score will be obtained from the patient after both the investigational CT scan and gravity stress X-ray. The actual amount of weight borne by the patient at the time of the CT scan will be measured by a scale embedded in the device.

9.7 For HUD uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.

Response: Not applicable, this study does not involve a HUD device.

10.0 Data and Specimen Banking

10.1 If data or specimens will be banked for future use, describe where the data/specimens will be stored, how long they will be stored, how the data/specimens will be accessed, and who will have access to the data/specimens.

Response: The images obtained from the investigational cone beam CT scan will be saved for future use. The images will be de-identified and saved in the PACS system at the Erie County Medical Center. The study investigators and Carestream Health, Inc. will have access to these files.

10.2 List the data to be stored or associated with each specimen.

Response: The images obtained from the investigational cone beam CT scans will be saved for future use.

10.3 Describe the procedures to release data or specimens, including: the process to request a release, approvals required for release, who can obtain data or specimens, and the data to be provided with specimens.

Response: Requests for data will be accepted verbally or in writing. The principal investigator will approve all requests for data. Only the study investigators and Carestream Health, Inc. will be granted access to the data. The images will be de-identified before they are released. Carestream Health, Inc. will be requesting de-identified images, from the study-related cone beam CT scans only, for promotion & marketing purposes, and to refine the methodology of the scanner.

11.0 Data Management

11.1 Describe the data analysis plan, including any statistical procedures.

Response: To test for a difference in medial clear space between gravity stress X-ray and weight bearing cone beam CT, we will use a paired t-test. Intraclass correlation coefficients (ICC) and corresponding 95% confidence intervals will be computed as a measure of inter-rater reliability for the two radiologists who will assess the medial clear space. Bland-Altman plots will be used to visually assess agreement.

We will also conduct receiver operating characteristic (ROC) curve analysis and report the area under the curve (AUC) and corresponding 95% confidence interval. Using medial clear space >4mm for the gravity stress X-ray as the gold standard, we will determine the optimal cut-point for the cone beam CT scan.

11.2 Provide a power analysis.

Response: Sample size calculation was based on paired t-test. Estimates from the literature suggest the standard deviation of the difference of

medial clear space is around 1.5 mm. For a sample size of 20 patients and at the 0.05 significance level, we can obtain 80% power to detect a difference of at least 1mm.

11.3 Describe the steps that will be taken secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.

Response: Data collection will be conducted by trained study personnel who have completed IRB training. Data (i.e., demographics and CT and X-ray measures) will be entered into an Excel spreadsheet. The images will be de-identified and saved electronically in the PACS system at Erie County Medical Center. Data will be password protected and subject identity will be coded to ensure confidentiality of information. Patient names will not be stored with the images and patient data, instead each subject will be assigned an ID number. A separate password-protected spreadsheet will contain subject names and ID numbers to link the two together. The PI will assume primary responsibility for the ongoing monitoring of the data and safety of the study. Consent forms and other identifiable information will be stored in locked files separately from the study data. All data will be stored in password protected files in the research office at UBMD Orthopaedics Location 2 at ECMC.

11.4 Describe any procedures that will be used for quality control of collected data.

Response: Data will be entered and verified at 100%. We will utilize the services of the UB Clinical Research Office (CRO) for routine study monitoring activity. The UB CRO monitor will source verify the data, including consent process, following first subject enrollment. Subsequent monitoring activities will be arranged with the CRO depending on subject enrollment. The images from the gravity stress X-ray and investigational CT scan will be provided to the participating radiologist in a blinded and random fashion. When all subjects have been enrolled and undergone their scans, the scans will be presented randomly without any identifying information, on two separate occasions for measurement. The average of the two sets of measurements will be used for primary analysis.

11.5 Describe how data and specimens will be handled study-wide:

Response: Screening data will be collected on forms by the surgeon, research coordinator and other trained study staff. Demographic data will be documented on forms by the research coordinator or assistant. Data from the CT scan and X-ray will be documented on forms by the radiologist. The images will be de-identified and saved on the PACS system at ECMC. All data and collections forms (see **Attachments A & D**) will be collected by the research coordinator and stored securely.

11.6 What information will be included in that data or associated with the specimens?

Response: The following data will be collected: medical history, demographics, VAS pain score, and X-ray and investigational cone beam CT data (see **Attachment D**).

11.7 Where and how data or specimens will be stored?

Response: Consent forms and source data forms will be stored in locked files in the research office at UBMD Orthopaedics Location 2 at ECMC. The images will be saved on the PACS system at ECMC. Electronic data will be stored on our department's secure network drive in password protected files.

11.8 How long the data or specimens will be stored?

Response: The data will be stored throughout the duration of the study and final data analysis. The data will then be stored for 3 more years after the study closing date in accordance with the IRB policies.

11.9 Who will have access to the data or specimens?

Response: The study investigators, research coordinator and research assistant will have access to the data. Carestream Health, Inc. will also have access to the images upon request and under approval of the principal investigator. Images will be de-identified before sharing with Carestream Health, Inc.

11.10 Who is responsible for receipt or transmission of the data or specimens?

Response: The research coordinator or assistant is responsible for retrieving and storing the data.

11.11 How data and specimens will be transported?

Response: The research coordinator or assistant will pick up the study forms directly from the consenting and enrolling physicians after enrollment on a daily basis.

12.0 Provisions to Monitor the Data and Ensure the Safety of Subjects

12.1 Describe the plan to periodically evaluate the data collected regarding both harms and benefits to determine whether subjects remain safe.

Response: Adverse events will be reported to the Data Safety Monitoring Board (DSMB) within 2 days to review safety of the study.

