Protocol Title: **Contrast-Enhanced Cone Beam Breast CT for Diagnostic Breast Imaging**

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IRB #: **RSRB00061893**

NCT #: **NCT03354611**

Principal Investigators: **Avice O'Connell, MD**

UR Medicine

Sponsor: **Koning Corporation**

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Date: **02/19/2020**

Revision: **3.5**

Protocol Agreement:

I have read the protocol specified below. As Investigator, I agree to conduct the study in accordance with GCP principles, Federal Regulations, and the terms of this protocol.

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Investigator:	**Avice O'Connell, MD**

Signature _____ Date _____

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Synopsis:

Title:	Contrast-Enhanced Cone Beam Breast CT for Diagnostic Breast Imaging
Sites:	UR Medicine Breast Imaging
Rationale:	CE-CBBCT has been proved to be potentially superior to diagnostic mammography. This study is to acquire diagnostic patients to merge with previous BIRADS 4, 5 cases and form a database consisting of 181 BIRADS 1-5 diagnostic patients with 68 confirmed cancers. The database will be representative of the intended use population of CE-CBBCT and will be used for a pivotal multi-reader multi-case (MRMC) reader study, whose primary endpoint is to compare CE-CBBCT+2-view mammograms to diagnostic mammography.
Study Design:	Up to one hundred (100) female patients will be enrolled and consented to participate in the study. These women will be enrolled from screening assigned BIRADS 0, patient complaint, or referral for second opinion. The enrolled patient will accept CE-CBBCT scans within 4 weeks of her diagnostic mammography and before breast biopsy if biopsy is needed. The final diagnostic workup outcome of these enrolled patients needs to include at least 30 confirmed cancers cases.
Primary Objective:	To acquire the CE-CBBCT scans of 100 evaluable diagnostic patients with at least 30 confirmed cancers cases.
Number of Subjects:	100

Inclusion/Exclusion Criteria	Inclusion Criteria:
	• Female sex
	• Age 35 years or older
	• Any ethnicity
	• Have an abnormality detected by Breast Self Exam (BSE), or Clinical Breast Exam (CBE), or have an abnormality detected by an imaging modality.
	• Will undergo study imaging within four weeks from the date of diagnostic mammography, prior to breast biopsy (if needed).
	• Able to provide informed consent
	• Post-menopausal, surgically sterile, or effective birth control. For women of childbearing potential, negative pregnancy test or has signed pregnancy test waiver
	• If required by standard of care, eGFR ≥45 within 48 hours to 6 weeks of CE-CBBCT exam
	Exclusion Criteria:
	• Pregnancy
	• Lactation
	• Unknown pregnancy status AND
	  ○ has refused pregnancy testing and
	  ○ has refused to sign a pregnancy test waiver
	• Women who are unable or unwilling to understand or to provide informed consent
	• Women with physical limitations that may prohibit resting prone on the exam table, such as, but not limited to: frozen shoulder, recent heart surgery, pace maker.
	• Women who are unable to tolerate study constraints.

	• Women who have received radiation treatments to the thorax or breast area for malignant and nonmalignant conditions, such as (but not limited to):
	  o Treatment for enlarged thymus gland as an infant
	  o Irradiation for benign breast conditions, including breast inflammation after giving birth
	  o Treatment for Hodgkin's disease
	• Women who have participated in a prior breast clinical trial that gave additional radiation dose, such as an additional mammogram.
	• Women who have received large numbers of diagnostic x-ray examinations for monitoring of disease such as (but not limited to):
	  o Tuberculosis
	  o Severe scoliosis
	<u>Additional Exclusion Criteria Due To Contrast Injection:</u>
	• Allergic to iodinated contrast material
	• Previous non-ionic contrast reaction
	• Any conditions below regardless of eGFR
	  o Renal Disease
	  ▪ Chronic renal dysfunction
	  ▪ Renal Transplant (or waiting for a transplant)
	  ▪ One kidney or other birth defect
	  ▪ Polycystic Kidneys
	  ▪ Renal Tumor/Renal Cancer
	  o History of liver failure/cirrhosis/liver transplant/pending liver transplant
	• Congestive heart failure
	• Multiple myeloma

	• Hyperthyroidism • Pheochromocytoma • Sickle Cell Disease • Asthma requiring <u>daily</u> use of inhaler <u>Additional exclusion criteria due to machine limitations</u> • Patient's body weight is over the limit of the scanner table (440 lbs or 200kg)
Primary Endpoints:	Enrollment of 100 evaluable diagnostic patients who successfully finish the study, including 30 cancer cases confirmed by pathology results.
Rationale for Subject Number:	To achieve the effective area under ROC curve difference of 0.08 between CE-CBBCT+2 view mammograms and diagnostic mammography, The MRMC reader study will use 12 readers and 100 BIRADS 1-5 cases, with the normal to cancer ratio of 1:1. Current CE-CBBCT database has 81 BIRADS 4&5 cases, with 38 cancers. FDA requires the pivotal MRMC study to include BIRADS 1 to 5 patients (final BIRADS) as a reasonable representative of diagnostic population. BIRADS 1, 2, 3 cases and additional cancers need to be acquired. In order to achieve the goals stated above and acquire some extra cases for reader training in MRMC study, 100 diagnostic cases need to be successfully acquired in this study, including BIRADS 1, 2, 3 cases and at least 30 confirmed cancers. After merging with previous cases, the final dataset for the MRMC is expected to consist of 181 BIRADS 1-5 patients with 68 confirmed cancers.

Revision History

Revision	Date	Section	Description
1.0	03/03/2016		Original submission to IRB
2.0	06/22/2016		Remove UMASS from the study sites
3.0	06/22/2016		Add study coordinator
3.1	03/31/2017		Change Appendix numbers into CRF numbers
3.2	11/15/2017	12	Add potential risk of machine failure
3.3	11/20/2017	5, 12,	Add NCT number, add body weight limit to exclusion criteria, more description about dose.
3.4	03/05/2018	5, 8	Remove the following from additional exclusion criteria: ≥60 years of age; Diabetes mellitus; Hypertension requiring medication Enable the collection of all anonymized diagnostic workup images (if available)
3.5		6, 12	Corrected typos, changed max limit of mA & dose from 200 mA to 160 mA due to new mA limit in new Koning Breast CT that will be used for the continuation of this clinical trial. (Installed in Oct 2019). Indicated breast tissue weighting factor (per current NCR definition) used in determining dose range.

1 BACKGROUND AND PRIOR EXPERIENCE

1.1 BACKGROUND

Non-contrast Cone Beam Breast CT (CBBCT) has received FDA PMA approval for diagnostic breast imaging. The CBBCT technique effectively removes overlap of breast structures, a confounding factor of the 2D mammogram study, and significantly improves the detectability of small breast tumors, independent of intravenous contrast agents, without vigorous breast compression. Of equal importance, results demonstrate that radiation exposure levels required for the CBBCT technique to detect small tumors (under 4 mm) and small calcifications (~0.2 mm) is within the same range of conventional diagnostic mammography [1].

The combination of detector resolution, small x-ray tube focal spot size, and imaging geometry enables the CBBCT system to achieve a reconstructed isotropic spatial resolution of (0.155 – 0.273 mm^3). Isotropic high resolution allows reconstruction in any plane, without loss of detail, and a 3D volume reconstruction of superior spatial resolution. Isotropic high resolution is unique to the CBBCT method and to-date has not been feasible in other 3D breast imaging techniques. Current methods, primarily breast magnetic resonance imaging, are hindered by slice thicknesses typically 3-5 mm or more, which limits multi-planar reconstruction and limits the usefulness of 3D volumetric reconstruction. Therefore, CBBCT for breast-imaging may be able to more accurately identify small carcinomas (< 4 mm) and better delineate the extent of disease. CBBCT for breast-imaging provides the potential for a superior alternative to standard breast imaging techniques. [2] [3]

To further improve the detection of tumors and to distinguish cancer from benign lesions, the CBBCT is supplemented with the use of intravenous contrast agent. A Contrast Enhanced CBBCT (CE-CBBCT) typically requires a pre-contrast acquisition and a post-contrast acquisition.

The value of functional imaging in breast cancer diagnosis to increase the diagnostic yield and to further contribute to the overall management of the breast cancer patient has been demonstrated in the literature. Intravenous dynamic contrast enhanced breast MRI (CE-BMRI) has become the standard of care in functional imaging of the breast. [4] [5] [6]. CE-BMRI is fully dependent on contrast resolution arising from intravenous contrast agents and the neovasculature associated with tumors. The difference between CE-BMRI imaging and all other imaging is that the image reflects contrast enhancement rather than actual breast anatomy. This dependence on contrast constrains the modality to balance spatial resolution against acquisition time. A CE-BMRI study typically takes 1.5-3 minutes for each of six required acquisitions to obtain sufficient image quality. Despite a 1 mm x 1 mm in-plane resolution, CE-BMRI typically has a 3 mm slice thickness, thus its evaluation of morphologic features suffers. While CE-BMRI is a tomographic study, its 3D rendering is poor because of the relatively large slice thickness, providing only a maximum contrast uptake

intensity projection (MIP) used for geographic location only, rather than a full isotropic 3D dataset with added diagnostic value. In addition, CE-BMRI is not able to distinguish calcifications, which are evident in up to 50% of breast cancers not associated with a mass [7]. Although CE-BMRI has a high sensitivity for invasive cancers, current techniques may be limited in detecting ductal carcinoma in situ (DCIS), because of its weakness in imaging calcifications. Recent study on the brain deposits of gadolinium-based contrast agents for MRI has raised concern about using this type of contrast agents for breast imaging [8]. Although further evaluation of gadolinium-based contrast agents is being carried out by researchers, it is necessary to investigate other modalities for enhanced breast imaging.

CE-CBBCT does not compromise spatial resolution for temporal resolution and can visualize calcifications. In addition, CE-CBBCT may identify a unique pattern to malignant tumor vessels not previously described [9]. CE-CBBCT uses non-ionic iodinated contrast agents which does not create the same risks as gadolinium-based contrast agents except other risks well known to the care providers. Previous studies have been done to study CE-CBBCT's performance in BIRADS 4 and 5 patients. The results show that CE-CBBCT not only has high sensitivity, show greater extent of disease, but is capable of detecting new malignant lesions not otherwise detected on diagnostic workup [10].

1.2 PREVIOUS STUDIES

Approximately 600 CBBCT patients have been acquired in the United States under 5 IRB approved protocols including 81 BIRADS 4 & 5 patients who received CE-CBBCT scans. No adverse events were reported in these studies.

Based on clinical data from the previous studies, the CBBCT is comparable or exceeds breast tissue coverage as compared to mammography. Density is readily and reliably assessed. Breast anatomy is displayed exquisitely, showing vessels to <1 mm. Calcifications < 200μm are visualized with greater conspicuity, and distribution can be determined in 3D space. The CBBCT is equal or better than mammography for visualization of mass for conspicuity, border, and sharpness. The non-contrast CBBCT also assesses mass density accurately; but CT number alone may not improve specificity in the absence of IV contrast. Cancer size on CBBCT agrees with measurement from histopathology. Contrast enhancement is needed to further improve specificity. In the Contrast Enhanced CBBCT study, CE-CBBCT has high sensitivity, show greater extent of disease, and is able to detect new malignant lesions not previously detected on diagnostic work up or non-contrast CBBCT [1] [10] [11] [12] [13].