12.2 Describe what data are reviewed, including safety data, untoward events, and efficacy data.

Response: Any adverse events will be reported to the research coordinator and reviewed by the DSMB within 2 days of notification of the event.

12.3 Describe how the safety information will be collected (e.g., with case report forms, at study visits, by telephone calls with participants).

Response: Adverse events will be documented in writing during study visits.

12.4 Describe the frequency of data collection, including when safety data collection starts.

Response: Safety data collection will begin after signed informed consent is obtained and continues until all data has been collected from 20 patients.

12.5 Describe who will review the data.

Response: Data collection will be monitored by the University at Buffalo Clinical Research Office for appropriate reporting of all adverse events and any serious adverse events that may occur during the course of the trial. The PI will have oversight of all of the subject data.

12.6 Describe the frequency or periodicity of review of cumulative data.

Response: Given the small sample size and relative low risk of the study and procedures, cumulative data will be analyzed when 20 subjects have been enrolled.

12.7 Describe the statistical tests for analyzing the safety data to determine whether harm is occurring.

Response: Adverse events will be reviewed by the DSMB on a case-by-case basis to determine if harm is occurring.

12.8 Describe any conditions that trigger an immediate suspension of the research.

Response: This study is low risk and we are not aware of a specific condition that would suspend the study. The DSMB will review all adverse events and assist in determining if the study needs to be suspended.

13.0 Withdrawal of Subjects

13.1 Describe anticipated circumstances under which subjects will be withdrawn from the research without their consent.

Response: If the patient is noncompliant or unable to stand in the weight bearing position, they will be withdrawn. If the subject exhibits any discomfort the study will be stopped immediately.

13.2 Describe any procedures for orderly termination.

Response: Subjects will be withdrawn from the study by the principal investigator if they do not complete the investigational CBCT scan. Subjects can withdraw from the study at any time, for any reason.

13.3 Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection.

Response: If the patient does not complete the investigational cone beam CT scan, none of their data will be retained.

14.0 Risks to Subjects

14.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.

Response: The risks involved in inclusion in the study include the risk of additional exposure to radiation from the investigational CBCT scan. The investigational cone beam CT scanner exposes the patient to approximately 50% less radiation per scan than a conventional CT scanner, the total dose delivered to study subjects will be half that of a single conventional CT scan. (Carrino et al 2014) The investigational scanner will be shielded per manufacturer specifications (see **Attachment B**). The subject will be shielded from radiation to the thyroid and genitals with commercially available shields. To address the risk of pain caused by the need for weight bearing and/or flexion of an injured knee, the scan will only last about 25 seconds. The subject will be provided with assistance entering and exiting the scanner, and the handles attached to the housing of the scanner can be held by the subject for balance (but not for substantial unloading of weight bearing) on the extremity to prevent falling.

14.2 If applicable, indicate which procedures may have risks to the subjects that are currently unforeseeable.

Response: There are no unforeseeable risks to report.

14.3 If applicable, indicate which procedures may have risks to an embryo or fetus should the subject be or become pregnant.

Response: The CBCT scan does involve a low dose of radiation, thus women who are currently pregnant will not be included in the study.

14.4 If applicable, describe risks to others who are not subjects.

Response: Technicians who are running the CBCT scanner will be properly trained in safety and take the necessary precautions to protect themselves from radiation exposure. There are no risks to family or those in close contact with the subject during their participation in the trial (see **Attachment B**).

15.0 Potential Benefits to Subjects

15.1 Describe the potential benefits that individual subjects may experience from taking part in the research. Include as may be useful for the IRB's consideration, the probability, magnitude, and duration of the potential benefits.

Response: There may be no potential benefits to subjects who enroll in the study.

15.2 Indicate if there is no direct benefit. Do not include benefits to society or others.

Response: There are no direct benefits to subjects who enroll in the study.

16.0 Vulnerable Populations

16.1 If the research involves individuals who are vulnerable to coercion or undue influence, describe additional safeguards included to protect their rights and welfare.

- *If the research involves pregnant women, review "CHECKLIST: Pregnant Women (HRP-412)" to ensure that you have provided sufficient information.*
- *If the research involves neonates of uncertain viability or non-viable neonates, review "CHECKLIST: Neonates (HRP-413)" or "HRP-414 – CHECKLIST: Neonates of Uncertain Viability (HRP-414)" to ensure that you have provided sufficient information.*
- *If the research involves prisoners, review "CHECKLIST: Prisoners (HRP-415)" to ensure that you have provided sufficient information.*
- *If the research involves persons who have not attained the legal age for consent to treatments or procedures involved in the research ("children"), review the "CHECKLIST: Children (HRP-416)" to ensure that you have provided sufficient information.*
- *If the research involves cognitively impaired adults, review "CHECKLIST: Cognitively Impaired Adults (HRP-417)" to ensure that you have provided sufficient information.*
- *Consider if other specifically targeted populations such as students, employees of a specific firm or*

educationally/economically disadvantaged persons are vulnerable to coercion or undue influence. The checklists listed above for other populations should be used as a guide to ensure that you have provided sufficient information.

Response: This research does not involve any of these vulnerable populations.

17.0 Community-Based Participatory Research

17.1 Describe involvement of the community in the design and conduct of the research.

Response: NA, this is not a community-based study.

Note: "Community-based Participatory Research" is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. Community-based Participatory Research begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

18.0 Sharing of Results with Subjects

18.1 Describe whether or not results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared.

Response: The study results or individual subject results, such as results of investigational diagnostic imaging, will be shared with the study subjects if requested verbally or in writing. The study results may become public knowledge if included in a manuscript accepted for publication in peer reviewed scientific literature. Any and all identifying features of individual images will be de-identified before publication.