The CBBCT system has the feature to automatically determine the best mA required for the scan. This feature uses the two scout images at 0 and 90 degrees to estimate breast size, density, and automatically select the best mA to optimize image quality while keep the radiation dose as low as reasonably achievable. Analysis based on data from 220 patients has shown that the average mean glandular dose of one CBBCT scan and one diagnostic mammography exam is 10.6 mGy (standard

deviation 3.89) and 9.57 mGy (standard deviation 5.16). The overall dose range is comparable and the dose values are less variable for the CBBCT [14].

Contrast-Enhanced CBBCT scan doubles the dose with a pre-contrast scan and a post-contrast scan. However, the total dose of a CE-CBBCT exam is 11.6mGy for a standard size, average dense breast. Given the tissue weighting factor of breast tissue is 0.12, a CE-CBBCT exam's effective dose is 1.39 mSv, which is about 5 months of nature background radiation dose in the United States [15].

Although Non-contrast CBBCT has received FDA PMA approval, FDA requires a separate PMA submission to prove the safety and effectiveness of CE-CBBCT within diagnostic population. A multi-reader multi-case (MRMC) pivotal reader study has been designed to compare CE-CBBCT+2-view mammograms to diagnostic mammography, the primary modality in diagnostic workup, to prove the hypothesis that CE-CBBCT is superior to diagnostic mammography in the diagnosis of breast cancer. Previous studies acquired only BIRADS 4 and 5 patients. New acquisition study is necessary so that the final database used for the MRMC study can cover the full diagnostic population of breast cancer.

2 STUDY OBJECTIVES

The primary objective of this study is:

- To acquire up to 100 diagnostic patients, including at least 30 confirmed cancer cases.

3 STUDY ENDPOINT

The primary endpoint of this study is:

- Enrollment of up to 100 evaluable diagnostic patients who successfully finish the study including 30 cancer cases confirmed by pathology results

4 STUDY RATIONALE

An MRMC readers study has been designed to compare CE-CBBCT with diagnostic mammography in the accuracy of breast cancer diagnosis. A sample size is estimated based on a previous pilot reader study. To achieve the area under the ROC curve difference of 0.08, 12 readers and 100 cases are needed. The normal to cancer ratio of the cases dataset is set to 1:1. Some extra normal and abnormal cases are also needed to train the readers in the MRMC study. FDA further requires that the case dataset needs to be a representative of the diagnostic population, which covers various numbers of BIRADS 1-5 diagnostic patients.

We have acquired 81 BIRADS 4 & 5 CE-CBBCT cases with 38 confirmed cancers in previous clinical trials. To meet the sample size requirement and FDA's expectation, additional diagnostic patients must be acquired, to insure inclusion of various numbers of BIRADS 1, 2, 3 cases and at least 30

more cancers from diagnostic population. After merging with previous cases, the final dataset for the MRMC is expected to consist of 181 BIRADS 1-5 CE-CBBCT cases with 68 confirmed cancers.

5 STUDY DESIGN

5.1 OVERVIEW

Up to one hundred (100) diagnostic patients will be enrolled and consented to participate in the study. These women will be enrolled from screening recall assigned BIRADS 0, patient complaint, and referral for second opinion. The enrolled patient will accept CE-CBBCT scans within 4 weeks of her diagnostic mammography and before breast biopsy if biopsy is needed. The final diagnostic workup outcome of these enrolled patients needs to include at least 30 confirmed cancers and various numbers of BIRADS 1, 2, 3 cases.

5.2 STUDY SITES

The study will take place at:

UR Medicine Breast Imaging

500 Red Creek Drive

Rochester, NY 14623

The subject enrollment and scan will take place at UR Medicine Breast Imaging.

5.3 NUMBER OF SUBJECTS

Up to one hundred (100) diagnostic patients will be enrolled and consented to participate in the study. These women will be enrolled from screening recall assigned BIRADS 0, patient complaint, and referral for second opinion. The final diagnostic workup outcome of these enrolled patients need to include:

- At least thirty (30) pathology confirmed cancers
- Various numbers of all BIRADS cases

5.4 GENDER OF SUBJECTS

Only women will be recruited for this study. Although men can get breast cancer, male breast cancer incidence is low and is not considered to be a great health issue. Thus, this study will exclude males with breast disease.

5.5 AGE OF SUBJECTS

Women of ages 35 and above will be recruited into this study. Younger women and minors (less than 18 years) will be excluded due to their extremely low incidence of breast cancer.

5.6 RACIAL AND ETHNIC ORIGIN

There are no enrollment restrictions based on race or ethnic origin. The community served by the UR Medicine is sufficiently varied that we might anticipate adequate enrollment of females from diverse backgrounds to ensure that the benefits and burdens of research are equitably distributed.

5.7 INCLUSION CRITERIA

- Female sex
- Age 35 years or older
- Any ethnicity
- Have an abnormality detected by Breast Self Exam (BSE), or Clinical Breast Exam (CBE), or have an abnormality detected by an imaging modality.
- Will undergo study imaging within four weeks from the date of diagnostic mammography, prior to breast biopsy (if needed).
- Able to provide informed consent
- Post-menopausal, surgically sterile, or effective birth control. For women of childbearing potential, negative pregnancy test or has signed pregnancy test waiver
- If required by standard of care, eGFR ≥45 within 48 hours to 6 weeks of CE-CBBCT exam

5.8 EXCLUSION CRITERIA

- Pregnancy
- Lactation
- Unknown pregnancy status AND
  - has refused pregnancy testing and
  - has refused to sign a pregnancy test waiver
- Women who are unable or unwilling to understand or to provide informed consent
- Women with physical limitations that may prohibit resting prone on the exam table, such as, but not limited to: frozen shoulder, recent heart surgery, pace maker.
- Women who are unable to tolerate study constraints.
- Women who have received radiation treatments to the thorax or breast area for malignant and nonmalignant conditions, such as (but not limited to):
  - Treatment for enlarged thymus gland as an infant
  - Irradiation for benign breast conditions, including breast inflammation after giving birth
  - Treatment for Hodgkin's disease

- Women who have participated in a prior breast clinical trial that gave additional radiation dose, such as an additional mammogram.
- Women who have received large numbers of diagnostic x-ray examinations for monitoring of disease such as (but not limited to):
    - Tuberculosis
    - Severe scoliosis

Additional exclusion criteria due to contrast injection:

- Allergic to iodinated contrast material
- Previous non-ionic contrast reaction
- Any conditions below regardless of eGFR:
    - Renal Disease
        - Chronic Renal Insufficiency
        - Renal Transplant (or waiting for a transplant)
        - One Kidney or other birth defect
        - Polycystic Kidneys
        - Renal Tumor/Renal Cancer
    - Liver Failure
    - Cirrhosis
    - Liver Transplant (or waiting for liver transplant)
- Congestive heart failure
- Multiple myeloma
- Hyperthyroidism
- Pheochromocytoma
- Sickle Cell Disease
- Asthma requiring daily use of inhaler

Additional exclusion criteria due to machine limitations

- Patient's body weight is over the limit of the scanner table (440 lbs. or 200kg)

5.9 VULNERABLE SUBJECTS

Vulnerable subjects will not be enrolled.

6 METHODS AND PROCEDURES

The Study Group will consist of up to 100 female subjects, age 35 years or older and determined to require diagnostic workup. Preferentially the subjects will undergo CE-CBBCT on the same day that diagnostic work-up takes place or may be performed no later than four weeks from the date work-up is completed but before breast biopsy if biopsy is required. Subjects can have a history of prior biopsies or breast surgeries performed.

The technologist performing the CE-CBBCT will have the original mammogram (a digitized scan) or a copy (when the original is not available) so that optimized positioning can be achieved. This will allow for the most accurate spatial comparison between the two tests. There may be new findings based on the CE-CBBCT study alone. The study radiologist may recommend additional imaging and physical exam and/or interval imaging. The subject and her referring physician will be informed of the new findings and the recommendations. Information from additional work-up and/or biopsy, based on follow-up imaging will be collected.

6.1 CE-CBBCT PROCEDURE

The subjects will first have a pre-contrast CBBCT scan. Iodinated contrast will be injected intravenously, and then another CBBCT scans will be performed to capture the tumor vasculature enhancement. Features to look for are degree of enhancement pattern of the lesion as compared to surrounding pattern. Delay times and contrast volume/rate will be determined initially through previous CT studies then optimized through this CBBCT study. Each CBBCT scan takes 10 seconds and delivers a glandular dose similar to a diagnostic mammography exam. State board-certified and Mammography Quality Standards Act (MQSA) qualified mammographers will evaluate the CBBCT high resolution 3D images and compare them to the subjects' mammograms. If the subject had an MRI or ultrasound, then these would be compared as well. If the patient's diagnostic outcome is BIRADS 4 and above and has biopsy or surgery, pathology will provide final confirmation. If the patient's diagnostic outcome is BIRADS 1, 2, 3, follow up results will provide final confirmation.

Physicians familiar with contrast-enhanced multislice CT procedures will be available during the CE-CBBCT procedures and will advise on modifications.

Once all the projections are acquired, projections will then be used for volume reconstruction. Since a malignant tumor has many blood vessels, it will be enhanced in the post-contrast reconstructed image. The contrast enhancement of the malignant tumor will be quantified by CT number measurements. To explore dynamic contrast-enhanced vasculature patterns (wash-in, wash-out), we propose to select the scan at various delay times on different subjects with similar lesions to see if we can get preliminary data on this functional effect while keeping the dose to individual subjects low.

The radiographic technique will be 49 kVp, 8 ms/projection image, and 300 images per scan. The mA will be automatically selected by the CBBCT system from 50 to 160 mA, depending on size and density of the breast. This translates to a range of average glandular dose to the breast from ~4

mGy to ~13 mGy per scan, depending on breast size and density, or similar to the subject's diagnostic mammogram. In this study, the dose for a full two-scan contrast imaging will be ~ 8 to 32 mGy, or similar to two diagnostic mammography exams.

6.2 CE-CBBCT TECHNICAL DETAILS

6.2.1 CBBCT for Breast Imaging System:

The CBBCT system employs a horizontally oriented gantry beneath a subject support table, which incorporates an x-ray tube with a 0.3 mm focal spot at one end and a high-resolution, 40 x 30 cm real-time flat panel detector (FPD) at the opposite end. The extensive detector dynamic range (>16 bit) along with the 3D imaging technique provides up to 30x greater contrast resolution than standard imaging. The system is designed and built in compliance with the national and international safety standards for medical equipment.