19.0 Setting

19.1 Describe the sites or locations where your research team will conduct the research.

Response: Research will be conducted at UBMD Orthopaedics & Sports Medicine. The investigational CBCT scanner will be located in the SkyView Room of the radiology department at ECMC.

19.2 Identify where your research team will identify and recruit potential subjects.

Response: Subjects will be recruited & consented after undergoing an orthopaedic consultation at the ECMC Emergency Department or in the offices of the physicians of UBMD Orthopedics and Sports Medicine at ECMC or the Northtowns office (4949 Harlem Rd., Amherst, NY 14226).

19.3 Identify where research procedures will be performed.

Response: Subjects will be recruited & consented at ECMC Emergency Department or in the offices of the physicians of UBMD Orthopedics and Sports Medicine at ECMC or the Northtowns office (4949 Harlem Rd., Amherst, NY 14226). The investigational CBCT scan will be done in the SkyView room of the radiology department at ECMC.

19.4 Describe the composition and involvement of any community advisory board.

Response: NA, there will be no community advisory board involved in this study.

19.5 For research conducted outside of the organization and its affiliates describe:

- *Site-specific regulations or customs affecting the research for research outside the organization.*
- *Local scientific and ethical review structure outside the organization.*

Response: NA, research will not be conducted outside of the organization.

20.0 Resources Available

20.1 Describe the qualifications (e.g., training, experience, oversight) of you and your staff as required to perform their role. When applicable describe their knowledge of the local study sites, culture, and society. Provide enough information to convince the IRB that you have qualified staff for the proposed research. Note- If you specify a person by name, a change to that person will require prior approval by the IRB. If you specify people by role (e.g., coordinator, research assistant, co-investigator, or pharmacist), a change to that person will not usually require prior approval by the IRB, provided that person meets the qualifications described to fulfill their roles.

Response: John Marzo, MD is the principal investigator and Associate Professor of Clinical Orthopedics, SUNY University at Buffalo, and has extensive experience in clinical research. Christopher Ritter, MD, Christopher Mutty, MD, and Mark Anders, MD are all faculty members of UBMD Orthopaedics & Sports Medicine and very active traumatologists experienced in treating SER fractures. They are all active in clinical research of orthopaedic trauma. Collaborating investigators, Michael

Manka currently serves as the Chief of Emergency Medicine at Erie County Medical Center, and Jon Marshall, MD and Keyur Shah, MD are both Board Certified in Radiology. Several orthopaedic residents at UBMD Orthopaedics and Sports Medicine will assist with obtaining informed consent and all have extensive experience in patient interaction (Matthew Binkley, MD, Matthew Brown, MD, Timothy Bryan, MD, Samir Nayyar, MD, Christopher Urband, MD, Richard Ahn, MD, Rishi Dave, MD, Paul Phillips, MD, Andrew Baron, MD, Alexander Boiwka, MD, Kathleen Boyle, MD, Tyler Miller, MD, and Nicholas Valente, MD). Melissa Kluczynski has a MS in Epidemiology and has been a Clinical Research Associate at UBMD Orthopaedics & Sports Medicine for several years. She is productive and experienced in orthopaedic research and clinical trials. Laura Ryan, MPH and Kathleen Lafferty are Research Assistants at UBMD Orthopaedics & Sports Medicine and are very experienced in assisting with orthopaedic research studies. All of the above investigators have integral knowledge of the local study sites, culture, and society. All personnel mentioned have CITI and GCP training.

Describe other resources available to conduct the research: For example, as appropriate:

20.2 Justify the feasibility of recruiting the required number of suitable subjects within the agreed recruitment period. For example, how many potential subjects do you have access to? What percentage of those potential subjects do you need to recruit?

Response: In the past year, approximately 50-60 patients with potentially unstable SER type ankle fractures were treated by the study investigators. Based on our sample size calculation, we need to enroll 20 patients. Thus we should have a sufficient pool of subjects to recruit from.

20.3 Describe the time that you will devote to conducting and completing the research.

Response: We estimate that it will take about 8 months to 1 year to enroll all subjects, and about 6 months after that to complete the analysis and a manuscript.

20.4 Describe your facilities.

Response: Erie County Medical Center is a hospital with 550 licensed beds located in Buffalo, New York and is a member of the Great Lakes Health System. The hospital is affiliated with the University at Buffalo. The hospital is equipped with the latest information technology, including an electronic medical record system.

20.5 Describe the availability of medical or psychological resources that subjects might need as a result of an anticipated consequences of the human research.

Response: The radiology technician will periodically evaluate acquisition of the first CBCT scan to ensure maximum patient comfort and safety. Modifications will be made as appropriate and may include cushions, padding, external supports, or other changes when they add patient comfort or safety. Subjects will be withdrawn from the study if they cannot complete the investigational CBCT scan. Subjects can withdraw from the study at any time, for any reason. No other medical or psychological issues are expected to occur as a result of this study.

20.6 Describe your process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions.

Response: Each of the persons assisting with the research has been involved in designing the study, and writing of this proposal. The investigative team will meet periodically to discuss the protocol, modify the research procedures as necessary, and review the results. All study personnel will be involved in preparing a manuscript based on the results of the study.

21.0 Prior Approvals

21.1 Describe any approvals that will be obtained prior to commencing the research. (E.g., school, external site. funding agency, laboratory, radiation safety, or biosafety approval.)

Response: Prior to commencing the research, a basic research agreement will be executed between The Research Foundation for the State University of New York ("Institution") on behalf of the University at Buffalo ("University") with a business address of 402 Crofts Hall, University at Buffalo, Buffalo, New York 14260-7016 and Carestream Health, Inc. (funding agency), a Delaware Corporation with its principal office located at 150 Verona Street, Rochester, New York 14608.