For a CBBCT scan, the subject lies prone on the support table. The breast of interest is placed through the opening in the table and the breast is positioned in the imaging field. The table sits above a motorized scanning arm carrying an x-ray source and image detector that allows a 360° rotational x-ray sequence in ~10 seconds. To acquire the 10 second, full-volume scan of the breast, the CBBCT gantry rotates 360° around the subject's breast, acquiring 300 pulsed projection images at ~8 ms each. Acquired image data is sent to a computer to perform 3D reconstruction. Specialized 3D visualization software constructs a three-dimensional model of the breast from the images taken during the rotational x-ray sequence. Once the data is reconstructed, it provides the radiologist with $(0.27\ mm)^3$ (standard resolution) cross-sectional slice data displayed in any plane as well as a 3D rendering. The data set can be reconstructed to $(0.155\ mm)^3$ with a sharp ramp filter for high resolution volume of interest (especially for calcifications) without having to re-scan the subject.

Our previous studies to-date has illustrated the capacity of the non-contrast CBBCT to image the breast without structure overlap and with superior contrast resolution as compared with standard breast imaging. The study results illustrate that the CBBCT system is able to image the entire breast from axillary region to chest wall with clinically acceptable image quality and radiation dose comparable to conventional mammography. Cancers are better visualized as well as defined. In general, it is observed, that cancerous tissues absorb more x-rays than normal tissues, as determined by a higher Hounsfield unit, (CT number or x-ray attenuation coefficient), but the CT number of some benign entities can match that of cancer.

6.2.2 Subject Positioning and Image Acquisition:

A unilateral 3D CE-CBBCT for breast imaging study will be performed. After intravenous access is accomplished, the subject will be placed on the imaging table in the prone position in a left or right anterior oblique position so that the breast of interest suspends through the table opening into the volume of image acquisition. A radiologic technologist, registered in radiography and

mammography through the ARRT and who is also trained in 3D CE-CBBCT acquisition, will position the breast and acquire the images.

6.2.3 Pre-study Screening:

As per department protocol, subjects will undergo pre-study screening (including POCT and serum eGFR as indicated) to avoid contrast reaction and toxicity. If there are any potential contraindications to the use of contrast with a study subject, the subject will be excluded. (Appendices A, B, C)

6.2.4 Contrast Injection:

A nurse, trained in intravenous contrast injections and reactions, will establish intravenous access through a peripheral vein using a catheter. The arm opposite of the breast to be scanned will be used to administer the IV contrast to reduce the chance of the contrast directly entering the veins of the scanned breast. The nurse will be present through the study. A physician will supervise the injections. A clinically certified power injector will be used to deliver a bolus injection. As a starting point, 1.5-2ml/kg body weight (100 ml maximum) of a low osmolar, nonionic, 300-350 mgI/ml iodinated contrast agent, will be injected at a rate of ~2.0 ml/s, for a total injection time of 30-60 seconds (for a 50 kg subject). This will be immediately followed by a saline "chaser" from 20 to 40 ml at ~2 ml/s (20 seconds) to maximize dynamic enhancement. A bolus test with small amount of contrast to determine the timing of the particular subject's peak enhancement could be performed using a series of low dose pulsed scout images. (Appendices D, E, F)

For those subjects who are found to have limited IV access, hand injection will be used to deliver the contrast agent. Using the same formula of 2ml/kg body weight, up to 100ml of low osmolar, nonionic 300-350 mgI/ml iodinated contrast agent will be injected over 30-60 seconds. This will be followed by a 20 to 40ml saline bolus delivered also by hand injection.

6.2.5 Contrast-enhanced Scan Protocol:

For iodinated contrast studies of the breast, we propose to initially perform a pre-contrast scan and one post-contrast scans. Exact timing of the post-contrast scans needs to be explored as part of this study. As a starting point:

- Pre-contrast scan
- Begin contrast injection (and saline chaser)
- Start time of post-contrast CE-CBBCT scan is 90-200 seconds after start of injection, depending on method of contrast delivery (bolus vs hand injection)

6.2.6 Power Injector:

A power injection system will be utilized. If a power injector is not available, hand injection by a certified physician or nurse is also acceptable.

6.2.7 Post-study Monitoring:

We will observe department protocol for patient follow-up after IV contrast injection.

6.3 CE-CBBCT EVALUATION

6.3.1 Dose Considerations:

For iodinated contrast studies of the breast, we propose to initially perform a pre-contrast scan and 1 post-contrast scan. Exact timing of the post-contrast scans needs to be explored as part of this study. The average glandular dose to the breast volume per scan will be 4 mGy to 13 mGy per scan (+/-20%), depending on breast size and density or similar to the subject's diagnostic mammogram. Thus, the dose for a full two-scan protocol will be ~ 8 to 26 mGy, or similar to two diagnostic mammography exams.

By comparison, this dose is up to 2-3 times lower than multi-slice CT scans of the breast, which results in a $CTDI_{100}$ ~12-18 mGy glandular dose/scan. In addition, these multi-slice CT scans radiate the entire thorax in addition to the breast at much higher photon energies (120 kVp compared to 49 kVp). The effective dose from a conventional chest CT scan is 7 mSv, which is equivalent to 2 years of natural background radiation [16]. The effective dose from a two-scan, single breast CE-CBBCT exam is from 0.1.2 mSv to 3.8 mSv, which is equivalent to approximately 4.6 months to 14.7 months of natural background radiation. This conversion is based on a breast tissue weighting factor of 0.15 per NRC 10CFR 20.1003 Definitions.