Additionally, research approval will be obtained from ECMC's Clinical Research Department.

22.0 Recruitment Methods

22.1 Describe when, where, and how potential subjects will be recruited.

Response: Subjects will be recruited after presenting to the ECMC emergency department or the physician's office with a potentially unstable SER type ankle fracture as clinically diagnosed by a consulting orthopaedic physician. The study will be explained to subjects who are

deemed to be eligible for this study. Consent will be obtained from subjects who agree to participate.

22.2 Describe the source of subjects.

Response: Subjects will be patients who present to the emergency department at ECMC or to the physician's office with a potentially unstable SER type ankle fracture who are receiving medical care from one of the study investigators.

22.3 Describe the methods that will be used to identify potential subjects.

Response: Subjects will be screened by one of the consulting orthopedic physicians (included as study personnel) during their visit. Each subject's medical record will be reviewed to determine if the subject is eligible. The **Eligibility Checklist** (see **Attachment A**) will be completed for each patient who is screened.

22.4 Describe materials that will be used to recruit subjects. (Attach copies of these documents with the application. For advertisements, attach the final copy of printed advertisements. When advertisements are taped for broadcast, attach the final audio/video tape. You may submit the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording, provided the IRB reviews the final audio/video tape.)

Response: NA, there are no recruitment materials.

22.5 Describe the amount and timing of any payments to subjects.

Response: NA, subjects will not be compensated for their participation in this study.

23.0 Local Number of Subjects

23.1 Indicate the total number of subjects to be accrued locally.

Response: A total of 20 patients will be enrolled locally.

23.2 If applicable, distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)

Response: Based on last year's records, approximately 50-60 patients were diagnosed with SER fractures by the study investigators. Thus, at most we expect to screen 60 patients and exclude 20-30% due to ineligibility or lack of interest in participating. Our sample size analysis indicated that we need to enroll 20 patients that will complete the study procedures.

24.0 Confidentiality

Describe the local procedures for maintenance of confidentiality.

24.1 Where and how data or specimens will be stored locally?

Response: All study participants will be assigned an ID number to protect their anonymity and confidentiality. De-identified data will be stored in password protected files in the research office at UBMD Orthopaedics Location 2 at ECMC until publication, followed by storage on disks in locked files in the same room. The consent forms and source data forms will be stored in locked files in the same office mentioned above.

24.2 How long the data or specimens will be stored locally?

Response: The data will be stored throughout the duration of the study (approximately 1.5 years), and for three years after the study closes in accordance with IRB regulations.

24.3 Who will have access to the data or specimens locally?

Response: The study investigators, research coordinator and assistant will have access to the data.

24.4 Who is responsible for receipt or transmission of the data or specimens locally?

Response: The research coordinator and assistant are responsible for retrieving and storing the consent forms and source data forms.

24.5 How data and specimens will be transported locally?

Response: The research coordinator or assistant will pick up study forms directly from the study physicians and data collectors at ECMC.

25.0 Provisions to Protect the Privacy Interests of Subjects

25.1 Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.

Response: The consent form that subjects will sign, includes a HIPAA authorization which all study personnel will uphold. All subjects will be assigned an ID number for the study to protect their privacy and only study personnel will have access to the data.

25.2 Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.

Response: Subjects are not going to be asked any sensitive questions. The only procedure that the subject will undergo for this study is an

investigational cone beam CT scan. If the patient feels uncomfortable for any reason, either emotionally or physically, the study will be stopped. The imaging technicians are trained in making the patient feel at ease during the procedure.

25.3 Indicate how the research team is permitted to access any sources of information about the subjects.

Response: The research team has access to the subjects' medical records via our electronic medical record system. The research coordinator will manage all study data and the research team will be given access to the data as necessary. Carestream Health will not have access to the subject's medical records.

26.0 Compensation for Research-Related Injury

26.1 If the research involves more than Minimal Risk to subjects, describe the available compensation in the event of research related injury.

Response: It is unlikely that a patient will become ill or injured from this study. However, if the patient is injured as a direct result of their participation the patient will be responsible for paying for their own medical care.

26.2 Provide a copy of contract language, if any, relevant to compensation for research-related injury.

Response: The contract stipulates the following: "Carestream will reimburse Institution for direct, reasonable and necessary medical expenses incurred by Institution for the treatment of any adverse experiences by, illness of, or bodily injury to a Protocol subject that is caused by treatment of the Protocol subject in accordance with the Protocol. Carestream will not be responsible for paying medical expenses associated with treatment of the normal progression of the subject's disease, nor for injuries resulting from interventions that the subject would have incurred had they not participated in the Protocol."

27.0 Economic Burden to Subjects

27.1 Describe any costs that subjects may be responsible for because of participation in the research.

Response: The patient will be responsible for providing their own transportation to and from ECMC for the investigational CT scans.

28.0 Consent Process

28.1 Indicate whether you will be obtaining consent

Response: Consent will be obtained from all subjects who agree to participate in this study.

28.2 Describe where the consent process take place

Response: Subjects will be consented in the ECMC emergency department or physician's offices.

28.3 Describe any waiting period available between informing the prospective subject and obtaining the consent.

Response: Subjects will be consented when they are initially diagnosed with a potentially unstable SER type ankle fracture and before they are sent for their gravity stress x-ray and investigational cone beam CT scan.

28.4 Describe any process to ensure ongoing consent.

Response: Subjects will be consented once at the beginning of the study. There is only one study visit so ongoing consent is not necessary.

28.5 Describe whether you will be following "SOP: Informed Consent Process for Research (HRP-090)." If not, describe:

- *The role of the individuals listed in the application as being involved in the consent process.*
- *The time that will be devoted to the consent discussion.*
- *Steps that will be taken to minimize the possibility of coercion or undue influence.*
- *Steps that will be taken to ensure the subjects' understanding.*

Response: Yes, HRP-090 will be followed when consenting.

Non-English Speaking Subjects

28.6 Indicate what language(s) other than English are likely to be spoken/understood by your prospective study population or their legally authorized representatives.

Response: Spanish is the most likely non-English language that we might encounter in this study population. Non-English speakers will be included in this study. Information for non-English speakers will be provided in oral form with the use of an interpreter.

28.7 If subjects who do not speak English will be enrolled, describe the process to ensure that the oral and written information provided to those subjects will be in that language. Indicate the language that will be used by those obtaining consent.

Response: Based on previous experience, we expect that most if not all of our potential study subjects will speak English. However, if we encounter a non-English speaking subject we will find someone who can orally translate (i.e., fluently speaks the same language as the subject, such as a family member) the study description and consent form to the subject.

Waiver or Alteration of Consent Process (consent will not be obtained, required information will not be disclosed, or the research involves deception)

28.8 Review the "CHECKLIST: Waiver or Alteration of Consent Process (HRP-410)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response: Not applicable, consent will not be waived for this study.

28.9 If the research involves a waiver the consent process for planned emergency research, please review the "CHECKLIST: Waiver of Consent for Emergency Research (HRP-419)" to ensure you have provided sufficient information for the IRB to make these determinations. Provide any additional information necessary here:

Response: Not applicable, this study does not involve Emergency Research.

Subjects who are not yet adults (infants, children, teenagers)

28.10 Describe the criteria that will be used to determine whether a prospective subject has not attained the legal age for consent to treatments or procedures involved in the research under the applicable law of the jurisdiction in which the research will be conducted. (E.g., individuals under the age of 18 years.) For research conducted in NY state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "children."

Response: Not applicable, this study does not include subjects under 18 years of age.

28.11For research conducted outside of NY state, provide information that describes which persons have not attained the legal age for consent to treatments or procedures involved the research, under the applicable law of the jurisdiction in which research will be conducted. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "children" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

Response: Not applicable, this study will not be conducted outside of NYS.

28.12Describe whether parental permission will be obtained from:

- *Both parents unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.*
- *One parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.*

Response: Not applicable, this study does not include subjects under 18 years of age.

28.13Describe whether permission will be obtained from individuals other than parents, and if so, who will be allowed to provide permission. Describe the process used to determine these individuals' authority to consent to each child's general medical care.

Response: Not applicable, this study does not include subjects under 18 years of age.

28.14Indicate whether assent will be obtained from all, some, or none of the children. If assent will be obtained from some children, indicate which children will be required to assent.

Response: Not applicable, this study does not include subjects under 18 years of age.

28.15When assent of children is obtained describe whether and how it will be documented.

Response: Not applicable, this study does not include subjects under 18 years of age.

Cognitively Impaired Adults

28.16Describe the process to determine whether an individual is capable of consent. The IRB sometimes allows the person obtaining assent to document assent on the consent document and does not automatically require assent documents to be used.

Response: Not applicable, cognitively impaired adults will not be included in this study.

Adults Unable to Consent

When a person is not capable of consent due to cognitive impairment, a legally authorized representative should be used to provide consent and, where possible, assent of the individual should also be solicited.

28.17List the individuals from whom permission will be obtained in order of priority. (e.g., durable power of attorney for health care, court appointed guardian for health care decisions, spouse, and adult child.) For research conducted in NY state, review "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)" to be aware of which individuals in the state meet the definition of "legally authorized representative." The list in the consent template signature section corresponds to the priority list for NYS.

Response: Not applicable, cognitively impaired adults will not be included in this study.

28.18For research conducted outside of NY state, provide information that describes which individuals are authorized under applicable law to consent on behalf of a prospective subject to their participation in the procedure(s) involved in this research. One method of obtaining this information is to have a legal counsel or authority review your protocol along the definition of "legally authorized representative" in "SOP: Legally Authorized Representatives, Children, and Guardians (HRP-013)."

Response: Not applicable, this study does not involve research outside of NYS.

28.19Describe the process for assent of the subjects. Indicate whether:

- *Assent will be required of all, some, or none of the subjects. If some, indicated, which subjects will be required to assent and which will not.*
- *If assent will not be obtained from some or all subjects, an explanation of why not.*
- *Describe whether assent of the subjects will be documented and the process to document assent. The IRB allows the person obtaining assent to document assent on the consent document and does not routinely require assent documents and does not routinely require subjects to sign assent documents.*

Response: Consent will be obtained from all adult subjects over 18 years-old, this study does not include subjects under 18 years of age.

28.20For HUD uses provide a description of how the patient will be informed of the potential risks and benefits of the HUD and any procedures associated with its use.

Response: Not applicable, this is not a HUD study.

29.0 Process to Document Consent in Writing

If your research presents no more than minimal risk of harm to subjects and involves no procedures for which written documentation of consent is normally required outside of the research context, the IRB will generally waive the requirement to obtain written documentation of consent.

(If you will document consent in writing, attach a consent document. If you will obtain consent, but not document consent in writing, attach a consent script. Review "CHECKLIST: Waiver of Written Documentation of Consent (HRP-411)" to ensure that you have provided sufficient information. You may use "TEMPLATE CONSENT DOCUMENT (HRP-502)"to create the consent document or script.)