Two scans are typically performed at ~30 seconds and 2 minutes after contrast injection. In addition, 3 mm thick slices are taken to scan the breast volume. At 0.8 sec/rotation and a pitch of 1, it takes ~40 seconds to cover ~150 mm distance to capture the full breast. Contrast enhancement can change significantly during this time. The CBBCT scan, however, takes only 10 seconds to scan a full breast volume thus capturing a volume "snapshot" of the contrast-enhanced tumors at that time.

6.3.2 Image Processing:

CE-CBBCT scans will be reconstructed to maximize dynamic enhancement data. The various time-dependent reconstructions and approaches will be tested and evaluated to determine the optimized time delay after contrast injection before start of the scan.

6.3.3 Review of the CE-CBBCT:

Two MQSA qualified board-certified mammography radiologists will evaluate the CE-CBBCT study along with all prior imaging and histological results to determine the added value of CE-CBBCT. Initially, the radiologists will review the CE-CBBCT images and make independent diagnostic decisions blindly from MRI and ultrasound image results, if available. Next, they will compare the results of CE-CBBCT to diagnostic mammography, non-contrast CBBCT, MRI, and ultrasound images. Finally, they will compare their findings for each case to histological results, which are considered to be the quantitatively gold standard in diagnosis. The comparison will answer three questions:

1. Can the CE-CBBCT detect lesions that not detected by other modalities?
2. Can the CE-CBBCT better distinguish between benign and malignant masses?
3. Can the CE-CBBCT help show the extent of disease?

7 DATA RECORDING

Information to be recorded on the participants includes:

- Subject age
- Date of Birth
- Height and weight
- Ethnic category
- Body habitus
- Measurement of breast
- Information to be recorded about imaging
    - Date of breast imaging studies
    - Date of CE-CBBCT imaging
- Pertinent clinical information, imaging data, interpretation data, and biopsy data will be recorded by hand through data sheets (CRF 1-13). All data will be subsequently entered into Excel spreadsheets to track results.

8 DATA COLLECTION

The following represents source documentation for data to be collected:

- Original mammogram OR reasonable quality copies of the subject's mammogram
- CE-CBBCT images
- Ultrasound images (if any)
- MR images (if any)
- CRF 1-6
- CRF 7-10 as appropriate
- Physicians Reports if performed for:

- Mammogram
- Ultrasound
- Breast MRI
- Pathology Reports
- Definitive Surgery

9 ANALYSIS OF RESULTS

All data will be collected in a spreadsheet.

Contrast-enhanced CBBCT (CE-CBBCT) for breast imaging will be evaluated, tabulated, and analyzed in terms of lesion conspicuity and detail in comparison with the non-contrast CBBCT exam, mammogram, and contrast-enhanced breast MRI. We will evaluate wash in and wash out patterns and degree of enhancement of the lesion as compared to surrounding pattern.

Demographic and clinical characteristics of the study population will be described using mean and standard deviation for quantitative variables such as age, or percentage and percentiles for qualitative variables such gender, race, and cancer staging.

Reported adverse events will be tabulated according to its description, severity, and relationship to the specific imaging or clinical procedures. All patients will be included in the safety analysis.

Paired t-test (for quantitative measurements such as tumor size, time of wash in and wash out) or McNemar's test (for qualitative data such as type of mass, type of calcification) will be used for comparisons between the CE-CBBCT and other modalities.

Accuracy of diagnosis will be evaluated in terms of sensitivity and specificity by comparing the test results from each imaging modality to that of the biopsy (the gold standard). When sufficient data is available, comparisons between CE-CBBCT and the other modalities will then be conducted using McNemar's test.

No imputation will be used for missing data (i.e., only patients who have the specific data available will be included in a particular analysis.) Statistical analysis will be performed using SAS (SAS Institute, Cary, N.C., U.S.A.). All tests will be 2-sided with the confidence level set to 95%.

10 PATIENT CONFIDENTIALITY

The recruiting sites will be responsible for providing source documentation, such as images and reports. In order to minimize the use of PHI in communications between the study coordinator and recruiting sites, study packets, each with a unique study identifier, will be provided to each recruiting site. At recruitment, each volunteer is issued a study packet with a unique study identifier. Unused ID numbers will not be re-issued. The recruiting sites will keep a database that connects the subject name and medical record number with the unique study ID number. This computer will be password protected and locked down when user not engaged and accessible only

to study personnel at recruiting sites. The primary computer databases will be established at the Highland Breast Imaging, and will connect the study ID number with the subject name and other demographics. This computers will be password protected and locked down when user not engaged and accessible only to study personnel.

A request for source documentation from recruiting sites, such as images and reports will be managed through study ID and subject initials.

In addition to study personnel directly involved with this clinical trial, only the University of Rochester, and the Department of Health and Human Services will have access to subject files for purposes of audit. CRO personnel and monitor will also have access to subject files for purposes of monitoring and audit

De-identified images and data from this study may be used to apply for grants to support future studies, or may be used for other studies. In addition, the University of Rochester may license de-identified images and data to Koning Corporation, who has exclusive rights to market the CBBCT machine.

Any images used for evaluation or publication will be scrubbed of personal identifiers.

11 RESEARCH INFORMATION IN MEDICAL RECORDS

The following information will be included in the subject's electronic health record:

- Documenting participation
- A copy of the signed consent form
- Results of all testing done as part of this study

12 POTENTIAL RISKS OF THE STUDY

12.1 ADDITIONAL DIAGNOSTIC WORKUP

It is possible that the CE-CBBCT will detect an abnormality not previously evident by conventional imaging methods. This may lead to further focused imaging work-up, which may include ultrasound, mammography, or breast MRI. Biopsy or short-term follow-up may be recommended based on this additional work-up. The subject and her doctor will be informed of any new findings based on the CE-CBBCT. This added work-up might cause the subject undue anxiety and additional investment of time.