29.1 Describe whether you will be following "SOP: Written Documentation of Consent (HRP-091)." If not, describe whether and how consent of the subject will be obtained including whether or not it will be documented in writing.

Response: HRP-091 will be followed when consenting subjects.

30.0 Drugs or Devices

PROTOCOL TITLE: Comparison of a novel weight bearing cone beam computed tomography (CT) scan to gravity stress X-ray for determining instability of supination-external rotation type ankle fractures

30.1 If the research involves drugs or device, describe your plans to store, handle, and administer those drugs or devices so that they will be used only on subjects and be used only by authorized investigators.

Response: The CBCT scanner will be stored in a locked room at ECMC and only trained study staff will have access to it. A trained technician will operate the CBCT scanner. The CBCT scanner will only be used for study procedures approved by the UB IRB.

If the drug is investigational (has an IND) or the device has an IDE or a claim of abbreviated IDE (non-significant risk device), include the following information:

30.2 Identify the holder of the IND/IDE/Abbreviated IDE.

Response: The investigational cone beam CT scanner is being provided by Carestream Health, Inc. This device poses non-significant risk (see **Attachment B**).

30.3 Explain procedures followed to comply with FDA sponsor requirements for the following:

	Applicable to:		
FDA Regulation	***IND Studies***	***IDE studies***	***Abbreviated IDE studies***
21 CFR 11	***X***	***X***	
21 CFR 54	***X***	***X***	
21 CFR 210	***X***		
21 CFR 211	***X***		
21 CFR 312	***X***		
21 CFR 812		***X***	***X***
21 CFR 820		***X***	

Response: Not applicable, this is not an FDA study.

Attachment A. Eligibility Form

SER Ankle Fracture Instability STUDY

ELIGIBILITY QUESTIONS

TODAY'S DATE: _____

PATIENT'S NAME: _____

Please answer the following questions for ALL patients diagnosed with a suspected unstable supination-external rotation type ankle fracture requiring a gravity stress X-ray. Please refer to the Inclusion Criteria column to determine if the patient is eligible.

Question	Answer	Inclusion Criteria
1.) Does the patient have a diagnosis of a potentially unstable SER type (Weber B) ankle fracture?	YES / NO	The patient's X-ray must show medial clear space less than 5 mm with clinical suspicion of instability
2.) Is the patient able to provide written informed consent?	YES / NO	Patients must be able to provide written informed consent.
3.) Is the currently imprisoned?	YES / NO	Patients must not be in prison.
4.) How old is the patient?	Age = _____	Patients must be at least 18 years-old.
5.) Did the patient have an open fracture?	YES / NO	Patients must NOT have an open fracture.
6.) Does the patient have clinical signs of ankle deformity?	YES / NO	Patient must NOT have clinical signs of ankle deformity.
7.) Did the patient have any type of previous ankle trauma or surgery on the affected ankle?	YES / NO	Patient must NOT have had any type of previous ankle trauma or surgery on the affected ankle.
8.) Does the patient have significant osteoarthritis or pre-existing ligamentous instability or pain in the affected ankle?	YES / NO	Patient must NOT have significant osteoarthritis or pre-existing ligamentous instability or pain in the affected ankle.

10.) Is the patient pregnant?	Patient Verbal Response: YES / NO Urine pregnancy test result (<u>for females who consent ONLY</u>): Positive / Negative	The patient must NOT be pregnant. Females who consent to participate MUST have a negative urine pregnancy test.
11.) Can the patient stand in the weight bearing position?	YES / NO	The patient MUST be able to stand in the weight bearing position for the cone beam CT scan.
IS PATIENT ELIGIBLE FOR THE STUDY? YES / NO		
DID THE PATIENT CHOOSE TO ENROLL IN THE STUDY? YES / NO		
NOTES:		