12.2 RADIATION EXPOSURE

There will be radiation exposure to the breast(s) resulting from the CE-CBBCT study. The relationship between breast cancer and radiation has been studied extensively. It is known that female breast tissue is sensitive to ionizing radiation [16]. However, risk is highly influenced by previous radiation dose to the breast as there is a linear relationship between dose and risk, although the time intervals between exposures may reduce the cumulative effects. Of significant importance is the age at which exposure occurs. At high doses of 100cGy (1000 mGy), in a *young* woman, relative risk of developing breast cancer at a later age (typically 35-40 years later), is increased from 1.0 to 1.4 (2.0 would be double the risk), which is equivalent to the increase in risk from other factors, such as: nulliparity, early age at first menarche (under age 11 years), and having a very late age at menopause [16]. There is no proof of "*statistically significant increases below a dose of about 20 cGy* (200 mGy)" … and further, "*for exposure after the age of about 45 years there is little evidence that radiation increases the occurrence of breast cancer*" [16]. The FDA mandates dose limits for screening mammography, because the benefit of screening mammography lies in the need for annual repeat exams to reap the benefits of early detection. The FDA sets a limit of 6 mGy for a two-view screening mammogram, for a 4.2 cm compressed breast with a 50/50 distribution of fat to glandular tissue [17]. The dose for a CBBCT scan to obtain a CNR of ~8, for a 4.2 cm breast equivalent phantom with a 50/50 distribution, is approximately 5.8 mGy. A CNR of ~8 has been determined to be the level needed for *diagnostic* adequacy (it is likely that screening dose will be more readily understood from the results of this study). There is no mandate that controls the dose for diagnostic mammography because the benefit/risk ratio is considerably higher in the diagnostic population. Also, the radiologist may require an unknown number of extra mammographic views in order to make a diagnostic decision. The American College of Radiology and the Radiologic Society of North America equates the effective whole body dose of a mammographic exam (0.7 mSv) to about 3 months of background radiation [18].

Analysis based on data from 220 diagnostic patients, which are representative of the range of breast thicknesses and densities found in a female population, has shown that the average mean glandular dose of one CBBCT scan and one diagnostic mammography exam is 10.6 mGy (standard deviation 3.89) and 9.57 mGy (standard deviation 5.16), respectively. The overall dose range is comparable and the dose values are less variable for the CBBCT [14].

The CBBCT study includes two low dose scout images, acquired at a standard dose (~0.30 each for the two images; 0.6 mGy total), and the CBBCT scan. For the CBBCT scan, we propose delivering the *minimal* average glandular dose level required to maintain sufficient image quality for each subject. The dose from the CBBCT scan varies with breast size and density and is determined for each individual breast from the two low-dose scout images. Dose from the CBBCT scan will range from ~4 mGy to no more than ~16 mGy (+/- 20%) (depending on breast size and density) to provide a CNR of ~8, the level needed for diagnostic adequacy. The amount of radiation exposure from one CBBCT scan of one breast is equivalent to an effective whole body dose of ~0.6 - 1.9 mSv. Thus, the highest dose from the CBBCT of 1.9 mSv would approximate the same dose received from about 7

½ months of background radiation. The CBBCT dose is within the range of what could be expected from diagnostic mammography studies.

The dose range of the CBBCT study is substantially less than the minimum dose recognized to induce an increased risk for breast cancer. In addition, we will institute a data safety and monitoring plan for this study to assure that dose remains within the stated limits, while continuously evaluating image quality along with improvements that may reduce the dose of the CBBCT study.

For CE-CBBCT exam (one pre- and one post-contrast) the dose and associated risk increases linearly by the number of scans. The dose from a CE-CBBCT exam of one breast is ~8mGy to ~32mGy (+/- 20%) (depending on breast size and density). The amount of radiation exposure from one CE-CBBCT exam of one breast is equivalent to an effective whole-body dose of 1.2 mSv to 3.8 mSv, which is equivalent to approximately 4.6 months to 14.7 months of natural background radiation. This conversion is based on a breast tissue weighting factor of 0.15 per NRC 10CFR 20.1003 Definitions. In addition, this is meant to be a one-time study, not a periodic screening routine.

12.3 ALLERGIC REACTION TO CONTRAST INJECTION

Possible allergic reaction to the contrast injection must be addressed. A physician experienced with contrast reactions will be available during the contrast scan along with a trained nurse to monitor the subject. The patient will be constantly monitored for contrast reactions, such as itchiness, hives, breathing difficulties. Suitable medical supplies will be on-hand to treat the subject in the rare case of an adverse contrast reaction. See "Management of Acute Reactions to Contrast Media in Adults" document (Appendices G, H), which includes Hives/Urticaria, Diffuse Erythema, Bronchospasm, Laryngeal Edema, Hypotension, Hypertensive Crisis, Pulmonary Edema, Seizures/Convulsions, Hypoglycemia, Anxiety/Panic Attack, and Reaction Rebound Prevention. In the rare case of a severe reaction, the infusion will be stopped immediately, the subject will be treated with suitable medical supplies on hand and 911 will be called. The subject will be transported to the Emergency Department at the University of Rochester, Strong Memorial Hospital.

Possible infection, hematoma and contrast extravasation from IV access may also occur after the IV contrast injection. After the CT exam, the subject will be under observation for at least one hour while she is still in the facility. In the rare case of a severe event, the subject will be treated with suitable medical supplies on hand. (Appendix I)

12.4 MACHINE FAILURE

There is a small risk that the scans may be interrupted by machine failure. If the machine fails during the pre-contrast scan and the contrast injection is not started, the subject may choose to continue the study or withdraw from the study. If the subject chooses to continue the study, the pre-contrast scan will be repeated, followed by contrast injection and post-contrast scan.

The repeat of the pre-contrast scan will cause extra radiation dose up to one full CBBCT scan (4mGy to 16mGy). Thus, the total radiation dose in case of machine failure will be up to 12mGy to 48mGy depending on breast size and density.

If the machine fails after the contrast injection is started, the scan will not be repeated. The acquired images will be postprocessed to see if the images can be recovered or corrected. If the images can be corrected, the subject will still be included in the study. Otherwise, the subject will be excluded from the study.

There may be risks that are not known at this time.

13 DATA SAFETY AND MONITORING PLAN

It is prudent to assure that doses remain within the stated limits while continuously monitoring for image quality. We will manage this with the following plan, which will be overseen by the principal investigators:

- The CE-CBBCT system will be calibrated and documented, and periodic quality control testing will be completed and documented to ensure the machine is giving the correct doses of radiation.
- Calculations for target mA and the actual x-ray techniques used will be documented on updated "Technologist Evaluation Form (CRF 3)." This will be used in the annual report to the Radiation Safety Committee which will compare the dose actually used with the radiation estimates provided in the Human Use of Radiation Committee application.
- The ordering and administration of the contrast material and timing of injection and scans will be documented in CRF 3 "Technologist Evaluation Form."
- The exclusion criteria will filter out subjects that have had prior high radiation dose exposure.
- The following will be completed by the Principal Investigator:
    - A periodic review of the Calibration and QC records
    - Review of the mA determination and other technical factors actually used for each subject.
    - Periodically review a sampling of the inclusion/exclusion forms.
- Possible allergic reaction can occur but is rare when using IV contrast agents. A physician and trained nurse experienced with IV contrast reactions will be available during the contrast scan to monitor the subject. Suitable medical supplies will be on hand to treat the subject in the rare case of an adverse contrast reaction.

14 POTENTIAL BENEFITS

The subject may or may not benefit from this study. Although CBBCT device has been approved by the FDA, the use of contrast agent in CBBCT scan has not received FDA approval. If unusual/unexpected findings are noted only in CE-CBBCT, the patient will be referred for further

workups. It is possible, though not probable, that the patient may have important breast problems identified because of the additional imaging she undergoes with CE−CBBCT.

15 ALTERNATIVES TO PARTICIPATION

The subject may choose not to participate in this trial. Patient care will proceed as normal for each recruiting site. If the patient chooses not to participate in this trial, it will in no way jeopardize current or future care within UR Medicine.

16 RECRUITMENT METHODS

Recruitment of volunteers will be accomplished by each participating site by face-to-face recruitment by the site research coordinator, or radiologist investigators. Site personnel may use appointment schedules to identify patients who may qualify for this study. Every effort will be made to recruit volunteers of ethnic minorities.

Any member of the approved study team will ask the patient if she is interested in hearing about the clinical trial. If the patient is interested, she will be treated as a prospective subject. If the patient meets all the inclusion criteria, none of the exclusion criteria and wishes to continue participating in the study, she will be enrolled into the study. Following this, one of the licensed physicians (MD) or physician assistant (PA) involved in this study will approve and order the contrast-enhanced CBBCT radiographic exam, per NY State laws.

17 CONSENT PROCESS

The study coordinator or any other member of the approved study team, with training through the RSRB Human Subjects Protection Program (or equivalent), will conduct the consent process. The goals of the consent process are to provide information through the IRB-approved study-specific consent form (SSCF) in a non-coercive environment and to engage in an exchange of information about the study in order to assure that the potential participant understands the information so that participation in the study will be voluntary. The consent process will be conducted in a quiet and private area. The prospective subject will be informed that she may take as much time as needed to read the SSCF and that she may also take the consent form home to discuss with family members. Once the potential volunteer has read the consent form, the person obtaining consent will engage in an exchange of information about the study and respond to all questions. If the potential participant indicates that she would like to participate, the person obtaining consent will ask if all her questions have been answered and if she has any other questions. If the prospective subject indicates all questions have been answered and she has nothing further to ask, she will proceed to the consent process: the prospective subject is asked to sign and date the two copies of the consent form. The person obtaining consent will also sign and date both consent forms in the presence of the participant. The subject will then be given one copy of the signed consent form for

her records, and will be told to call at any time with further questions or concerns about participation in the study.

18 ADVERSE EVENTS

Personnel within UR Medicine will inform the study coordinator of any reported adverse events within 24 hours of knowledge. The study coordinator will immediately report serious adverse events (including serious injury or death) to the IRB and the Sponsor.

19 COMPENSATION FOR INJURY

UR Medicine will provide medical care for any emergency medical problem that the subject may experience as a direct result of participation in this research. The subject will not have to pay for this emergency care, but the University may seek reimbursement for this care from the health insurance carrier or the study sponsor. Decisions regarding care and compensation for any other research related injury will be made on a case-by-case basis.

20 SPONSORSHIP

The study is funded by Koning Corporation, West Henrietta, NY.

21 COST TO THE SUBJECT

There will be no cost to the participant for the CE-CBBCT study.

The subject or her insurance carrier will be charged for focused work-ups based on new findings of the CE-CBBCT, if those occur.

Biopsy and other testing prompted by follow-up standard imaging will be charged to the subject or her insurer.

22 PAYMENT FOR PARTICIPATION

There is no payment to the subjects for participation in the study.

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