Attachment B: Installation instructions

Carestream

CBCT 3D Extremity Imaging System

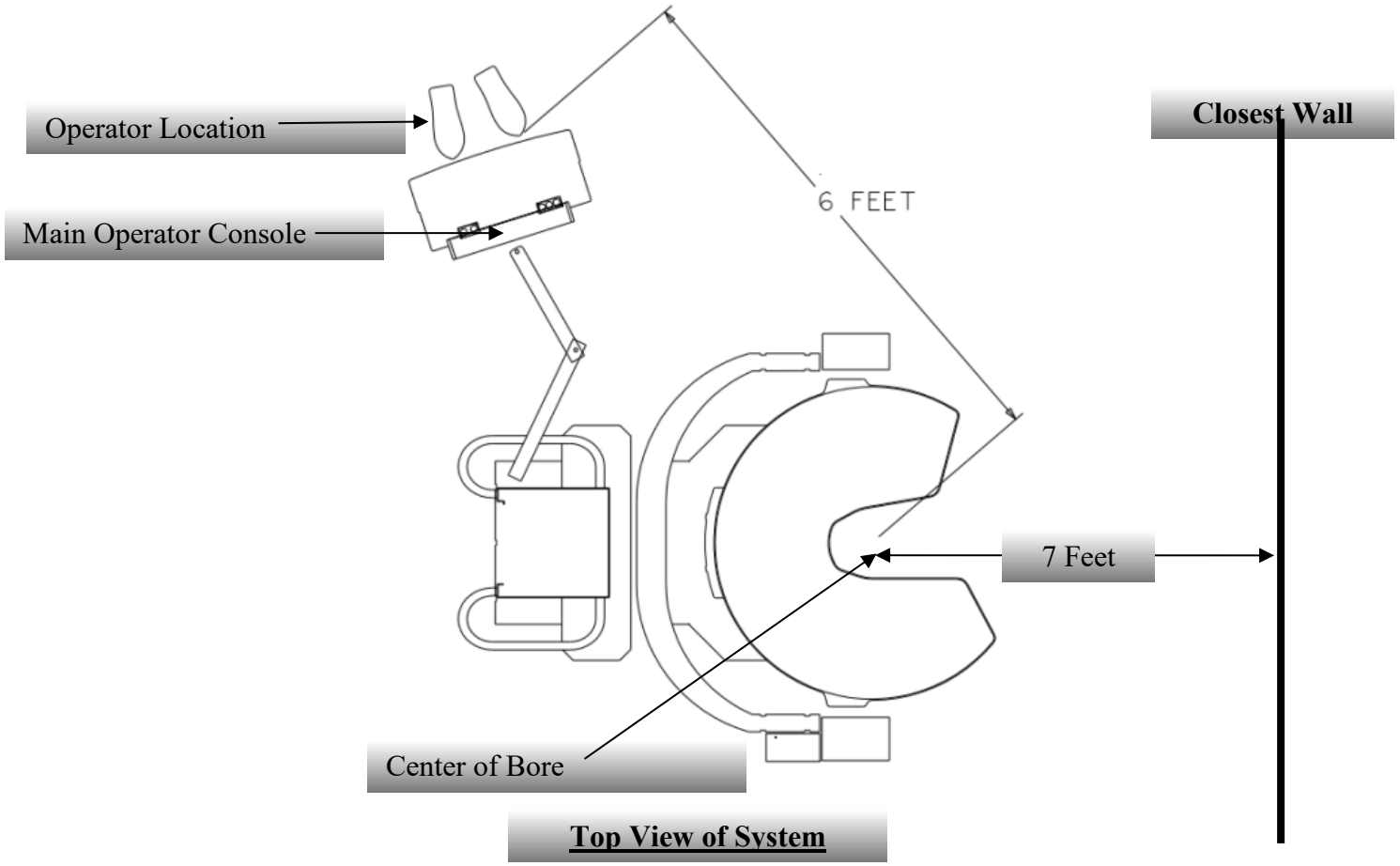
WARNING:

The system should always be located a minimum distance of 7 feet from the center of the bore to the closest wall.

Carestream scatter plot results show that at distances of 6 feet or greater from the center of the bore, the yearly exposure based on 1,000 exams would be <50 millirem. Correspondingly, 6,000 exams per year would be <300 millirem.

WARNING:

Operator should stand at least 6 feet away from the center of the bore during the entire exposure duration. It is recommended that the Main Operator Console be positioned in the following orientation to accomplish this:



Top View of System

WARNING:

The system is designed to attenuate most beam and scattered radiation in an effort to reduce shielding requirements for the operator. Lead lined walls generally will not be necessary, however because shielding regulatory requirements vary for a variety of factors and by region - A room evaluation should be done by a qualified medical physicist. Similar to Dental CBCT systems, small office environments can typically be accommodated without significant modification to existing structures or workflow.

Allowable annual NYS Operator dose < 500 millirem
Maximum annual scans = 1,000
Operator outside a 6 foot radius from isocenter will be < 50 millirem/year
Conclusion: System can be operated at the maximum use case
and be < 10% of the NYS allowable worker limit
without requiring additional operator shielding.
Allowable annual Public Space dose < 100 millirem
Maximum annual scans = 1,000
Dose absorption by double layer drywall = 50%
Maximum dose/year inside wall is 200 millirem
Conclusion: System can be installed adjacent to a fully occupied
public space separated by double drywall and
stay below the allowable public limit
without requiring additional room shielding
if a 3 foot minimum distance from isocenter is maintained.

PROTOCOL TITLE: Comparison of a novel weight bearing cone beam computed tomography (CT) scan to gravity stress X-ray for determining instability of supination-external rotation type ankle fractures

Attachment C: Statement of Non-significant risk

Carestream Health cone beam 3D CT scan
Justification for assessment of non-significant risk device

This assessment is drawn from FDA guidance documents, and from studies performed at Johns Hopkins University, where the prototype cone beam 3D CT scanning device was determine to be non-significant risk device. (IRB No. 00034417) The device used in this study is an upgraded version (3rd generation) of the previous cone beam 3D CT scanner, with improved software for data acquisition and image processing. There have also been changes to the physical configuration of the device, designed to improve patient set-up.

Description of device: The scanner is a diagnostic x-ray system intended to produce cross sectional images of the extremities of the body by computer reconstruction of x-ray transmission acquired at different angles. The prototype cone beam CT scanner is specifically designed for imaging of human extremities such as the shoulders, elbows, wrists, hands, knees, and ankles. The scanner has the following unique capabilities and characteristics:

- The unit is portable
- The ability to acquire images with the joints under weight bearing status
- The ability to acquire images of joints in various degrees of motion
- Lower radiation dose exposure
- No radiation shielding necessary
- Produces higher quality resolution of 3D images
- Allows measurement of surface area of contact in the joint

The scanner, because of some of the above capabilities, has potential usefulness in a hospital department, an office, or operating room setting. The intended use with respect to this document is to perform clinical research that demonstrates effectiveness of the device for diagnostic use in orthopedic surgery and radiology.

Risk to Human Subjects: The main risk to the subjects of study is due the use of ionizing radiation during the imaging procedure. The estimated dosage that will be received by the study participants is ~ 0.14 mSv. This dose is comparable to or less than the typical dose delivered during a conventional diagnostic CT scan – 0.16 mSv as reported by Biswas et al. (Radiation exposure from musculoskeletal computerized tomographic scans. JBJS A (91): 1882-1889, 2009) Radiation dose at less than 1 mSv is orders of magnitude less than that associated with possible long term health risks, even by the most conservative estimates. (Brenner and Hall. Computed tomography – an increasing source of radiation exposure. NEJM 375(22): 2277, 2007) This statement is also consistent with position statement of the American Association of Physicists in Medicine(AAPM), which states: "risks of medical imaging at effective doses below 50 mSv for single procedures or 100 mSv for multiple procedures over short periods are too low to be detectable and may be nonexistent."

The prototype of the scanner to be used in this study was previously reported by Carrino et al (Dedicated cone-beam CT system for extremity imaging. Radiology 270(3): 816-824, 2014) to deliver absolute dose of 9.0 mGy, compared to 39.7 mGy for the same scan on a conventional CT scanner. As further outlined by Biswas; these levels of radiation dose are approximately equal to the dose of two PA chest radiographs, or two transatlantic flights on a commercial airplane, and are "essentially neglible/trivial…" within the context of patient risk associated with radiation exposure. In most patients, it would be expected that the diagnositic information yielded by the CT scan would supersede any concern about excessive radiation exposure.

It is therefore contended that the dose levels associated with the proposed protocol will present negligible risk to the health, safety, or welfare of the study participants.

Risk Determination: Guidance for determination of significant(SR) or non-significant risk(NSR) risk can be found in part 812.3(m) of the CFR Title 21 and in the FDA document *Information sheet guidance for IRBs, clinical investigators, and sponsors.*

The FDA definition of a significant risk device is that the device:

• Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
Assessment: The scanner is **not** intended as an implant

• Is purported or represented to be for use supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
Assessment: The scanner is **not** for use in supporting or sustaining human life…

• Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject;
Assessment: In this study, the scanner is **not** for use in diagnosing, curing, mitigating, or treating disease. Enrolled subjects will undergo the normal physician encounter and diagnositic testing associated with their clinical condition. The imaging

procedure for this study will be taken in addition to the normal diagnostic testing(conventional CT scan). The scan results will not influence patient treatment or clinical management decisions before the diagnosis is established by the medically established standards of history, physical examination, and imaging studies.

• Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Assessment: With regard to the use of ionizing radiation, the primary potential risk to be considered is the induction of cancer, which is a function of many factors – most notably the level of radiation dose and the age of the patient at the time of exposure. The study only includes subjects 16 years or older. As noted above, the radiation dose associated with the scanner is ~0.14 mSv, which is comparable to or less than that of conventional diagnostic CT of the extremities. As noted by Biswas; these levels of radiation dose are "essentially neglible/trivial…" within the context of patient risk associated with radiation exposure. Radiation dose at less than ~1 mSv is orders of magnitude lower than the dose believed to be associated with health risk, even by the most conservative of estimates. Together, these factors suggest an insignificant risk to study participants associated with radiation exposure.

According to the FDA document *Information sheet guidance for IRBs, clinical investigators, and sponsors: "*an NSR devise study is one that does not meet the definition for an SR device study." As outlined in the items above, the proposed study device **does not meet** the definition of a significant risk device study, and is therefore NSR.

Additional Supporting Information: We note the following examples as precedent support for the use of an xray producing system in an NSR device study:

The determination of NSR at Johns Hopkins University for study of the prototype scanner to be used in this study (IRB No. 00034417)

The FDA document *Information sheet guidance for IRBs, clinical investigators, and sponsors* specifically uses digital mammography as an example of an NSR device

The University of Pennsylvania Center for Advanced Computed Tomography Imaging Services, under their Human Policies and Procedures, allows CT device protocols to be classified as either NSR or SR. (see http:www.uphs.upenn.edu/radiology/research/labs/cactis/policies/human-studies.html)

The Form 10-K/A SEC filing for a cone beam volumetric scanner with intended use in orthopedic imaging and image-guided procedures identifies the system as a class II NSR device which subsequently gained 510(k) clearance. (O-arm, Imaging 3, Burbank, CA)

Attachment D: Data Form

SER Ankle Fracture Instability STUDY: DEMOGRAPHIC DATA COLLECTION FORM

STUDY ID#: _____ **TODAY'S DATE: _____**

AGE: _____

GENDER (check one): _____ Male

_____ Female

RACE: _____

HEIGHT: _____ **WEIGHT**: _____

PATIENT'S DOCTOR: _____

AFFECTED SIDE: _____ Right

_____ Left

COURSE OF TREATMENT: _____

PROTOCOL TITLE: Comparison of a novel weight bearing cone beam computed tomography (CT) scan to gravity stress X-ray for determining instability of supination-external rotation type ankle fractures

SER Ankle Fracture Instability STUDY: CT DATA COLLECTION FORM

STUDY ID #: _____

DATE OF CT SCAN: _____

RADIOLOGIST: _____

RESULTS OF CT SCAN:

Date of Measurement: _____

Medial Clear Space Distance: _____

Superior Clear Space Distance: _____

Lateral Overlap Distance: _____

Lateral Clear Space Distance: _____

Lateral Talar Shift: _____

Total Weight Bearing: _____

Percent Weight Bearing: _____

SER Ankle Fracture Instability STUDY: X-RAY DATA COLLECTION FORM

STUDY ID #: _____

DATE OF X-RAY: _____

RADIOLOGIST: _____

RESULTS OF X-RAY:

Date of Measurement: _____

Medial Clear Space Distance: _____

Superior Clear Space Distance: _____

Lateral Overlap Distance: _____

Lateral Clear Space Distance: _____

Lateral Talar Shift: _____

Visual Analogue Scale

On a scale of 0 to 10, where 0 equals no pain and 10 equals extreme pain, please circle the number that best represents how much ankle pain you experienced during the scan.

0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**